Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper

Written by MGP Zuidgeest, MJC Willemen and JN van den Anker

Background Paper 7.1
Priority Medicines for Children

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Executive summary and key research points

Children are entitled to safe, efficacious, and age-appropriate medicines. However, the provision of optimal medicines for children is limited by the lack of commercial incentives, a dearth of clinical trials on paediatric medicines, delays in licensing medicines for children, and the absence of suitable formulations for children. Children are not small adults, but rather a vulnerable population with specific needs resulting from their changing physiology, who make up a heterogeneous patient group with a scope of diseases different than those of adults, and for whom there is a scarcity of data on appropriate medicines delivery and use. Therefore, these needs are discussed in detail in this background paper; the challenges and opportunities for improvement and further research are also identified.

Demographics and diseases faced by children

Children in Europe represent 20% of the total population and child mortality rates are low in the European Union. Worldwide under-five mortality steadily declined, from 10.4 million in 2004 to 6.9 million in 2011, but it remains a significant and inequitable problem. Children suffer from a different range of diseases than adults, as some diseases only occur in children, while others occur in both adults and children, but with different pathophysiology, severity, course, and response to treatment across the life span.

Asthma is the most common chronic childhood disease in Europe, affecting 5–20% of school-aged children in Europe. It is assumed that the recent decrease in the prevalence of asthma may correspond with improved environmental control measures. The childhood type 1 diabetes incidence rate continues to rise across Europe by 3-4% per year, and the risk of type 2 diabetes in adolescents is increasing due to overweight and obesity. Mental disorders are increasingly important causes of ill health and disability in children and adolescents, but the recent broadening of age ranges and the scope of diseases has led to debates on the medicalisation of certain conditions. Despite the increasing prevalence of chronic diseases, infectious diseases remain the most common cause of illness in children in the developing world and a predominant cause of childhood mortality in these countries. A study on paediatric drug utilisation in Europe (TEDDY) illustrated that anti-infectives, dermatological and respiratory drugs were the most frequently used medicines in children.

Product related issues in children

The 2004 Priority Medicines Report called for public investments to reverse the insufficient funding for research on children-specific medicine formulations. An effective paediatric therapy requires medicines adjusted to a child's body development, medicines-related toxicity, and the taste preferences of children. To meet these requirements, it may be necessary to develop age-appropriate medicines with strengths and dosage forms suitable for each paediatric subpopulation using the medicine.

Liquid formulations used to be considered the most suitable form for children under six years of age. In 2008, a WHO expert forum proposed a global paradigm shift towards solid oral dosage forms for paediatric medicines, and solid, oral, flexible dosage forms (orodispersible tablets and tablets for oral liquid preparation) became the recommended

paediatric dosage forms. For oral medicines with precise dose measurements, a new flexible platform technology was proposed to produce multiparticulate solids (mini-tablets and spherical granules - pellets) and dosage forms that are dispersible into liquids or that can be mixed with food. The advantages of novel, solid dosage forms are their dose flexibility for different patient ages and weights, and their easier administration in younger children. Following recent studies on mini-tablets, the age at which young children can safely swallow orally administered solid forms is decreasing. With the development of orally disintegrating mini-tablets, there are more promising results for infants younger than two years of age.

Recently various innovative, oral, solid dosage forms and drug devices for paediatric use have become commercially available or are under development. These developments should be accompanied by studies on price implications and access to innovative products, children's preferences and adherence to different dosage forms, safe excipients for children, and new routes of administration (mainly for neonates). The industry should implement the acquired knowledge about more suitable formulations for paediatric use.

Regulatory aspects related to children

The European Union adopted the Paediatric Regulation in 2007 to support the development and administration of appropriate paediatric medicines and to improve the information available on their use. The Regulation combines requirements for paediatric drug development (paediatric investigation plans - PIPs) with incentives for the pharmaceutical industry to test medicines in children (extension of the supplementary protection certificate - SPC and Paediatric Use Marketing Authorisation - PUMA). The long-term aim of the Paediatric Regulation is to achieve the goal of an integrated approach to the development of paediatric medicines in the overall medicines development area. Nevertheless, paediatric therapeutic areas addressed by the industry since 2007 seem more aligned with adult drug development than to indicated unmet public health needs of children (paediatric oncology, pain, neonatal morbidity). In addition, the awarding of SPC extensions to paediatric medicines may increase public expenditures for healthcare and have cost implications for the public purse. Such effects have to be identified and negotiated according to the available budgets. The fact that only one PUMA has been granted since 2008 indicates that it may not be an adequate incentive to the industry for the development of off-patent drugs. As a response, a priority list of studies into off-patent paediatric medicines has been produced by EMA to serve as a basis for EU public sector research funding. As a complementary measure that addresses the lack of paediatric clinical trials for off-patent medicines, existing patient records on the use of off-label medicines could be systematically collected and evaluated to contribute towards more evidence-based medicines use. Off-label medicines are those prescribed outside their authorised indications with respect to age, dosage, indication or route.

The paediatric usage environment

Based on an EMA survey published in 2010, 45-60% of all medicines given to children in the EU were used outside their marketing authorisation (off-label), especially in neonates, patients with serious conditions and those in intensive care units. The most frequently used off-label and unlicensed medicines in children were the anti-arrhythmics, anti-hypertensives, proton pump inhibitors, H2-receptor antagonists, anti-asthmatics, and antidepressants. Preterm neonates were the most vulnerable patient group, as they were exposed to a high

numbers of medicines (mostly unlicensed or off-label), at a higher risk for adverse drug reactions, and without information on safety and efficacy in preterms available in the Summary of Product Characteristics (SmPC).

Inappropriate antibiotic prescribing for children was common in Europe, with marked differences between Northern and Southern Europe as well as difference within countries being seen. Of particular concern was the issue of prescribing antibiotics for viral infections because of the problem of antibiotic resistance. Antimicrobials were also among the most commonly prescribed drugs in hospitals. The European Surveillance of Antimicrobial Consumption (ESAC) study in paediatric units in 2008 revealed that a third of paediatric patients were on antimicrobials, with a high proportion of them receiving antimicrobial combinations. The targets for quality improvement included the excessive use of antimicrobial combinations, high proportion of parenteral antimicrobials, and long surgical prophylaxis times.

Psychotropic prescribing has risen in European children in the last decade. The most widely used drug subclasses have been the selective serotonin reuptake inhibitor antidepressants and the atypical antipsychotics. Some of the worrisome aspects of this increased use are the lack of well investigated psychotropic medicines, their side-effects (especially long-term effects), and the increase in children and adolescents receiving these medications.

Similarly, the irrational use of medications has posed significant challenges for most common childhood diseases (pneumonia, diarrhoea, and malaria) in resource poor settings. A WHO systematic global review of interventions to improve paediatric treatments suggested that the most effective interventions were multifaceted and took place at the system level, as opposed to the individual prescriber level.

As definitive data on dosing, efficacy and safety of medicines used in children are seldom demonstrated in paediatric trials, concerted efforts are needed to produce universally accpeted dosing recommendations in children, derived from an integrated analysis of pharmacokinetic and pharmacodynamic data, specific disease factors and developmental growth. This is particularly relevant to the frequent off-label use of paediatric medicines, which lacks the adequate information about possible indications, dosing regimens, dose adjustments, and how they should be administered. Some recent initiatives to improve information dissemination on medicines use in children included the new websites 'Paediatric Medicines in the Netherlands', "Medicines for children" in the United Kingdom, the British National Formulary for Children and the WHO Model Formulary for Children. Nonetheless, it should be explored whether the existing information with precise outcome elements within the electronic patient-based system can be utilised to improve the prescribing and utilisation of medicines in children in daily clinical practice.

In summary, the following key research priorities for children have been identified:

Collection of data on disease burden and medicines use in children across Europe

- Use of data on disease burden, prevalence and incidence, as well as medicine use in children collected at country level to allow for inter-country comparisons and comprehensive EU analysis of trends and variations over time

- Improvement of the methodological quality of data collection and provision of EU support for more multinational collaborative studies of medicines use in children

Further research into development of age-appropriate medicines

- Further research on (younger) children's ability to swallow solid oral formulations
- Study on children's preferences and adherence to different dosage forms
- Development of new routes of administration, such as oral-transmusosal (buccal strips), intra-nasal and trans-dermal routes (including needs in neonates)
- More research into safe use of excipients for children, and data sharing within the research community
- Need for additional pharmacological data on optimal dosing, efficacy and safety of medicines in children

Study effects of development of age-appropriate medications and paediatric regulations

- Study the impact of different paediatric formulations on patients' outcomes
- Stimulate research on alternative methodological approaches to classical clinical trials to facilitate and optimize clinical trials in children
- Monitor effects of the development of age-appropriate medications and their introduction on the national markets (increased public expenditure, poor quality products with reference to labelling and packaging)

Increase efficiency of the Paediatric Regulation with a focus on real paediatric needs

- Indicate clinical trials on certain priority medicines with significant therapeutic benefits in children (including neonates)
- Evaluate new EU Pharmacovigilance Regulation's potential added value in providing safety and efficacy data on off-label-medicines use in children

Improve (information on) rational use of paediatric medicines

- Collect existing individual (electronic) patient records to produce evidence on safety and efficacy of off-label medicines use in children
- Collect data to measure medicines use in children and assess the effectiveness of interventions to improve treatments
- Evaluate the impact of adherence-promoting interventions in children
- Evaluate how healthcare professionals obtain information to treat children in daily practice
- Evaluate the impact of new information sources on medicines use in children, on better use of medicines and on improved adherence to treatments.

1. Introduction

Paediatric patients have specific needs that may not be covered in other parts of the Priority Medicines for Europe and the World 2013 report, since children suffer from a different range of diseases than adults. They are a heterogeneous patient group with developmental, physiological, and psychological differences between age groups and from adults. The provision of optimal medicines for children is limited by various barriers that include insufficient research in children, delays in licensing medicines for children, inadequate development of appropriate formulations for children, and knowledge deficiencies that would enable optimal prescribing.

This background paper provides an update on the activities undertaken to provide optimal medicines for children since the previous version of the report published in 2004. It identifies knowledge gaps related to children and discusses potential areas for further research, identifying issues that need more attention and analysis in the future.

2. Demographics and diseases faced by children

In this section, we will concentrate on childhood mortality, as well as the diseases that are most prevalent in children. We will provide an overview of their trends over time, identify novel insights that have been gained since 2004, and discuss the strategies needed to decrease disease burden in childhood. This section complements Background Paper 5 of the report on general demography, and various parts of Chapter 6 that cover additional childhood conditions (neonatal morbidity, infectious diseases and pneumonia, childhood cancers, orphan diseases, etc.). Nevertheless, we do not intend to provide a full overview of research gaps in the management of specific childhood diseases.

Additionally, patterns of general medicines use are studied to provide data about the suboptimal use of medicines, uncover undesirable prescribing practices in childhood diseases, and inform decisions on the prioritisation of research.

2.1 Childhood mortality

Most children and adolescents in the European Union enjoy a high standard of health and well-being. The paediatric population (0-18 years) represents about 100 million people or 20% of the total population. The crude birth rates have increased modestly from 10.4 in 2004 to 10.7 births per 1 000 inhabitants in 2010, with 5.4 million children having been born in 2010.[1, 2]

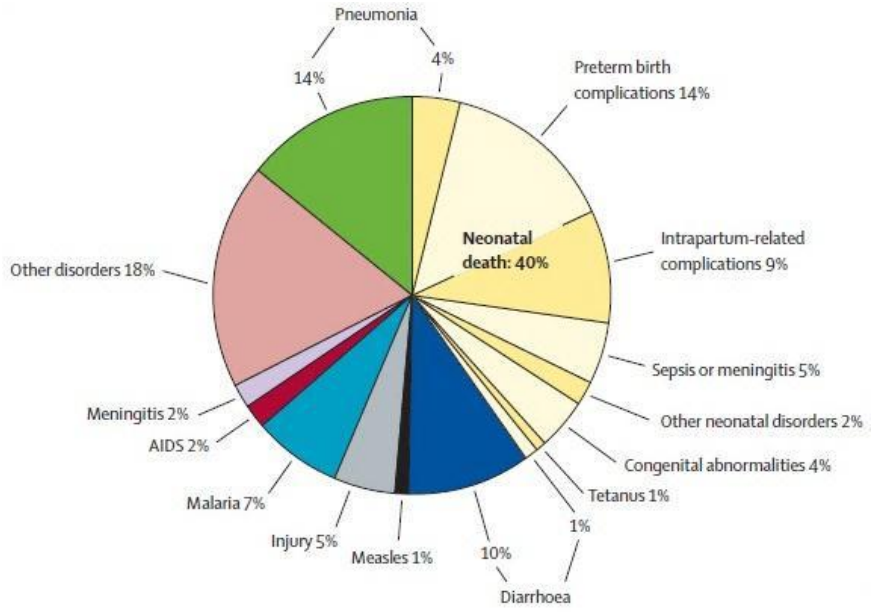
The child mortality rates are low in the European Union. The average EU mortality rates in the first year of life declined from 5.1 deaths in 2004 to 4.2 deaths in 2010. Annex 7.1.1 shows that the rates ranged from three deaths per 1 000 live births in most Nordic countries, Portugal, Slovenia, and the Czech Republic, up to 9.4 and 9.8 deaths per 1 000 live births in Bulgaria and Romania respectively, and 13.6 deaths in Turkey.[3] An infant`s risk of dying in Europe is greatest during the first four weeks of life. According to the statistics, two-thirds of

neonatal deaths in the first year of life occurred due to prematurity, congenital abnormalities and birth asphyxia.[3]
In the WHO European region, 160 000 children died before the age of five in 2010. As shown in Annex 7.1.2, half of them were neonatal deaths (49%), related to preterm birth or intra-partum complications, congenital anomalies, neonatal disorders, sepsis, or meningitis.[4] Other common causes for death in children under age five were pneumonia, injuries, diarrhoea, and undefined disorders.[4]

Worldwide, under-five mortality has steadily declined from 10.4 million in 2004 to 6.9 million in 2011.[5] The most significant causes of death in children under the age of five worldwide were pneumonia, preterm birth complications, diarrhoeal diseases, child birth complications, and, malaria. About 40% of children younger than five years of age died during the neonatal period due to preterm birth complications, birth sepsis, and asphyxia.[4] (Figure 7.1.1)

In older age groups, infectious diseases, HIV and tuberculosis, injuries, and some cancers predominated, although overall mortality was lower.[5,6] During adolescence, the leading causes of death were accidents, suicide, violence, pregnancy related complications, communicable diseases (tuberculosis, meningitis, and HIV/AIDS), and non-communicable diseases (diabetes and cancer).[7]

Figure 7.1.1: Global causes of childhood deaths in 2010



Source: Liu L, Johnson HL, Cousens S, et al, for the Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012; 379: 2151–61[4]

2.2 Childhood morbidity

Children suffer from a different range of diseases than adults. Firstly, some diseases such as prematurity, congenital abnormalities, respiratory distress, certain leukaemias, or genetic conditions like phenylketonuria only occur in children. The diagnosis, prevention and treatment of these conditions cannot be adequately investigated without studying children.

Secondly, other conditions, such as influenza, asthma, mental health problems, certain cancers, and forms of arthritis, occur in both adults and children, but their pathophysiology, severity, course, and response to treatment may differ across the life span. Thus, treatments that are safe and effective for adults may be dangerous or ineffective for children. Furthermore, certain diseases like asthma and psychiatric disorders may start in childhood and continue into adult life, so effective treatment at an early stage of the disease may be beneficial. Also, lifestyles started in childhood may lead to chronic diseases later (e.g. hypertension, obesity, diabetes mellitus, asthma, and mental diseases). Therefore, research in children is necessary to establish the causes and natural history of diseases and to enable the employment of primary prevention strategies to counter risk factors and behaviours in childhood and adolescence.[8]

2.2.1 Asthma in children

Asthma is the most common chronic childhood disease in Europe, affecting 5–20% of school-aged children in Europe.[9] Its prevalence varies widely across Europe, with a rate up to ten times higher being reported in Western Europe than in Eastern Europe, possibly due to different exposure to respiratory infections, pollution and diet.[10] On the other hand, under-five morbidity rates are not known because most surveys, including the International Study of Asthma and Allergies in Childhood (ISAAC; 1993-2003), have not studied this age group.[11] The underlying reasons are the difficulties in making a confident diagnosis of asthma and the variability of wheezy phenotypes in very young children.[12] The global ISAAC research has been discontinued, but new evidence coming from high-prevalence European countries showed that childhood asthma rates increased steadily for several decades and then levelled off, or even declined. In a study of six to nine year-old Irish children, the asthma prevalence remained stable at 21.7% in 2002 and 23.5% in 2007.[13] Moreover, a respiratory health survey of primary school children in England showed a significant decrease in the prevalence of asthma, wheezing, and allergies between 1998 (29.8%) and 2006 (19.4%), coinciding with improved environmental control measures in the area.[14]

Asthma affects lung growth in children, which is a determinant of lung function in adult life, so optimal treatment is of major concern for long-term prognosis.[15, 16] In recent years, several efforts have been made to provide a uniform definition of asthma severity, and to improve knowledge about its pathophysiology, prevention, diagnosis, treatment, and monitoring.[12,17] In 2007, a project funded by the EU's Sixth Framework Programme (GABRIEL) succeeded in identifying new genetic markers that raise the risk of asthma in infancy.[18] However, given the heterogeneity of asthma, the identification of its diverse childhood phenotypes, including those that develop into adult asthma, still remains. The identification of these diverse phenotypes will further contribute to a more personalised patient approach.[19]

2.2.2 Diabetes in children

According to the European diabetes registry, EURODIAB, the type 1 childhood diabetes incidence rate continues to rise across Europe by 3-4% per year. During the period of 2004-2008 incidence rates varied from 5.8 per 100 000 in the Republic of Macedonia to 36.6 per 100 000 in the Stockholm area of Sweden. The evidence pointed to an interplay between genes and environmental factors (e.g. lifestyle, diet, virus infections), which may differ between populations.[20] Between 2005 and 2020, EURODIAB research has estimated a doubling of new cases of diabetes in children under five years of age and an increase of the prevalence in the

under 15-year-olds by 70%. The most striking changes over time are expected in central and eastern European countries with currently lower incidence rates,[21] presumably due to improvements in their case detection and detrimental changes in their lifestyle habits. Type 1 diabetes is the most prominent form of diabetes seen in childhood, especially in children under 10-years-old. However the trend towards overweight and obesity is driving the development of type 2 diabetes in youths, particularly after the onset of adolescence.[22]

2.2.3 Mental diseases in children

Mental disorders are increasingly recognised as a significant causes of ill health and disability in children and adolescents globally, including Europe.[23] Research has shown that mental health is the largest contributor to the burden of disease in young people aged 10–24 years (45%), clearly ahead of unintentional injuries (12%) and infectious and parasitic diseases (10%).[7] In Europe, the prevalence of mental illness prior to 2004 was 8-23% in the child and adolescent population.[24] For the 2010 study on mental and neurological disorders in the EU, the European Brain Council broadened the age range and scope of diseases studied, including childhood and adolescence brain disorders. According to the age-specific data, an estimated 3 million children suffered from attention-deficit hyperactivity disorders and hyperkinetic disorders, 0.6 million from pervasive developmental disorders (e.g. autism, Asperger's syndrome), and 2.1 million from conduct disorders.[25] Similarly, bipolar disorder has been progressively more often diagnosed in children, despite the previous psychiatric consensus that manic-depressive illness rarely has its onset before adolescence.[26] The total disease burden of paediatric mental health diseases has not yet been fully elucidated because of the many complexities involved, in terms of defining diagnostic categories and health measurements in children. It is a well-established fact that many of the mental disorders seen in children can be precursors of much more disabling disorders in later life.[27] On the other hand, the increased prevalence rates led to debates on the medicalization of certain conditions, the diagnostic validity and the true size of mental disorders.[28, 29]

2.2.4 Infectious diseases in children

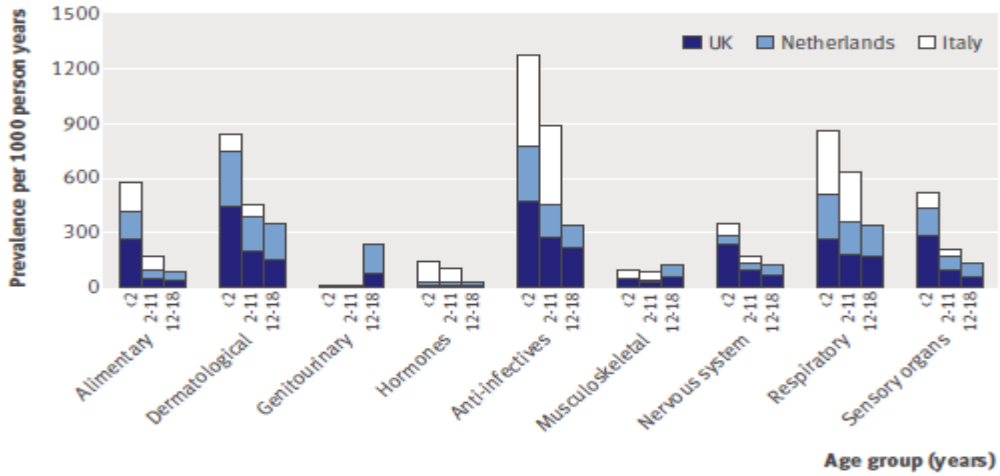
Despite improved living conditions and health care (e.g. use of antibiotics and vaccines), infectious diseases remain the most common cause of illness in children in the developing world and are a predominant cause of childhood mortality in these countries.[4] In the category of infectious diseases, the most serious are acute respiratory diseases (including pneumonia and influenza), HIV/AIDS, diarrhoea, tuberculosis, malaria, and measles.[4] Even though the prevalence and burden of infectious diseases is much lower in Europe[4], their public health effects extend beyond direct disability and death. Increased global mobility can lead to an increased risk of epidemics, while the irrational use of medicines can contribute to the emergence of antimicrobial and multidrug resistance, further complicating the management of subsequent infections. Thus, new and re-emerging infectious diseases present a global health concern, which necessitates investments in effective surveillance networks and targeted prevention and intervention strategies. For more information on infectious diseases and resistance, see the background paper on antimicrobial resistance (6.1).

2.3 General use of medicines in children

A literature review (1994-2008) on drug utilisation in paediatric outpatients found only a few countries involved in research (mostly from Europe and North America) and large differences between studies with regards to data source, sample size, and age range. The drug utilisation prevalence rate was higher in preschool children and lower in older children.[30] More than half of the children (51-70%) in outpatient care received at least one medication. Each child treated received, on average, between 1.3 and 5.3 prescriptions, and 60% of children received an average of three drug prescriptions in a one-year period. Antibiotics were the most frequently prescribed drugs (20–33% of all prescriptions), followed by anti-asthmatics (10–25%).[30]

Patterns of paediatric drug utilisation in Europe were specifically studied using three population based databases from Italy, the United Kingdom and the Netherlands for the period 2000-2005. The analysis revealed that prescription rates were highest for children less than two years of age, and they were higher in the United Kingdom and Italy when compared to the Netherlands in each of the age groups. Furthermore, certain gender patterns were observed with more prescriptions being written for girls than for boys after the age of ten, as opposed to the pattern seen in the younger age groups. The user prevalence rates for the year 2005 showed that anti-infective, dermatological, and respiratory drugs were in the high-use group for all age categories, whereas cardiovascular and anti-neoplastic drugs were in the low-use group, corresponding to the childhood morbidity rates.[31] (Figure 7.1.2)

Figure 7.1.2: Year prevalence of drug use (per 1000 person years) by age (<2, 2-11, 12-18), country, and anatomical class for most prevalently used drug classes (data for Italy excluded age category 12-18)



Source: Sturkenboom MC, Verhamme KM, Nicolosi A, et al; TEDDY European Network of Excellence. Drug use in children: cohort study in three European countries. BMJ 2008;337:a2245.[31]

This general drug use overview, based on multiple European paediatric populations, was conducted for the TEDDY (Task Force in Europe for Drug Development for the Young) project, co-funded by the European Commission within the Sixth Framework Programme (2005-2010).[32] Lamentably, no similar initiative in the paediatric field, including a wider range of countries and more recent data, has been supported with EU funding.

2.4 Conclusions

Addressing the gaps and identifying future priorities for paediatric medicines requires information on burden of diseases and use of medicines in children. Data routinely collected at national or local levels can prove to be a valuable source for inter-country comparisons and comprehensive EU analysis of trends and variations over time. Although individual countries and research communities may study particular aspects of childhood diseases and maintain prescription databases, the process of data gathering and analysis at the EU level is not very common. The lack of systematic and continuous monitoring in all EU countries and the heterogeneity between studies make comparative evaluations difficult or incomplete. Therefore, the methodological quality of data collection should be improved, and more multinational collaborative studies should be performed with EU support.

3. Product related issues in children

It is well established that children are not small adults, but rather distinct entities with regards to pharmacotherapy. First, they differ from adults with regards to their body development, their medicines related toxicity and their taste preferences.[33] As a result, an effective paediatric therapy requires medicines adjusted to the needs of children. Second, children are a heterogeneous patient group that may need age-appropriate medicines suitable for each paediatric subpopulation. These two important factors affecting drug delivery in children require novel formulations with dose flexibility and also medical devices for easier administration of paediatric medicines, as discussed in this section.

3.1 Paediatric age-appropriate dosing and formulations

Children are different from adults in many respects, including their body development, pharmacokinetics and pharmacodynamics. Infants have slower gastrointestinal, but faster intramuscular (IM) absorption, limited protein binding and immature enzymes.[34] Their livers are immature and may not metabolise drugs as rapidly as expected; their kidneys are also small and immature. Drug distribution is also different because a neonate´s body contains 80% water (adult proportion is 55–60%), and the water is distributed more into the extracellular than into the intracellular space when compared to adults. Furthermore, children have larger liver/body and brain/body weight ratios and higher blood–brain barrier permeability, and small infants often have a two to three times longer half-life for elimination of medicines than adults, requiring lower doses of medicines. Consequently, even when a medicine has a known effect in adults, a linear dose-per-kg correlation often does not hold true with regards to small children, as shown in Annex 7.1.3.[33,35]

Given the information above, it is clear that paediatric dosage regimens cannot simply be extrapolated from adult data, as an effective therapy requires medicines adapted to the needs of children. In addition, the knowledge on optimal dosing for efficacy and safety is very important for deciding on the appropriateness of a formulation. It is vital to consider the 'criticality' of the dose (i.e. steep dose/pharmacodynamics response curve, narrow therapeutic window) and the dosing regimen (i.e. dose calculation, dose titration, flexibility of dosing).[36]

The purpose of good paediatric formulations is to achieve safe and accurate dose administration, reduce the risks of medication errors and enhance medication compliance.[37] Selection of appropriate formulations should be based on a case-by-case basis, including the age, size, condition of the child (e.g. critical illness, concomitant medication, ability to swallow dose), usage environment, and the expected duration of the therapy.[38]
Further basic criteria for paediatric medicines include:

- sufficient bioavailability
- minimal dosage frequency
- safe excipients
- minimum impact on lifestyle
- good taste acceptance
- socio-cultural acceptability
- clear product information[39]

The development of suitable paediatric medicines is a complex task with a range of technical challenges, such as:

- diversity of children
- accuracy of dosing with lower paediatric doses and volumes
- inability to swallow solid dosage forms
- taste masking in oral forms
- stability and unsafe excipients
- needle phobia and small veins for parenteral forms, etc.[39]

Body size and weight increase up to twentyfold from birth to adulthood, and the magnitude of doses administered throughout childhood can vary a hundredfold. Plus, the ability to take medicines (i.e. cognitive and motor skills, dependence on caregivers) and dosage form preferences differ greatly across the age spectrum.[38] Accordingly, it may be necessary to develop age-appropriate medicines with strengths and dosage forms suitable for each paediatric subpopulation using the medicine.[38] Table 7.1.1 and the EMA Matrix (Annex 7.1.4) illustrate suitable dosing and dosage forms as a function of the child's age.

Table 7.1.1 Change in magnitude of dose and the ability to cope with dosage forms

BNFC[1] age-based dosing guidelines for Paracetamol	
Age	*Dose*
Baby	30 - 60 mg
1 year	60 - 120 mg
6 years	120 - 250 mg
12 years	250-500 mg
Adolescent	0.5-1 g

Change in ability to cope with dosage forms	
Age	*Dosage forms*
Baby	drops
1 year	liquid, 'melts'
6 years	liquid, tablets, 'melts'
12 years	tablets
Adolescent	tablets/capsules

[1] British National Formulary for Children 2006

Source: Nunn T. Presentation: Age-appropriate formulations – paediatric needs. EMA Workshop on Paediatric Formulations II 8 November 2011 http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/01/WC500121603.pdf. Accessed April 29, 2013.[40]

3.2 New oral paediatric formulations

In general, oral formulations are preferred for long-term use in children, whereas parenteral administration is likely to remain the first choice during the neonatal period and for emergency cases. Alternative routes of administration under investigation include transdermal (for constant blood levels), or the less invasive buccal, nasal and pulmonary drug delivery systems.[38]

Tablets have not been ideal dosage forms for all paediatric patients due to difficulties in swallowing and in the division of the tablet dose based on weight. Thus, liquid formulations used to be considered the most suitable for children less than six years of age[3838], despite their major disadvantages such as chemical, physical or microbial instability, taste issues, and lack of controlled release properties.[41] In 2008, a WHO expert forum proposed a paradigm shift towards solid, oral dosage forms for paediatric medicines, in view of stability problems with liquid formulations in different climate zones and the high costs of their transportation and storage.[42] Oral, solid flexible dosage forms, such as orodispersible tablets, and/or tablets used to prepare oral liquid preparation suitable for younger age groups became the recommended paediatric dosage forms for global use.[42] The following year, Coartem® Dispersible was the first dispersible artemisinin-combination therapy for children (5-35 kg) launched in Africa by Novartis and the Medicines for Malaria Venture.[43] A clinical study in Tanzania confirmed a high cure rate of 97.8% with the pleasant tasting suspension, comparable to that of the bitter Coartem® tablet (98.5%).[44]

For oral medicines requiring precise dose measurement, a new flexible platform technology was proposed to produce multiparticulate solids (mini-tablets and spherical granules –

pellets) and dosage forms dispersible into liquids or to be mixed with food.[42] Since then, various innovative oral, solid dosage forms for paediatric use, such as multiparticulate and flexible dispersible solids, have been commercially available or are under development. (Table 7.1.2 and Annex 7.1.5 for branded products).[43,45]

Table 7.1.2:Novel oral drug formulations for children

Multiparticulates	Flexible dispersible formulations	Other oral preparations
Granules	Dispersible tablets	Chewable tablets
Sprinkles	Oral lyophilistaes	Gummy bears
Pellets	Orally disintegrating tablets – lozenges	Chewing gum
Mini-tablets	Oral strips / Buccal wafers	
	Medicated lollipop (melt-away lozenge with applicator)	
	Orally disintegrating mini-tablets (experimental)	

Sources: Stoltenberg I, Winzerburg G, Breitkreutz J. Solid oral forms for children – formulations, excipients and acceptance issues. Journal of Applied Therapeutic Research, 2010; 7(4): 141-146.[43]

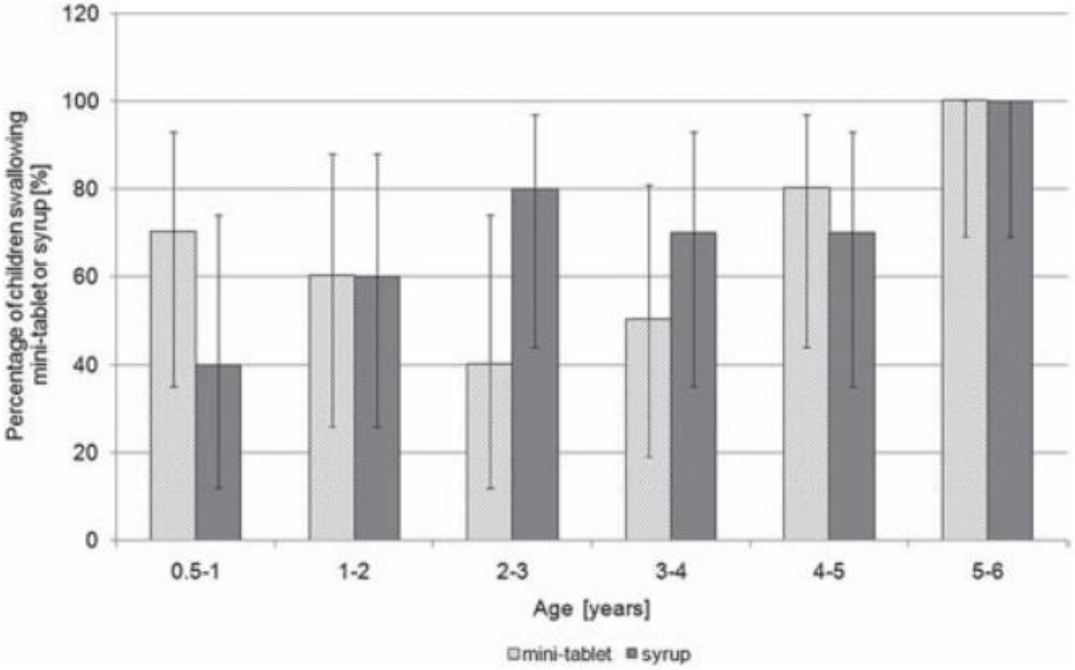
Breitkreutz J. Nach der EU-Reform. Arzneiformen für Kinder. Pharm. Unserer Zeit 2009;38: 30-37[4545]

The advantages of these novel, solid dosage forms over the conventional ones are not only in their dose flexibility for different patient ages and weights, but also in their ease of administration in younger children.[46] For a while, there have been concerns and uncertainties about the age at which young children can safely swallow orally administered tablets and capsules. It is generally accepted that the age at which children can swallow intact tablets or capsules is highly dependent on the individuals and the training and the support they receive from healthcare professionals and caregivers.[36] The matrix combining different age groups, routes of administration and dosage forms, developed by EMA (Annex 7.1.4), reflects on the variability in children's ability to swallow solid dosage forms. EMA considers tablets as potentially acceptable from the age of three.[36] Studies have reported tablet use in three year-old children for the treatment of long-term illnesses.[47]

However, in 2009 the acceptability of and the ability to swallow these innovative mini-tablets (3 mm in diameter) was explored in children aged two to five years. Forty-six per cent of the children aged two years, and up to 86% of the five-year-old children swallowed the mini-tablets; no children choked or aspirated the mini-tablets. To improve the acceptability of mini-tablets by parents, suitable dosing devices that automatically count a variable number of mini-tablets or electronic dispensers were suggested.[48]

A recent exploratory study illustrated a high acceptance and ability of children aged 0.5–6 years to swallow uncoated drug-free mini-tablets (2 mm in diameter) compared with a sweet testing syrup.[49] (Figure 7.1.3) The study is currently being repeated with a larger cohort to confirm safety and to explore whether the observed chewing before swallowing has an impact on the usability of uncoated mini-tablets. Its results may convince the EMA to consider uncoated 2 mm mini-tablets for children aged six months in its new guidelines.[49]

Figure 7.1.3: Children's ability to completely swallow mini-tablets and glucose syrup (n=10 children per age group; mean ± 95% CI).



Source: Spomer N, Klingmann , Stoltenberg I, et al. Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study. Arch Dis Child 2012;97:283–286.[49]

There are more promising results coming for infants younger than two years with the development of orally disintegrating mini-tablets (ODMTs) — a novel, solid oral dosage form that combines mini-tablets and fast-dissolving dosage forms. A 1 mg ODMT was produced as a novel paediatric medicine using the diuretic hydrochlorothiazide. The aim was to offer a suitable therapeutic option for very young children, as only tablets and capsules of 12.5 mg are available on the market. The ODMT was manufactured with safe excipients and it has passed all required laboratory tests. Further investigations, with regard to taste masking, dissolution, advanced suitable dosing systems, and acceptability still have to be performed.[50]

The innovations regarding paediatric formulations remain to be implemented by the industry during the process of the development of medicines for paediatric use. The new technologies must be applied outside the academic setting, in particular where dosing flexibility, taste masking and administration flexibility is needed.

3.3 Novel paediatric drug devices

Some of the obstacles and limitations in ensuring the delivery of a correct dose born by currently available paediatric formulations can be overcome by new technologies. Over 100 patents have been filed for novel paediatric dosing devices in order to ensure the accurate and consistent administration of paediatric formulations.[39] The majority of these patents relate to the delivery of liquids to very small children orally, such as modified feeding bottles, modified pacifiers and teats with the required dose of medicine placed in a reservoir.[39] Also, the dose sipping technology, consisting of a straw with film-coated micro-

pellets ingested in a liquid of choice, has been developed to improve the problem related to the palatability of oral solution. The manufacturer's internal studies showed an improved adherence in children, but compatibility studies with the drink are still required.[3939]

Table 7.1.3:Novel drug devices for children

Novel dosing instruments for oral liquids
Teat/Pacifier with reservoir
Single-use spoon filled with medicine
Dropper tube
Dose sipping technology - straw with taste
Solid dosage pen
Coated particles for oral administration
Coated particles on dosage spoon
Coated particles in suspension
Coated particles in tablets for preparing a suspension
Coated particles on dosage spoon
Needle-free injection devices
Jet injectors (drive small droplets through the skin by high pressure)
Microstructured transdermal systems for intradermal vaccines
Novel devices for inhalation therapy
Nebuliser with spacer/valved holding chamber and face mask
Nebulisers with a vibrating mesh technology for aerosol generation
Nebuliser with an electronic unit
Dry powder inhalers

Sources: Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. Exp Opin Drug Deliv 2007; 4:37–45[39]

Walsh J,Bickmann D, Breitkreutz J, Chariot-Goulet M, on behalf of the European Paediatric Formulation Initiative (EuPFI). Delivery devices for the administration of paediatric formulations: Overview of current practice, challenges and recent developments. International Journal of Pharmaceutics 2011;415:221– 231[51]

Table 7.1.3 and Annex 7.1.6— listing branded products, provide an overview of currently available paediatric administration devices for the parenteral, oral, and inhaled administration of paediatric formulations. However, although many paediatric drug delivery devices have been developed, some of which may offer tangible patient benefits, there appears to be very few available on the current market. This is likely due to their high costs, as many novel technologies are protected by patents, and to the (un)willingness of health insurance bodies to reimburse for the use of these devices.[51]

3.4 Taste and palatability of paediatric dosage forms

Paediatric dosage forms must also be designed to ensure patient compliance, either by having a minimal impact on lifestyle or by having an appropriate appearance (colour and palatability) especially for oral liquids and powders.[52] It is often difficult to assess the taste attributes of the drug formulation, particularly in younger children who are not capable of

expressing their taste sensations and mouth feelings adequately. In addition, taste masking of certain solid paediatric dosage forms, such as chewable tablets or fast dissolving preparations (e.g. orodispersible tablets and films), can be particularly challenging, especially for high solubility drugs that dissolve rapidly in the mouth.[52]

Some paediatric formulations take into account the individual taste preferences of the child. Examples include Children's Tylenol® with 'Flavor Creator', where sachets of different flavouring agents can be added to the liquid prior to administration. A similar concept is that of the FLAVORx™ system, which consists of various flavours that can be added to oral medications to improve palatability, and that has been used in Thai AIDS patients to increase adherence with antiretroviral medicines.[53] The limitation of this approach is that the compatibility of the flavours with the medication is often unknown, potentially impacting formulation stability.[53] Another example is the previously mentioned dose sipping technology using a drinking straw with taste-masked granules.[52]

Alternative approaches to facilitating taste masking of paediatric solid preparations include the coating of a drug substance prior to incorporation into formulations or the film-coating of small dosage forms such as pellets or mini-tablets. It is essential that all taste masking approaches are guided by the specific safety considerations of paediatric drug development.[52]

3.5 Use of excipients in paediatric dosage forms

One critical element in the development of paediatric formulations is the selection and use of excipients, as their safety in paediatric subpopulations is often unknown. As a result of age differences, there are elevated toxicological risks in young children for some excipients, such as ethanol, propylene glycol, benzyl alcohol, polysorbate, parabens, etc. (Table 7.1.4) in their metabolism and elimination as compared to adults.[39] In 2011, the FDA issued a drug safety communication and changed the drug label of Kaletra® (lopinavir/ritonavir) because of some serious health problems that arose in premature newborns related to the propylene glycol contained in the oral solution.[54] In 2012, the EMA issued a concept paper to get input from the public on revisions to its excipient guidelines on labelling and packaging in order to include safety concerns for paediatric populations and pregnant women, since the current 2003 guidelines do not address these safety issues.[55]

Table 7.1.4: Excipients with elevated toxicological risks for the paediatric population (preterm and term neonates, infants less than 6 months of age

Excipient	Administration	Adverse reaction
Benzyl alcohol	Oral, parenteral	Neurotoxicity, metabolic acidosis
Ethanol	Oral, parenteral	Neurotoxicity
Polyethylene glycol	Parenteral	Metabolic acidosis
Polysorbate 20 and 80	Parenteral	Lives and kidney failure
Propylene glycol	Oral, parenteral	Seizures, neurotoxicity, hyperosmolarity

Source: Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. Exp Opin Drug Deliv 2007; 4:37–45[39]

Even though the demand for paediatric data on the safety of excipients has grown considerably, there is very limited paediatric excipient safety data, and it is distributed throughout many sources.[56] As a result, the EU and the United States Paediatric Formulation Initiatives are creating a Database of Safety and Toxicity of Excipients for Paediatrics (STEP) to incorporate this safety data into a single comprehensive and readily accessible database. This repository of excipient information (e.g. dose information, pharmacokinetics (PK)) is expected to provide a basis for screening and selecting excipients for use in paediatric product development and further accelerate product-specific safety and toxicity studies. The first prototype version database was launched in 2012.[56]

To support the task of safe use of medicines in children, there is an urgent need for concerted action toward obtaining the missing data on safety of excipients for paediatric use. While the companies are responsible for providing data on safety of excipients in paediatric medicines, EU programmes are also needed to fund related research activities and fill this information gap.

3.6 Clinical evidence on impact of paediatric pharmaceutical development

Despite all the research on novel paediatric products, the literature suggests limited clinical evidence to support pharmaceutical development programmes in children. A recent systematic review identified 94 articles on oral medicines for use in children and adolescents that reported the effects of three pharmaceutical technologic aspects (formulation and dosage form; route and frequency of administration; and packaging, administration device, and user instruction) on six patient-related outcomes (clinical efficacy, side effects and tolerability, patient preference, patient acceptance, administration errors, and adherence). The majority of the studies (90%) were conducted on children aged 2 to 12 years, which can be explained by a lack of clinical trials in neonates and infants, as a result of the limited market potential of products for this population. Only two publications were of good methodologic quality, suggesting that paediatric pharmaceutical development studies may need more suitable instruments to measure their methodological quality, as randomized controlled and double blind trials might not be always appropriate. Table 7.1.5 demonstrates that side effects, tolerability and administration errors received limited attention, resulting in no evidence being available to substantiate that improved formulations lead to fewer side effects.[57]

Based on the study findings, the authors encouraged an agreement on taxonomy of pharmaceutical technological aspects and patient-related outcomes, and the creation of a global database with literature on the development of paediatric pharmaceuticals to promote research in these neglected areas.[57]

Table 7.1.5: Impact of pharmaceutical technologic aspects on patient-related outcomes parameters.

Patient-Related Outcomes Parameter	Pharmaceutical Technologic aspect			All Assessments (n=176) *
	Formulation and Dosage Form (n=85)	Route and Frequency of Administration (n=77)	Packaging, Adminstration Device, and User Instruction (n=14)	
Patient acceptance	38 (45) **	5 (6)	1 (7)	44 (25)
Patient preference	19 (22)	4 (5)	0	23 (13)
Adherence	11 (13)	15 (19)	6 (43)	32 (18)
Clinical efficacy	8 (9)	31 (40)	2 (14)	41 (23)
Side effects and tolerability	8 (9)	22 (29)	0	30 (17)
Administration errors	1 (1)	0	5 (36)	6 (3)

* Two investigations assessed >1 pharmaceutical technologic aspect.
** Data are number (%) of assessments

Source: van Riet-Nales DA, Schobben AF, Egberts TC, Rademaker CM. Effects of the pharmaceutical technologic aspects of oral pediatric drugs on patient-related outcomes. Clin Ther 2010;32(5):924-38[57]

3.7 WHO activities towards better medicines for children

To address the lack of child-specific medicines, the Member States of the World Health Organization (WHO) passed a resolution on 'Better Medicines for Children' WHA 60.20 during the 2007 World Health Assembly. The resolution mandates the WHO to explore ways to promote more research and development into paediatric medicines and to improve knowledge on the quality, effectiveness and safety of these medicines.

Following this breakthrough event, the WHO commenced work on a number of activities to improve the availability of better medicines for children. In December 2007 the WHO launched its initiative 'Make medicines child size'[58] in order to raise awareness and to accelerate action in order to meet the need for improved availability and access to child-specific medicines. The same year, the WHO Subcommittee on Selection and Use of Essential Medicines developed the first Model List of Essential Medicines for Children,[59] and has been revising and updating it every two years to include missing essential medicines for children, using evidence-based clinical guidelines. The list was developed to serve as a reference for countries in developing national lists according to their specific public health priorities and to ensure that child-specific medicines are developed and delivered to the intended patient groups. As a follow up, the WHO Model Formulary for Children was created in 2010 to provide independent prescriber information on dosage and treatment guidance for medicines based on the WHO Model List of Essential Medicines for Children. The publication 'Sources and Prices of Selected Medicines for Children'[60], produced annually by UNICEF and the WHO, identifies the sources and prices for selected products used in the treatment of childhood diseases and contributes to the effort to increase access to appropriate medicines.

As part of the 'Better Medicines for Children Project', funded by the Bill and Melinda Gates Foundation, the WHO has also helped in the foundation of an international regulatory working group (Paediatric Medicines Regulatory Network)[61], responsible for reviewing

existing regulatory standards and enhancing the availability of quality medicines for children by facilitating communication, collaboration, and regulatory coordination across the areas of manufacturing, licensing, and research. The Paediatric Medicines Regulators Network recently contributed to the development of the Guidance on Assessing Clinical Trials in Children, as well as the important documents 'Development of paediatric medicines: points to consider in formulation'[46] and a review on extemporaneous or compounded formulations.

Simultaneously, the WHO International Clinical Trials Registry Platform (ICTRP) launched the Clinical Trials in Children website,[62] with the aim of improving research transparency and making it easier to access accurate, up-to-date and understandable information relevant to the conducting of clinical trials in children.

In 2012, the list of 'Priority life-saving medicines for mothers and children' was updated,[63] highlighting the most important medicines for mothers and children that should be readily available throughout health systems. The list was compiled according to the global burden of disease and is based on evidence of efficacy and safety. Medicines were selected from the Model List of Essential Medicines and are included in current WHO treatment guidelines. Medicines for pneumonia, diarrhoea, malaria, neonatal sepsis, HIV/AIDS, and vitamin A deficiency are included on the priority list for children under five. Treatments for palliative care and pain for all children are included as well.

Additionally, the WHO Prequalification of Medicines Programme has been prequalifying new products specially designed to treat HIV/AIDS in children,[64] which is considered to be one of the priority paediatric treatment areas (Annex 7.1.7). The product prequalification represents a considerable advance in making user-friendly formulations that improve efficacy of treatment available.

Overall, the WHO has made progress on several fronts: essential tools, such as treatment guidelines and information on the use of essential medicines have been developed and published; relevant professional groups have been engaged; and key studies have been initiated. Further research and development for appropriate formulations, such as fixed-dose combination products, is expected to be directed towards paediatric tuberculosis treatment and treatment of HIV in young infants.

3.8 Conclusions

Much progress has been made in the development of age-appropriate paediatric formulations, especially those for oral administration. The current formulation research has been directed towards mini-tablets, chewable and dispersible tablets for younger children. Nevertheless, the ongoing research into the ability of children to swallow medication needs to be accompanied by studies on children's preferences and adherence to different dosage forms. In addition, new routes of administration such as oral-transmusosal (buccal strips), intra-nasal, and trans-dermal routes (for neonates mainly) are ripe for future developments and research. In neonates, particular caution is needed for these forms in terms of optimal use and dosing.

More research into alternative safe excipients for children is also expected, given the safety and toxicity concerns of some excipients in paediatric formulations. Yet, it is also essential to incorporate the available knowledge on excipients, generated through individual research, into a single and public repository. It would be helpful in avoiding a duplication of efforts, and encourage further discovery and innovation.

Despite all the technologic progress, the published clinical evidence on the impact of different paediatric formulations on patients' outcomes is still limited. This research should be central in order to support pharmaceutical development of paediatric medicines.

4. Regulatory aspects related to children

For years, the lack of information about the safety, efficacy and dosing data of paediatric medicines, as well as the lack of child-appropriate formulations resulted in the unsatisfactory treatment of paediatric patients. Healthcare professionals were left with no alternative but to use off-label and unauthorised products with their associated risks of inefficacy or adverse reactions (see Section 5 of this background paper). The lack of suitable, authorised medicinal products to treat conditions in children can be best explained by the fact that frequently pharmaceutical companies did not carry out the necessary research and development to adapt medicines to the needs of children. The underlying reason being that medicine development for paediatric patients is accompanied by numerous challenges for pharmaceutical companies, such as the diversity of children in different age groups, the consent and recruitment process or the ethical implications. Over the past decades, regulatory legislations for drug development in paediatric patients were passed worldwide to support the development and administration of appropriate paediatric medicines (see also Background Paper 8.2 'Regulatory incentives for innovation'). Progress is being made by combining requirements for paediatric drug development with market incentives for the pharmaceutical industry to (at least partly) cover the additional investment needed for testing drugs in children.

4.1 Implementation of the EU paediatric legal framework

Following the successful example of the United States paediatric initiative, the European Union adopted the Paediatric Regulation[65] in 2007, with its main provisions coming into effect in 2008 and 2009. The regulation aims to improve the health of children in Europe by increasing research, development and the authorisation of medicines for paediatric use.[66] Its policy objectives are as follows:

- to facilitate the development and accessibility of medicines for use in children
- to ensure that medicinal products used to treat children are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population
- to improve the information available on the use of medicines in the various paediatric populations.[66]

One key measure of the regulation is the creation of the Paediatric Committee (PDCO), a committee of scientific experts within EMA, whose principal task is to assess paediatric investigation plans (PIP) submitted by the pharmaceutical industry. A PIP is a development

plan which contains full details of the timing and the measures proposed to demonstrate the quality, safety and efficacy of the medicines in specified paediatric subsets. An approved PIP must always be demonstrated at the time of the marketing authorisation (MA) application for new products. This is also true for authorised products where new indications, new pharmaceutical forms and new routes are sought. A system of waivers and deferrals has been introduced to ensure that the requirements do not delay the authorisation of medicines in adults.[66] A waiver of the paediatric development can be granted for all (a full waiver) or subsets (a partial waiver) of the paediatric population on the basis of the lack of efficacy or safety of the medicine, when the disease or condition only occur in adults, or when the medicine does not have significant therapeutic benefit over existing therapies. A deferral allows postponing the initiation and/or the completion of the PIP measures to ensure that research is conducted only when it is safe and ethical and does not delay or block the marketing authorisation for adults.

The PIP requirements do not apply to generics. For medicines not yet authorised or still covered by intellectual property rights (IPRs), the regulation established rewards and incentives, such as a six month extension of the supplementary protection certificate (SPC), including adult use. In the case of orphan medicinal products, the incentive is the extension of market exclusivity (12 years instead of 10, see also Background Paper 6.19).[66] However, the additional market exclusivity granted for paediatric medicines may delay generic entry and have price implications.

In the case of authorised products no longer covered by IPRs, whose manufacturer voluntarily apply for a MA in children, the regulation establishes a new type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA), which provides data protection for a ten-year period. PUMA is granted to off-patent medicines adjusted exclusively for use in children to stimulate innovation in treating childhood diseases. It is, however, weaker than patent protection and does not guarantee market exclusivity, as competitors could carry out their own research and development on the same active substance, if they judge the market to be large enough.[66]

To generate studies on off-patent medicines the regulation provides an opportunity to access 'ad hoc' European funds for research and development through the EU Seventh Research Framework Programme (FP7).[66] Other PDCO specific functions include establishing an inventory of specific needs for paediatric medicinal products and the giving of free scientific input into the development of any documents related to achieving the regulation's objectives. [66]

In accordance with the Paediatric Regulation, the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) was set up in 2009 as a network of 38 national research networks, investigators and centres with expertise in performing clinical studies in children.[67] The objectives of the European network include coordinating studies relating to paediatric medicinal products, building up the necessary scientific and administrative competences at a European level, and avoiding unnecessary duplication of studies and testing in the paediatric population. There is no specific funding provided through the regulation for this European network. The network also works at an international level with the World Health Organization through the EMA's membership in the Paediatric Medicines Regulators' Network (PmNR) and with the U.S. FDA through the EMA's existing interaction on paediatric medicines. The Enpr-EMA still does not cover all

paediatric therapeutic areas and needs to foster further research in paediatric cardiology, gastroenterology, diabetes, and neonatology.[67]

There is also public access to information about trials using a paediatric population, including those that have been temporarily halted or prematurely terminated, via the EU Clinical Trials Register[68], launched in 2011, which is also a WHO Registry Network data provider.

4.2 Achievements of the EU Paediatric Regulation

The intended long-term impact of the Paediatric Regulation is the integration of paediatric development in the overall area of medicine development. Therefore, the regulation demands that each new compound is systematically evaluated during the research and development (R&D) process for its potential use in children. Its key measures (PDCO, PIP) set norms and standards for the suitable design of paediatric clinical trials in order to ensure the development of safe, efficacious, and age-appropriate paediatric medicines.[69] As a result, some companies have consulted with investigators during the development process, creating beneficial links between the industry and the research community. However, the paediatric requirements may also put an increased administrative burden on the industry. Moreover, many may see the compliance with PIP requirements as a fulfilment of regulatory obligations rather than as an establishment of a complete and independent R&D programme.[70]

Based on EudraCT data, the number of clinical trials with children in the European Union was stable over time during the period 2007-2011 with an average of 350 trials per year being conducted, with the number of trials in all populations declining by about 6% per year. (Table 7.1.6) One of the innovations introduced in paediatric research was the inclusion of younger children in clinical trials for cholesterol-lowering and anti-hypertensive medicines, juvenile idiopathic arthritis, diabetes mellitus, and haemophilia A and B.[69] To facilitate clinical trials in children or reduce the need for investigation in this vulnerable and limited population, it is important to encourage alternative methodological approaches to classical clinical trials, such as modelling and simulation techniques.
The Paediatric Regulation may contribute towards greater transparency in clinical trials by preventing unnecessary trials, since the protocol-related information for registered trials is made publicly available through EudraCT. [69]

Since 2008, approximately 70% of all PIPs evaluated by the PDCO proposed or required development of indications for the whole or some subsets of the paediatric population. This indicates an increase in the development of medicines for children, as only approximately 30% of medicines applied for and obtained a paediatric indication before the EU Paediatric Regulation came into force.[69] Nevertheless, therapeutic areas addressed by PIPs and agreed by PDCO primarily cover those diseases that affect adults and children similarly (e.g. endocrinology, gynaecology and fertility, metabolism, infectious diseases, oncology, cardiovascular diseases). Lamentably, the impact of the regulation on high priority and unmet therapeutic paediatric needs, including rare diseases or diseases that occur only in children (e.g. paediatric oncology, pain, neonatal morbidity), is not encouraging.[69] Only about 25% of all agreed PIPs were submitted exclusively for the therapeutic area of neonatology despite their having the highest need for medicine development. This indicates that paediatric development is significantly dependent on the adult development of

medicines, and thereby market oriented, and it does not correspond to unmet paediatric needs.

Table 7.1.6:Paediatric clinical trials by year of authorisation (or, if not available, by year of protocol uploaded into EudraCT)

	2005	2006	2007	2008	2009	2010	2011	2012
Paediatric trials (number)	253	315	351	341	401	379	360	
Paediatric trial that are part of an agreed PIP* (number)	1	0	1	4	12	22	70	21**
Proportion of paediatric trials that are part of an agreed PIP among paediatric trials*	0%	0%	0%	1%	3%	6%	19%	
Total number of trials (adults and/or children	3 327	3 951	4 730	4 506	4 411	4 019	3 622	
Proportion of paediatric trials among all trials	7.6%	8.0%	7.4%	7.6%	9.1%	9.4%	9.9%	

* This partial information requires sponsors using a Clinical Trial Application form that was available from November 2009 only, for use with version 8 of EudraCT available from 2011.
** Number of paediatric trials uploaded into EudraCT by 3 April 2012 for authorisation in 2012.

EudraCT Data Warehouse using pre-defined query on 3 April 2012 and counting the first authorised trial only, in case of more than one Member State. As National Competent Authorities of Member States upload data into EudraCT irrespective of the study population, the year of authorisation is a better indicator of the initiation than the year of upload.

Source: European Medicines Agency. Draft 5-year Report to the European Commission: General report on the experience acquired as a result of the application of the Paediatric Regulation. 8 July 2012 EMA/428172/2012.[69]

Between 2008 and 2012, 29 PIPs were completed in compliance with the PDCO decisions, which led to 24 new paediatric indications and seven new pharmaceutical forms appropriate for children. Centralized authorisations for paediatric use were obtained for 34 new medicines (Table 7.1.7), and 38 new paediatric indications, as variations of 33 already authorized medicines (Annex 7.1.8). In addition, 14 centrally authorized products had either a new pharmaceutical form, a new route of administration, or a new strength authorized for paediatric use.[69]

Rewards were obtained for 12 medicines; supplementary protection certificate (SPC) extensions for 11 medicines (Annex 7.1.9), and one PUMA exclusivity was provided for the midazolam paediatric oromucosal form.[69] As far as incentives are concerned, the value of a six-month extension of the SPC can vary widely. It can be economically significant, and even excessive, especially in the case of blockbusters, leading to unnecessary additional costs for consumers. Here, the introduction of a cap system for 'super profits' may be necessary to control the cost implications for the healthcare systems.[70] Many health workers may even prefer to use off-label medicines with the same active ingredient at a lower cost for children. The cost implication of the access to improved medicines is put in context of the drug development expenditures and the costs related to off label use and lack of available medicines.

Table 7.1.8: Medicinal products with initial marketing authorisation including a paediatric indication

Year of European Commission Decision	No. in year	Requirement to fulfil Paediatric Regulation at first authorisation	Indication is paediatric-only or "mixed" (adult and paediatric)	Active substance(s)	Trade Name (®)
2007	1	No	Mixed	Retapamulin	Altargo
2007	2	No	Mixed	Nelarabine	Atriance
2007	3	No	Mixed	Human papillomavirus vaccine [types 16 and 18]	Cervarix
2007	4	No	Mixed	Hydroxocobalamin	Cyanokit
2007	5	No	Mixed	Idursulfase	Elaprase
2007	6	No	Mixed	Gadoversetamide	Optimark
2007	7	No	Mixed	Betaine anhydrous	Cystadane
2007	8	No	Paediatric-only	Stiripentol	Diacomit
2007	9	No	Paediatric-only	Mecarsermin	Increlex
2007	10	No	Mixed	Rufinamide	Inovelon
2007	11	No	Mixed	Hydroxycarbamide	Siklos
2007	12	No	Mixed	Human normal immunoglobulin (ivig)	Flebogamma DIF
2008	1	No	Mixed	Fluticason fuorate	Avamys
2008	2	No	Mixed	Human normal immunoglobulin	Privigen
2008	3	No	Mixed	Lacosamide	Vimpat
2008	4	No	Mixed	Micafungin	Mycamine
2008	5	No	Mixed	Sapropterin	Kuvan
2008	6	No	Mixed	Sugammadex	Bridion
2009	1	No	Paediatric-only	Tocofersonal d-alpha tocopheryl polyethylene glycol succinate	Vedrop
2009	2	No	Mixed	Mifamurtide	Mepact
2009	3	No	Mixed	Rilonacept	Arcalyst
2009	4	No	Mixed	Tacrolimus	Modigraf
2009	5	Yes	Paediatric-only	Pneumococcal polysaccharide conjugate vaccine (absorbed)	Synfiorix
2009	6	Yes	Mixed	Canakinumab	Ilaris (PIP not yet completed)
2009	7	Yes	Paediatric-only	Pneumococcal polysaccharide conjugate vaccine (13-valent, absorbed)	Prevenar 13 (PIP not yet completed)

2010	1	Yes	Mixed	Meningococcal group a, c, w135 and 7 conjugate vaccine	Menveo (PIP completed)
2010	2	Yes	Mixed	Velaglucerase alfa	Vpriv (PIP not yet completed)
2011	1	Yes*	Paediatric-only	Influenza vaccine (live attenuated nasal)	Fluenz (Waiver)
2011	2	Yes	Mixed	C1 inhibitor, human	Cinryze (PIP not yet completed)
2011	3	Yes	Mixed	Dihydroartemisinin/ piperaquine phosphate	Eurartesim (PIP not yet completed)
2011	4	Yes (PUMA)	Paediatric-only	Midazolam	Buccolam (PIP completed)
2011	5	Yes**	Mixed	Everolimus	Votubia (PIP not yet completed)
2011	6	Yes**	Mixed	Tobramycin	TOBI Podhaler (PIP not yet completed)
2011	7	Yes	Mixed	Nomegestrol/ estradiol	IOA, Zoely (PIP completed)

* The PDCO opinion had granted a waiver for the full paediatric population.
** This was a new marketing authorisation for an orphan designated condition of a medicinal product that was already authorised in the EU for non-orphan designated condition(s).
PUMA = Paediatric use marketing authorisation.

Source: European Medicines Agency. Draft five-year Report to the European Commission: General report on the experience acquired as a result of the application of the Paediatric Regulation. 8 July 2012 EMA/428172/2012.[69]

The fact that to date only one PUMA has been granted demonstrates that in practice the incentive of 10 years of data exclusivity has not been an attractive option to the industry. This concept does not seem financially viable to companies, as the target population for a PUMA is too small. Plus, national reimbursement rules may not offer rewards great enough to make up for the costs of off-patent medicines. It is also questionable as to whether generic companies that hold authorisations for off-patent products have the necessary resources to invest in additional research. In addition, it has to be evaluated as to whether PUMA granted products have therapeutic benefit over existing treatments. As an illustration, the French National Authority for Health rated the midazolam paediatric oromucosal solution (Buccolam®) as representing only a minor therapeutic advance for paediatric seizure treatment.[71]

In order to identify gaps in paediatric treatments, a survey of all paediatric uses was undertaken in the EU in 2010. The objective was to produce an inventory of specific therapeutic needs for off-patent paediatric medicines.[72] The list includes 16 active substances/classes for the following paediatric therapeutic areas: pulmonology/respiratory diseases, psychiatry, dermatology, and endocrinology.[69] (Annex 7.1.9)

The Paediatric Regulation contains a provision for community funding for research into off-patent paediatric medicines. The funding is provided through the EU Framework Programmes for Research and Technological Development to cover the development of off-patent medicinal products by submitting PUMAs to PDCO. To ensure that funds are directed into research on medicines with the highest need in children in Europe, the PDCO adopted the priority list of off-patent products for which studies were required in January 2012.[73] The list includes specific recommendations on areas where data and studies were lacking, covering potentially all therapeutic areas and age groups (Cardiology, psychiatry, endocrinology, gastroenterology, haematology, immunology, infections, intensive care, metabolism, neonatology, nephrology, neurology, oncology, pain, pneumology and rheumatology). The list now serves as the basis for the EU Seventh Framework Programme (FP7) community funding for research into off-patent medicines. Annex 7.1.10 displays a list of 15 funded projects and two investigator-driven clinical trials for off-patent medicines (total value of €75 million).[69] As illustrated, a number of PIPs have been submitted by academia and SMEs and agreed with the PDCO with the view to apply for a PUMA. In addition, Annex 7.1.11 presents the remainder of the projects on the use of paediatric medicines, which were funded by the Sixth and Seventh Framework Programme (FP6, FP7).[74] Also, five EU countries introduced specific national paediatric research incentives to support paediatric medicines development (Belgium, Finland, France, Malta, Spain, United Kingdom).[69]

Complementary, to address the unmet needs of paediatric medicines, EMA has published a range of lists[75] covering specific substances within several therapeutic areas (anaesthesiology, anti-infectious therapy, cardiovascular diseases, chemotherapy, diabetes, epilepsy, gastroenterology, immunology, migraine, nephrology, obstructive lung disease, pain, psychiatry, rheumatology). The lists cover substances where off label use in children is significant and where data on pharmacokinetics, dosing, efficacy and safety in children is highly needed. The inventory is currently under revision, taking into account the EMA survey of all paediatric uses of medicines in Europe.[72]

Five years after the implementation of the Paediatric Regulation, paediatric therapeutic areas addressed by the industry seem more aligned with adult drug development than to the indicated unmet public health needs of children (paediatric oncology, pain, neonatal morbidity). Taking into consideration the lack of financial interest from the industry for the PUMA incentive, collecting and analysing existing knowledge on off-label use of medicines in children and disseminating the information among health practitioners could prove more sustainable (see Section 5 of this background paper).

The introduction of a new paediatric product (resulting from this EU regulation) on the market has to be accompanied by adequate regulatory, political and financial decisions at the national levels. Some undesirable issues that may have arisen from a deficient handling of a paediatric marketing authorisation are illustrated by the case of Cozaar® oral suspension. It is a paediatric form of the antihypertensive drug losartan that was given a six-month

extension to its market exclusivity in France.[71] (Table 7.1.8) It has resulted in higher healthcare spending in France than if a generic had been used, while the product is unsuitably packaged, difficult to obtain, not reimbursable, and not the standard treatment for children with hypertension.[71]

Table 7.1.8: Undesirable outcomes of the introduction of a new paediatric product on the market, an example of Cozaar® oral suspension

Name of the Medicine	Cozaar® oral suspension, paediatric form of the antihypertensive drug losartan
Paediatric Regulation reward	Six-months extension to its market exclusivity in France, including non-paediatric indications
Therapeutic use	Hypertension, but not standard treatment for hypertension in children
Packaging and labelling	Suspension not ready to use Not labelled properly Poor quality packaging prone to dosing mistakes (diluting)
Availability	Difficult to obtain from retail pharmacies via wholesalers
Price implications	Company did not ask for inclusion in the French reimbursement list Expensive, out-of-pocket expenditure High profitability for the company*

* According to figures from the French national health insurance fund for salaried workers (Cnamts) on reimbursement requests in France during 2009, reimbursements for losartan (excluding the losartan + hydrochlorothiazide combination) over a 6-month period totalled 27 million euros.

Source: Prescrire. Who Benefits from the European Paediatric Regulation? Response to the European Commission's public consultation on the lessons learnt from the first 5 years of application of the Paediatric Regulation. Paris, 2012.[71]

4.3 Patients' participation in the development of paediatric medicines

In addition to the active participation of two patients' representatives (families) since 2008 at PDCO, in 2011 the EMA initiated an innovative project to facilitate the direct participation of children and young people in the PDCO activities. The objective is to involve children and young people across a wide age range, disease groups, different Member States and cultural groups to provide a new age-appropriate dimension to the scientific aspects of the PIP evaluation process. Some of the proposed areas for consultation are as follows:

- evaluation of individual PIPs;
- definition of significant therapeutic needs according to therapeutic areas;
- clinical assessments used as endpoints;
- invasiveness, frequency and duration of tests;
- preferences for clinical trial design features: randomisation, placebo, frequency of visits, duration of study, number of tests, and medicines of choice;
- acceptability of route of administrations; and
- acceptability of formulations / preferred formulation type / palatability / frequency of dosing / container closure systems and other packaging issue.

The 'Concept paper on the involvement of children and young people at the Paediatric Committee' (PDCO) was released in September 2012 for public review, and the expected

date for adoption of the outcome is January 2013.[76] For more information on stakeholder involvement, please see Background Paper Chapter 8.5.

4.4 Conclusions

Overall, the Paediatric Regulation has put a framework and structure in place to encourage an integrated approach to the development of paediatric medicines. As a result, a systematic evaluation of each new compound to identify paediatric needs and potential value for children, has been embedded into the research and development (R&D) process. Its requirements and incentives system have produced initial results, addressing some of the complexities associated with paediatric studies and stimulating the paediatric research over time. The number of EU clinical trials with paediatric populations was stable during 2007-2011, and some innovations were introduced in clinical trials, such as the inclusion of younger children in certain circumstances. Alternative methodological approaches to classical clinical trials should be encouraged to facilitate clinical trials in children or reduce the need for investigation in this vulnerable and limited population. That includes the modelling and simulation approaches, as well as extrapolation, which depends on basic knowledge on specific diseases in children, such as pathophysiology, biomarkers and pharmacodynamic end-points.

The Paediatric Regulation led to an authorisation of a number of new paediatric indications and new pharmaceutical forms, routes of administration, or strengths for paediatric use. However, the current therapeutic areas covered by PIPs seem to be more in alignment with adult drug development than with the unmet public health needs in children. Moreover, it may be expected that the reward of six-month SPC extension may increase public expenditures and have cost implications for the public purse. A recent example has shown that a deficient market approval of a new paediatric product at national level may result in unsafe due to inadequate packaging and labelling. It is therefore, essential that regulatory authorities have robust approval systems in place, including active systems to detect and act on effects, resulting from the introduction of new paediatric products on the market.

The fact that only one PUMA (with limited therapeutic benefit) was granted, indicates that this reward may not be an adequate incentive to the industry for investments in off-patent drug research. This might be linked to reimbursement rules that may not recognize PUMA and thus attach little value to old medicines, even if they include new age-appropriate formulations. Where little industry interest has been expected, the EU Paediatric Regulation includes provisions for public sector research funding for off-patent medicines, and number of projects have been already initiated by academia and SMEs. Accordingly, the collaboration and active involvement of all stakeholders (governments, regulatory authorities, research institutions, pharmaceutical industry, and healthcare facilities) prove to be vital to effectively address off-label use of medicines in children. As an alternative to clinical trials in children, it may be necessary for healthcare professionals to systematically monitor the use of off-label medicines in paediatric clinical practice and share patient records to produce robust safety and efficacy data.

It is also expected that the new EU Pharmacovigilance Regulation will support the evidence-based use of off-label medicines in children, because it includes both marketed and unlicensed/off label medicines. Hence, it is important to evaluate the added value of this promising regulation with respect to children.

To ensure that children's priority therapeutic needs are met, the Paediatric Committee has been producing lists on unmet needs. Complementary, medicines with paediatric indications have to represent tangible progress with significant therapeutic benefits in paediatric treatment areas. A similar situation was previously observed in the US, when pharmaceutical companies did not willingly focus their paediatric R&D efforts on the priority needs of children. Consequently, a Best Pharmaceuticals for Children Act (BPCA)[77] was adopted in 2007 to allow the FDA to demand clinical trials on certain medicines (even with pre-specified trial design), based on an annual list of needs and priorities in paediatric medicines published by the FDA and the National Institute of Health (NIH).

5. The usage environment

This section discusses the common problem of off-label and unlicensed use of medicines in children, as well as the appropriateness of medicines used for some specific childhood diseases, in different healthcare settings, and at different national income levels. Furthermore, this section addresses important issues related to the availability of information on medicines used in children and the challenges associated with adherence to treatment.

5.1 Off-label and unlicensed use of medicines in children

Children have been commonly considered "therapeutic orphans" because the majority of medicines on the market have not been studied in the paediatric population, nor have they been approved by regulatory authorities for use in children. It has been estimated that only a third of all authorised medicines approved by the European Medicines Agency over the period 1995-2005 were licensed for use in paediatric patients. The main constraints to the development of paediatric drugs are ethical concerns, economic barriers, and logistical and technical issues.[76] As a result, many medicinal products are not available in formulations suitable for administration in paediatric patients. This often leaves no alternative for the prescriber other than to use adult medicines as off-label (medicines prescribed outside their authorised indications with respect to age, dosage, indication or route) or unlicensed medicines (modified formulations, extemporaneous preparations, imported or used medicines before the authorisation license is granted, or chemicals used for therapeutic purposes).[78]

An EMA survey published in 2010 explored unlicensed and off-label use of medicines in children based on data from 20 EU and two non-EU countries covering 50% of the total population in Europe.[72] Overall, the analysis revealed that 45 to 60% of all medicines used for children were used outside their marketing authorisation. Higher rates were reported in the premature (up to 90% of medicines) and term neonates, as well as in patients with serious conditions and those in intensive care units. The most frequently used off-label and unlicensed medicines belong to the following therapeutic classes:

- antiarrhythmics
- antihypertensives (renin-angiotensin inhibitors, beta blockers)
- proton pump inhibitors
- H2-receptor antagonists
- antiasthmatics

- antidepressants (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptakeinhibitors, tricyclic antidepressants).

Adolescents, mainly in Scandinavia, used high rates of off-label oral contraceptives. Off-label antimicrobials (e.g. macrolides, beta lactamines, plus beta-lactamase inhibitors and carbapenems) and corticosteroids (dexamethasone) were used extensively in very young children. The analysis of dosage forms showed that both oral and parenteral formulations were used off-label and unlicensed. Hospitalised children, as well as outpatients, were frequently treated with off-label medicines, and (preterm) neonates had the highest unmet therapeutic needs.

There were discrepancies across individual countries in the use of unapproved medicines due to differences in data collection methods, prescribing habits and a medicine's regulatory status (approved or not, in all or some subsets). For that reason, it should be a requirement that approved products be made available in all Member States. Likewise, regulatory action is needed to address the general lack of paediatric labelling in the Summary of Product Characteristics, and in order to foster the harmonisation of information on product labels (e.g. between different manufacturers of the same generic medicines, or different pharmaceutical forms and administration routes of the same medicine).

Using medicines that are not licensed means that there is limited available evidence or reporting on its safety, quality and efficacy and a potentially increased risk of adverse drug reactions (ADRs).[79] In 2004, the EMA reported an increased incidence of, seriousness in, and underreporting of adverse paediatric drug reactions related to off-label and unlicensed use of medicines.[80] The ADRs in children have been dominated by anti-infectives, anti-asthmatic, and gastrointestinal ADRs, reflecting the most common diseases in children; but central nervous system ADRs have been equally common.[80]

Despite the risks of harm, off-label use of medicines has become an accepted standard of medical practice, particularly in paediatric intensive care units, where approved medicines are scarce.[81,82,83] Denying the use of off-label medicines capable of providing benefits could be considered unethical in a given clinical context, especially for life-threatening or severe chronic illnesses (e.g. cancer therapy, epinephrine, albuterol, dopamine). Experts and health authorities have acknowledged that off-label drug use can be medically appropriate, if the benefits outweigh the potential risks.[84,85,86]

Given the lack of age-appropriate doses and formulations, healthcare professionals may change a medicine's administration route, or manipulate adult dosage forms (e.g. segmenting tablets and suppositories, cutting patches, dispersing open capsules, or crushed tablets in water, liquid, or food). These practices may affect a medicine's stability and bioavailability, and lead to considerable inaccuracies in dose delivery, causing overdoses (potential toxicity) or under-doses (potential inefficacy).[87] Dose calculation involves a systematic examination of both the available evidence on safety and efficacy and the seriousness of the condition being treated. Ideally, the evidence should be from a clinical trial and should also include information regarding the minimum effective dose. Unfortunately, for many conditions in paediatric patients, this detailed information is not available.[86]

Although the paediatric regulation imposes special attention to dose selection in paediatric clinical trials and evaluation of effective and safe doses in children, paediatric trials remain

difficult to accomplish. As children may often not be subject to dose-finding studies, empirical scaling from adults to children continues to be the mainstream method for dose selection in children. This implies paediatric dosing calculations by adult data extrapolation, based on the child's gestational and postnatal age, clinical condition, weight, and/or body surface area.[88] All these approaches have disadvantages, determined by differences in paediatric physiological development or pharmacodynamic and pharmacokinetic characteristics, such as variability due to age, gender, body composition, functionality of liver and kidneys and maturation of enzymatic systems throughout the life span from neonates to adults. This increases the risk of toxicity due to lack of understanding of the ontogeny of metabolic pathways, as for example in neonates and toddlers, or poor efficacy due to suboptimal dosing.[88]

Ideally, children's dose calculations should be based on dose scaling in paediatric trials, or at least on established paediatric dosage reference texts and formularies (British National Formulary for children–BNFc[89] and the WHO Model Formulary for Children[90]), even though these guidelines rely on dosing recommendations from clinical experience and off-label use rather than on randomized clinical trials.[90] For resource limited settings, the WHO recommends simplified dosing regimens for HIV and malaria treatments using a weight-based formula to predict body-surface area.[91]

Because any off-label or unlicensed product manipulation includes dose calculations, their use has great potential of introducing dosing errors. This is most likely the case in younger children, or in neonatal intensive care units, because their weights change rapidly, and the appropriate dosing becomes particularly difficult.[92] Hence, it is often a real challenge to prevent medical errors and to improve patient safety in the paediatric setting.[93]

In western healthcare systems, electronic prescribing systems are considered to be potentially helpful tools for reducing prescribing error rates and even death rates in paediatric patients.[94] But, as prescribing for children is different in comparison to adults, the systems require child-tailored solutions (integrated dose checking and obligatory entry fields for indications to check off-label use), as a well as clinical pharmacy interventions to check administration routes and dosing.[94]

More importantly, it can be argued that since off-label use of medicines in children is such a common practice, it already relies on sufficient data. Yet, existing electronic patient-level registries have not been routinely used to explore the efficiency and effectiveness of off-label use in children in a systematic manner. To produce evidence for appropriate evidence-based off label use it is important to have precise outcome elements within these electronic systems to generate sufficient data on dose, efficacy and safety for off-patent medicines. Hopefully, the expanded availability and use of electronic medical records will soon allow researchers to link clinical treatments and outcomes with off-label medication prescribing trends in order to elucidate the implications of off-label use of medicines in children. (See the Background Paper Chapter 8.4 'Real life data and learning from practice to advance innovation' for more information.)

5.2 Medicines use in children for specific diseases

Our focus is on the use of medicines for childhood conditions that are considered to be the most relevant to public health and that have the highest medical needs in children. The

studies on medicines use in children presented below address the issue of the rational use of medicines, which requires that patients receive appropriate medications (safe and effective) for their clinical conditions, in doses and formulations suitable to their personal requirements, for adequate periods of time, and at the lowest cost to their families and communities.[95]

5.2.1 Use of antibiotics in children

The majority of drug utilisation studies highlight the high rates of outpatient antibiotic prescribing in paediatric populations. Of particular concern is the issue of prescribing antibiotics for infections with predominantly viral aetiologies (e.g. most upper respiratory infections, diarrhoea) because of the problems with antibiotic resistance.[96,97] The inappropriate prescribing of antibiotics for children is common in Europe, with marked differences being seen between Northern and Southern Europe. This variation is caused not only by differences in patient populations, but also by differences in prescribing patterns based on differences in prescribers' and patients' attitudes toward antibiotics, as well as cultural and social factors and health-care systems.[98,99] Previous studies have even demonstrated considerable variations in antibiotic use in all of the neonatal intensive care units (NICUs) in one single country— the Netherlands, a country that is characterised by relatively low antibiotic utilisation rates in the EU context. All the while, the recommended treatment guidelines for neonatal infections within these NICUs were similar. Such in-country variations might be explained by the emergence of resistant microorganisms in one particular NICU requiring the consequent use of a broad range of different antibiotics, and the influence of different antibiotic stewardship on the prescription of antibiotics in a NICU.[100] Correspondingly, a recent United States study shows high rates of systemic antibiotics use that account for one-quarter of all the prescriptions dispensed to the paediatric population. Encouragingly, the study demonstrates a 14 per cent decrease in paediatric antibiotics utilisation rates from 2002 through 2010. It demonstrated the positive results of the numerous national initiatives launched to promote the appropriate use of antibiotics, particularly for acute respiratory tract infections, and acute otitis media.[101]

Urgent interventions for improved antibiotic use include implementation of antibiotic stewardship programmes; uniformity in antibiotic policies, including uniformity in dosage recommendations; educational programmes; surveillance systems; identification of children at risk for antibiotic resistant bacteria colonization; and the linkage of antibiotic usage data to antimicrobial resistance data.[102] For more information on antimicrobial use, see Background Paper Chapter 6.1.

5.2.2 Use of psychotropic medicines in children

Depression and other psychiatric disorders in paediatric patients can have significant consequences if not appropriately treated. Still, there have been ongoing debates on the augmented use of psychotropic medicines in children, as well as their safety and efficacy. Psychotropic prescribing has risen in both European and American children in the last decade, with greater annual prevalence in the USA due to differences in psychiatric practices, health service systems and financing and cultural beliefs.[103]

The selective serotonin reuptake inhibitor (SSRI) antidepressants and the atypical antipsychotics have been the most widely used drug subclasses. Yet, psychotropic medicines

used in bipolar disorder and attention deficit hyperactivity disorder, for instance, show fair short-term risk-benefit ratios and poor long-term benefits, and they still have not been properly evaluated for paediatric use. In the past few years, clinicians have recognised the side effects of these medications, including metabolic syndrome and diabetes. Concerns about the lack of well investigated psychotropic medicines, their side-effects, and the increase in children and adolescents receiving these medications, have been raised at all levels—parents, clinicians, researchers, the lay press, and government officials.[104]

One of the biggest worries has been that widely used antidepressant drugs might be associated with an increased risk of suicidality in paediatric patients. Although the findings of drug-induced suicidality, based on adverse event reporting in paediatric patients during short-term treatment with antidepressant drugs, seem to be robust, an overall interpretation of this finding and its implications for clinical practice are less clear, as it may result from greater reporting of suicidal thoughts and behaviours in these patients. The established boxed warning on the risk of suicidality is important in alerting patients and their families to the safety risk and in encouraging prescribers to balance this risk with clinical need and closely monitor patients.[105]

The lack of well investigated psychotropic medication for children is serious because it is inappropriate to extrapolate from adults due to the still developing paediatric brain and central nervous system during adolescence. This field remains relatively unresearched at the moment.[106]

5.2.3 Use of medicines in preterm newborns

The preterm birth prevalence rate has been increasing in Europe over the last 10 years, reaching 7% of all life births in 2010. Although their survival rates have improved, preterm infants are at greater risk for health complications in later life, such as cerebral palsy, respiratory illnesses, sensorial and motor disabilities, and learning and behavioural disorders (see Background Paper Chapter 6.23 for more detailed information on neonatal conditions).[107] The problem of newborn survival has received greater global attention lately, with the UN campaign 'Every Woman, Every Child' being launched to prevent preterm births and improve the survival and outcome of premature babies.[108,109,110]

Despite the fact that (preterm) neonates belong to the most vulnerable population, data on drug utilisation in neonatal intensive care units are limited. Preterm neonates are often multi-morbid, in need of intensive and complex medical care, exposed to a high number of drugs (mostly unlicensed or off-label), and at higher risk of adverse drug reactions.[111,112]

A German study in a neonatal intensive care unit (NICU) specialised in pre-term neonates confirmed the complexity of treatment strategies and the polypharmacy patterns as preterms received an average of eleven different medicines. Contrary to drug utilisation patterns in other newborns, the most frequently prescribed medications for preterms were systemic use anti-infectives, and central nervous system and respiratory system drugs.[113] All very preterm infants received at least one unlicensed or off-label medicine, with no information available on their safety and efficacy in preterms in the Summary of Product Characteristics (SmPC). In this context, the cardiovascular drugs, including diuretics and anaesthetics/analgesics were of major concern.[113] Similarly, a recent Estonian hospital study described extensive pharmacotherapy in (preterm) neonates, frequent use of off-label and unlicensed medicines

and large differences in the neonatal information provided by different sources (BNFc, Micromedex and the Estonian SPC).[114] Moreover, a United Kingdom study found potentially harmful substances and excipients (e.g. ethanol, propylene glycol) in the liquid medicines used in a NICU. During treatment, preterm newborns were regularly exposed to 20 different excipients that have the potential to cause nerve damage, including ethanol and propylene glycol chemicals. The level of the recommended maximum intake of sorbitol was also exceeded in the patients when it was calculated according to the baby's weight.[115] The European regulatory authorities have recognised this problem and some of the drugs frequently given to very preterm infants, such as midazolam, fentanyl, dobutamine, or hydrochlorothiazide, were included in their list of priority off-patent drugs.[73]

The lack of data on safety and efficacy leads to uncertainties in (preterm) neonatal drug therapy, so more information is urgently needed for optimal use of medicines prescribed in neonates. Randomised controlled trials have conventionally been regarded as the golden rule for data collection, but they might be impractical and unethical in neonates because of difficulties with randomisation or recruitment. Thus, it seems more appropriate to use the vast amount of clinical data that already exists in electronic medical records in order to improve the knowledge of safety and efficacy related to the use of medicines in preterm neonates.

Another concern is the lack of appropriate formulations for preterm newborns, especially for injection antibiotics (e.g. gentamicin), that are often misadministered due to low dosing. Therefore, innovations like pre-packaged doses and needle-free technology are needed.

5.3 Use of medicines in children in hospitals

Recent research has provided new data on the use of medicines in the hospital sector, an area generally characterized by a lack of knowledge and transparency. A multicentre study (ADVISE) was conducted on paediatric general medical wards in two European (United Kingdom, Germany) and three non-European (Malaysia, Australia and Hong Kong) hospitals in 2008-2009. On average, the children received three medicines during their hospitalization, with antibacterials for systemic use, analgesics, and drugs for obstructive airway diseases being the medicines most frequently prescribed to the cohorts.[116]

A study conducted at a large university hospital in Germany showed that while antibacterials for systemic use were prescribed most frequently, their use decreased between 1999 and 2008, whereas exposure to analgesics and anti-inflammatory drugs increased.[117] Antimicrobials are among the most commonly prescribed drugs in hospitals; therefore, in 2008 the European Surveillance for Antibiotic Consumption (ESAC) project performed a study in the paediatric units of 32 hospitals from 21 European countries. It revealed that a third of all paediatric patients were on antimicrobials, with a high proportion of them receiving antimicrobial combinations. The ESAC study identified the following targets for quality improvements of antimicrobial use in children: reducing the excessive use of antimicrobial combinations, high proportion of parenteral antimicrobials, and the long surgical prophylaxis times.[118]

A recent, large United States study showed serious polypharmacy in paediatric inpatients as a considerable fraction of them were exposed to five or more medicines, especially those patients with rare conditions.[119] Drug exposures were more prevalent in those children who

were older than one year and in children's hospitals. The most frequently used drugs and therapeutic agents included intravenous fluids, narcotics, antipyretics and analgesics, anti-infective agents, anaesthetic agents, gastrointestinal drugs, and medicines prescribed as part of a newborn's routine care.[119]

5.4 Use of medicines in children in developing and transitional countries

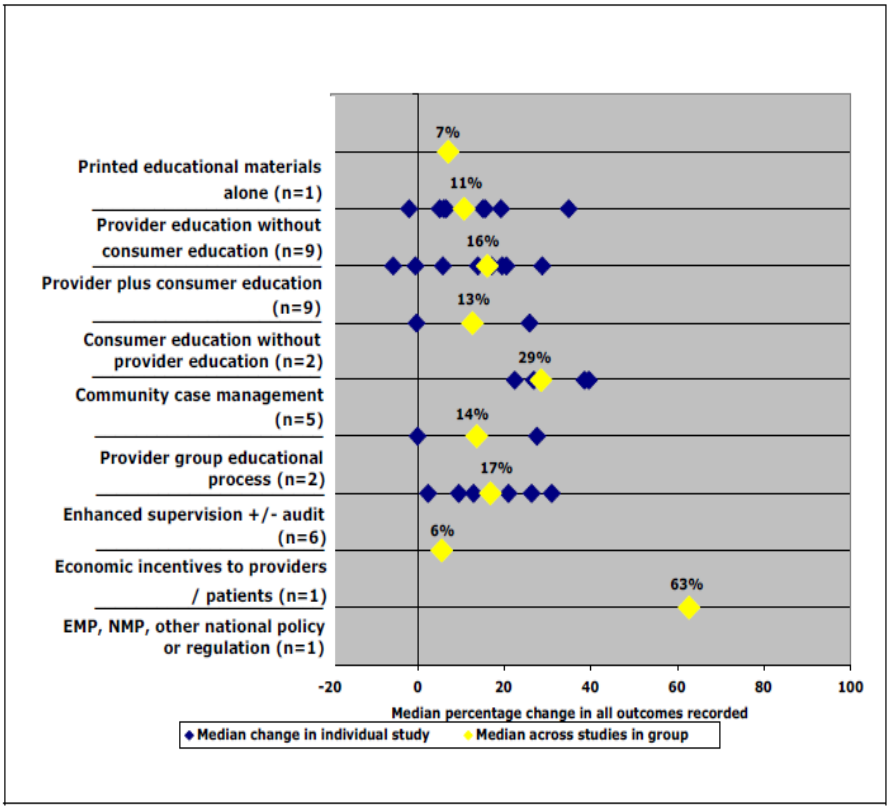
Similarly, the irrational use of medications poses significant challenges in resource poor settings. A WHO systematic review from 2007 assessed the progress and impact of interventions that have been undertaken to improve the treatment of childhood illness in developing countries.[120] The report indicated that regardless of the numerous national and international efforts, suboptimal treatment patterns of acute childhood diseases continued over the past 20 years. There has been improvement in the treatment of acute diarrhoea, reflected by an increased use of oral rehydration salts (ORS) and a decreased use of antidiarrheals and antibiotics. Optimal pneumonia treatment with appropriate antibiotics remained the same over time (80% of patients), while inappropriate use of antibiotics to treat viral upper respiratory tract infections (URTI) increased steadily, and malaria treatment with appropriate antimalarials deteriorated.[120] The use of medicines in the public sector was substantially better than in the private sector, but there were longer consultation times, better labelling, and better patient knowledge of dosing in the private sector. (Annex 7.1.13) Prescribing by the paramedical and nursing staff was similar to that of doctors for the common childhood diseases treated in health facilities.[120] (Annex 7.1.14)

The review suggests that the most effective interventions are multifaceted; target specific behaviours and assess local barriers to changing the behaviours; and take place at the system level, as opposed to the individual prescriber level. Effective intervention packages include educational materials, interactive lectures, educational outreach visits, audits and feedback, reminders, use of opinion leaders, policy changes, and the implementation of clinical protocols. (Figure 7.1.4)

In 2009, a systematic review examined interventions for changing physician prescribing practices and improving child health with regards to paediatric asthma, antibiotic prescription, treatment of malaria, and diarrheal disease.[121] Interventions focusing on structural changes in the design of current practices (e.g., implementation of a new asthma clinical pathway, an asthma peer leader with organization change, or restrictions on antibiotic use in a neonatal unit, etc.) were more successful than interventions focused on individual provider change (e.g., an educational conference for providers, or distribution of clinical practice guidelines to physicians).[121] As expected, multi-faceted interventions tended to be more successful than single interventions.[121]

Many industrialised countries have adopted activities to promote the more appropriate use of medicines, but it seems that their impacts have rarely been thoroughly evaluated. The WHO systematic review demonstrates that systematically collected and evaluated evidence provides a valuable opportunity for measuring medicine use within health systems and for testing the effectiveness of interventions to improve the use of medicines. Such studies are therefore also warranted in Europe.

Figure 7.1.4: Median reported percentage change across all prescribing outcomes for well-designed paediatric prescribing improvement interventions, by type of intervention.



Source: World Health Organization. Medicines use in primary care in developing and transitional countries: Fact book summarizing results from studies reported between 1990 and 2006. WHO/EMP/MAR/2009.3.[120]

5.5 Adherence to treatment in children

Poor compliance to medical regimens may have serious consequences for paediatric patients in terms of their health outcomes. Non-adherence may compromise the efficacy of drug regimens, thus diminishing the desired treatment goal, or may lead to changes in treatment regimens or dosages and an increase in toxicity, unnecessary investigations, and treatment costs. Estimates of non-compliance in children and adolescents (40-75%) are greater than in adults, particularly in adolescents.[122,123,124]

Many factors affect medication adherence and in most cases there are multiple causes. Factors affecting adherence may be related to illness and treatment regimens; characteristics of an individual child, including its age, race, socioeconomic status, developmental level, and psychopathology; and characteristics of the family system in which the child lives.[125,126,127] Importantly, children need appropriate parental and professional support in taking control of their medication and treatment.[125,126,127] (Table 7.1.9) A survey in the Netherlands in a multicultural population of children with asthma indicated that adherence to inhaled corticosteroids in children was a particular problem amongst ethnic minority patients, but further studies were recommended to clarify the causal mechanism.[128]

Table 7.1.9: Important factors and considerations for adherence to treatment in children

Reasons and barriers for non-adherence with medicines in children
The demands of daily schedules of activities, stress, and family dynamics
Parents' lack of understanding about the diagnosis, concerns about drug therapy effectiveness, and fears about medication side effects
Age, socioeconomic status, race, and family factors
Language barriers and low health literacy
Considerations for improved adherence with medicines in children
The triangle of communication between health professionals, parents , and children
The medication regimen should be tailored to the child and family's lifestyle and daily routine, taking into account the frequency and timing of administration
Consideration should be given to the palatability and formulations of medications prescribed for young children
Reinforcement of instructions by pharmacists or nurses, medication technique training (e.g., inhaler, injection, or dropper use)

Sources: Gardiner P, Dvorkin L, Promoting Medication Adherence in Children American Family Physician www.aafp.org/afp. Accessed April 29, 2013.[125]

Matsui D. Current Issues in Pediatric Medication Adherence. Pediatr Drugs 2007; 9 (5): 283-288.[126]

There has been limited research on the most effective methods for improving adherence to recommended treatment in children.[129] Methods that have proven to be successful in improving adherence in children were, as is also the case in adults, usually multifactorial and include: educational programmes, including information on the disease; explaining the purpose and potential benefits of the recommended medication; behavioural programmes that reward good compliance; and good supportive relationships and therapeutic alliances between patient and health professionals that include effective communication. Simplified regimens (with minimum effect on lifestyle) and palatable medications with age-appropriate formulations and delivery mechanisms may enhance the ability of paediatric patients to adhere to their medicines.[125125,126,127] (Table 7.1.9)

In addition, pharmaceutical companies have been developing innovative, child-friendly preparations appropriate for administration to infants and young children in terms of taste, formulation, and route of administration. But, the effects of newer formulations, such as effervescent and chewable dosage forms, granules and sprinkles, and the novel delivery system (Sip-Technology, that provides ready, easy-to-use, pre-measured dose of medication in a straw) are largely untested with regards to medication adherence, as previously stated in section 3 of this background paper.

Although there is no consensus as to what is the best approach to promote adherence with therapy, attention should be given to determining what barriers exist and trying to overcome them by involving children and their parents in the treatment planning process. It has even been suggested that perhaps perfect adherence is an ideal that will never be achieved, and that maybe the focus should be on determining how much adherence is enough to achieve the therapeutic goal. Further research in this direction is encouraged.[126]

5.6 Availability of information on (off-label) paediatric medicines and its dissemination to health workers and patients

One implication of the frequent, off-label use of paediatric medicines is the lack of adequate information about their possible indications, dosing regimens, dose adjustments, and administration. This information is neither included in the Summary of Product Characteristics (SmPC) for health-care professionals, nor in the patient information leaflets from the manufacturers or the media information resources for patients and their families/caregivers.

Historically, the lack of adequate information on paediatric medicines has been attributed to deficient scientific evidence to prescribe medicines in children, but nowadays there are also delays in updating the SmPCs with recently generated data. In order to provide better information on the use of medicines in children, the Paediatric Regulation has included an instrument for collecting existing paediatric studies. The Regulation has obliged companies holding data on the safety or efficacy of authorized medicines in children, as well as newly generated paediatric data, to submit those studies to the competent authorities, so that data can be assessed and authorized product information amended.[66] Since 2008 more than 18 000 study reports on 2 200 medicinal products have been submitted to the competent authorities, revealing the large amount of existing paediatric information available at company level. These study reports are being assessed by the authorities, resulting in the publishing of assessment reports on 140 active substances, and recommending changes to the SmPC for authorized products. However, marketing authorisation holders have not progressed much in updating the SmPC, so little of those new data have been systematically included in the SmPC.[69]

There have been recent improvements regarding information dissemination on medicine use in children for both healthcare workers and the public. The website 'Paediatric Medicines in the Netherlands'[130] is a multidisciplinary knowledge network initiated by the Dutch Knowledge Centre for Pharmacotherapy in Children (NKFK) and supported by the Ministry of Health, Welfare and Sport. The NKFK focuses primarily on improving the provision of information on the use of medicines in children to health professionals. Furthermore, the British National Formulary for Children[89] and the WHO Model Formulary for Children[90] provide dosage information for medicines used off-label in children. Patient information for unlicensed and off-label medicines is also available on the website 'Medicines for children', which consists of medicine information leaflets and provides opportunities for interactions between professionals and the public.

These encouraging developments should be supported by complementary research further exploring how healthcare professionals obtain their information to adequately treat children in daily practice and how this information becomes updated on a regular basis. In addition, more should be invested in evaluating the impact of existing information on medicine use in children to improve clinical practice and the adherence to treatments in children.

6. Identified gaps and recommendations for research and policy

Since 2004, numerous activities have been undertaken to support the development and administration of appropriate paediatric medicines and to improve the information available on their use. As a result, a legal EU framework has been put into place to encourage paediatric research, and various innovative, age-appropriate formulations, and drug devices for paediatric use have followed. Despite rapid technological advances and emerging networks for collaborations and expertise, we identified the following knowledge gaps and areas that need strengthening and/or future research in the area of medicine use in children.

Collection of data on disease burden and medicine use in children across Europe

In order to understand the burden of childhood diseases in the EU and set priorities, the collection of data on disease prevalence rates, and the use of medicines in children at a country level would allow inter-country comparisons and EU analysis of trends and variations over time. The main challenges for a complete and comprehensive evaluation are the lack of systematic and continuous monitoring in all EU countries and the disparity between studies. Therefore, the methodological quality of data collection should be improved and more multinational collaborative studies should be performed with EU support.

Further research into development of age-appropriate medicines

In recent years, much progress has been made in the development of age-appropriate novel, oral formulations with dose flexibility (mini-tablets, chewable, and orodispersible tablets for younger children, and dosage forms dispersible into liquids or mixed with food) and medical devices for easier administration of paediatric medicines. The ongoing research on the ability of children to swallow solid oral forms needs to be accompanied by studies on children's preferences and adherence to different dosage forms. In addition, new routes of administration, such as oral-transmusosal (buccal strips), intra-nasal and transdermal routes (for neonates mainly), are ripe for future development and research. In neonates, particular caution should is needed for these forms in terms of optimal use and dosing.

Given the safety and toxicity concerns of some excipients in paediatric formulations, more research is needed into alternative safe alternatives for children. It is also important to incorporate the available knowledge on excipients into a single, public repository to avoid a duplication of efforts and to encourage further discovery and innovation.

Study effects of development of age-appropriate medications and paediatric regulations

Irrespective of all technological developments, there is limited evidence on the impact of pharmaceutical formulations, routes, and dosage forms on patient-related outcomes (e.g. clinical efficacy, side effects and tolerability, and patient preference, acceptance, and adherence). This research should be central to the support of the pharmaceutical development of paediatric medicines with clear clinical advantages.

In addition, although many novel formulations and paediatric drug delivery devices have been developed, very few appear to be available on the market. This is most likely due to the

high costs of patent protection and the (un)willingness of health insurance bodies to reimburse for these new items. Therefore, current formulation research should also be accompanied by studies on price implications and access to innovative products that have tangible therapeutic benefit. Moreover, some paediatric medicines awarded six-month SPC extensions have cost implications and may increase public health expenditures. It is therefore essential that regulatory authorities have active systems in place to detect and act upon, resulting from the introduction of new paediatric products on the market.

Increase efficiency of the Paediatric Regulation with a focus on real paediatric needs

The Paediatric Regulation aims to achieve an integrated approach to the development of paediatric medicines in the overall medicine development area. However, current PIPS and their therapeutic areas covered by the industry seem to be more in alignment with adult drug development than with unmet public health needs in children (e.g. paediatric oncology, pain, neonatal morbidity). As a response, the Paediatric Committee has been producing lists on unmet therapeutic needs in children to identify priority research areas. This activity should be complemented by proactive demands for clinical trials on priority medicines with significant therapeutic benefits in children.

In addition, alternative methodological approaches to classical clinical trials should be encouraged to facilitate and optimize clinical trials in children, and potentially also reduce the need for (or size of) clinical trials in this vulnerable and limited population. Research in this field should be stimulated.

The new EU Pharmacovigilance Regulation may have potential added value in providing safety and efficacy data on off-label-medicine use in children, which should be evaluated.

Improve (information on) rational use of paediatric medicines

Various studies on medicine use trends and patterns in children indicate that more efforts are needed to guarantee the rational use of medicines, especially antibiotics, psychotropic medicines, medicines for neonates, and medicines used in hospitals. Effective interventions that are multifaceted and that take place at the system level must be considered in order improve the use of medicines. In addition, data should be systematically collected and evaluated to measure and to test the effectiveness of interventions in improving medicine use.

The off-label use of medicines has become an accepted standard of paediatric medical practice, particularly in areas where approved medicines are scarce. But, due to the lack of clinical trials using children, the available evidence on safety, quality, and efficacy and the knowledge of the potential risks of adverse drug reactions with off-label medicines used in children is limited. On the other hand, existing, electronic, anonymised, patient-level registries have not been used to explore the efficiency and effectiveness of off-label use in children. It is therefore essential to systematically collect and use the real life data on off-label or unlicensed medicine use in children to produce the evidence. Hopefully, the expanded availability and use of electronic medical records will soon allow researchers to link clinical treatments and outcomes with off-label medication prescribing trends and elucidate the implications of their use in children.

There has also been limited evidence on the most effective methods for improving adherence to recommended treatments in children. More research is needed to identify adherence-promoting interventions in children, and to evaluate their impact.

Recent improvements in information dissemination on medicine use in children for both healthcare workers and the public include the creation of websites ('Paediatric Medicines in the Netherlands' and 'Medicines for Children' in the United Kingdom), the BNFc and the WHO Model Formulary for Children. Complementary research should follow up on this to evaluate how healthcare professionals obtain information to treat children in daily practice and to evaluate what impact new information resources have on the use of medicines and adherence to treatment in children.

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Annexes

Annex 7.1.1: Infant mortality rates in Europe in 2010

Annex 7.1.2: Regional causes of childhood deaths in 2010

Annex 7.1.3: Developmental Changes in Physiology in Children

Annex 7.1.4: EMA Matrix – routes of administration/dosage form vs. age

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Annex 7.1.7: Paediatric products prequalified up to 2012

Annex 7.1.8: List of centrally authorised medicinal products for which the therapeutic indication was extended or amended to the paediatric population.

Annex 7.1.9: List of medicinal products and companies that have benefited from the 6-month extension of the supplementary protection certificate.

Annex 7.1.10: Funded off-patent medicine projects (start up to 1 January 2010) and agreed PIPs, if available.

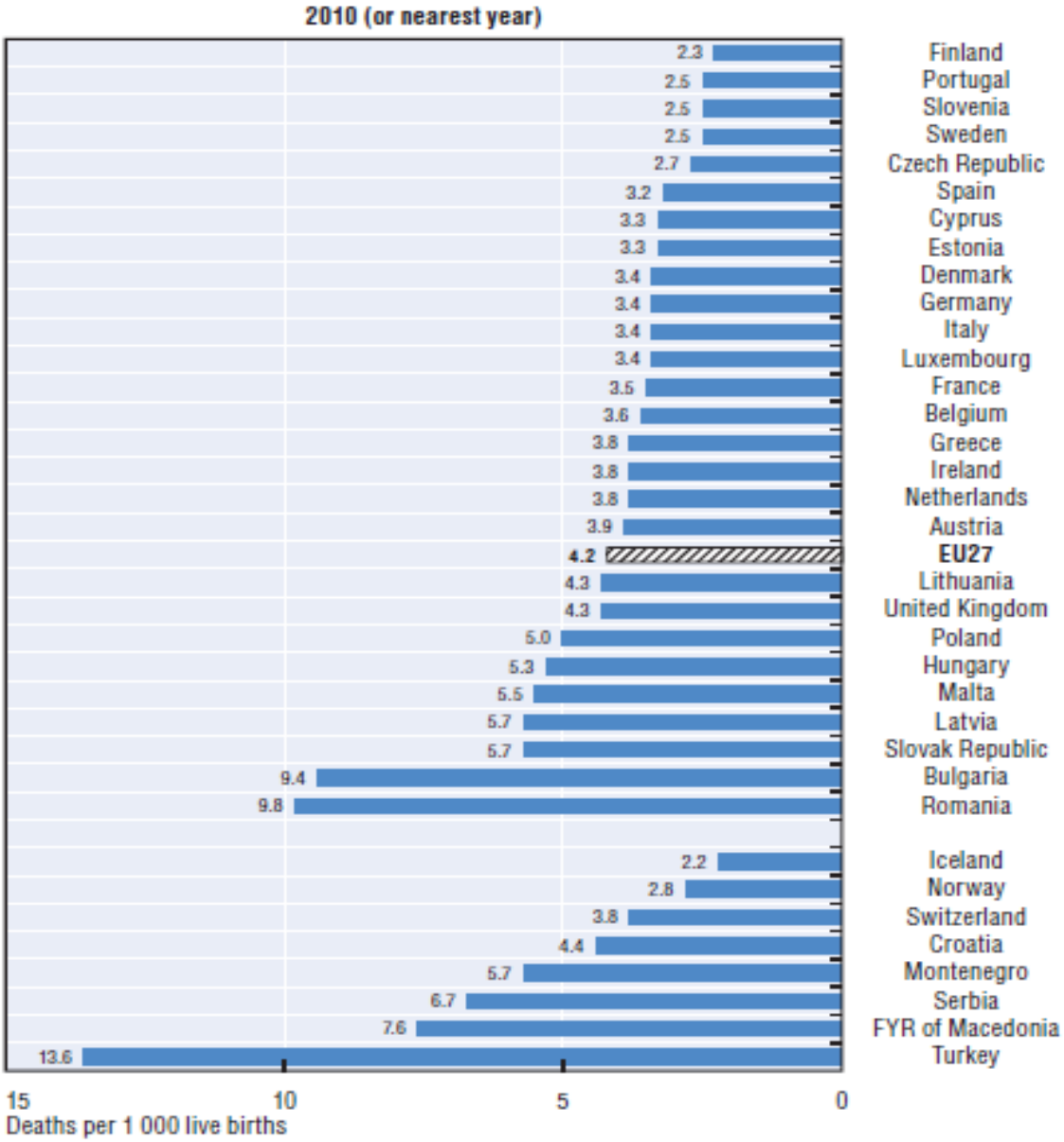
Annex 7.1.11: Therapeutic needs in the paediatric population according to the survey of all paediatric uses (EMA/794083/2009) and projects addressing the needs

Annex 7.1.12: Projects on use of paediatric medicines funded by the Sixth and Seventh Framework Programme (FP6, FP7), excluding off-patent funded projects, presented in Annex 7.1.8

Annex 7.1.13: WHO/INRUD prescribing indicators by health facility ownership

Annex 7.1.14: WHO/INRUD prescribing indicators by prescriber type

Annex 7.1.1: Infant mortality rates in Europe in 2010



Source: Eurostat Statistics Database.

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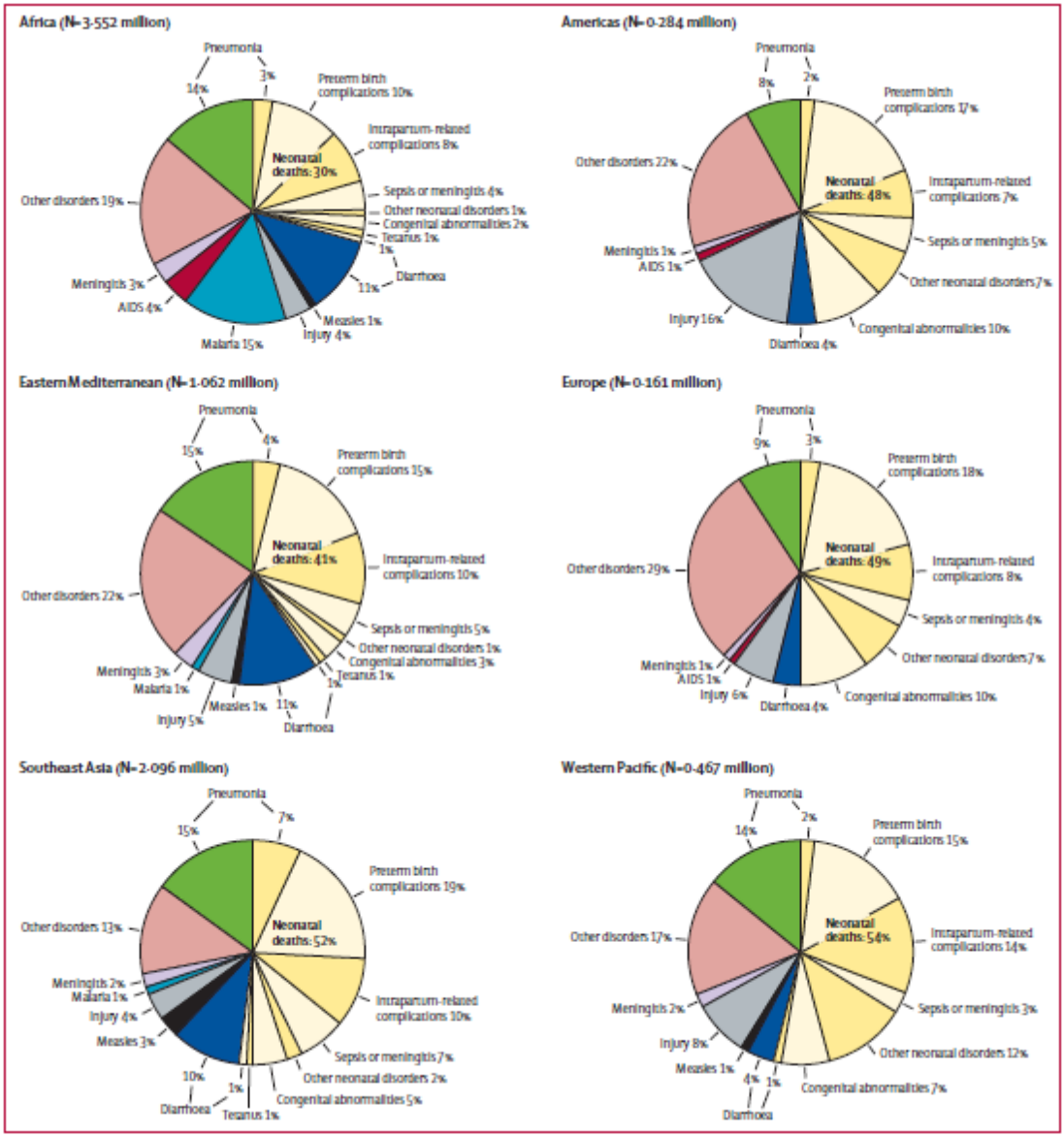
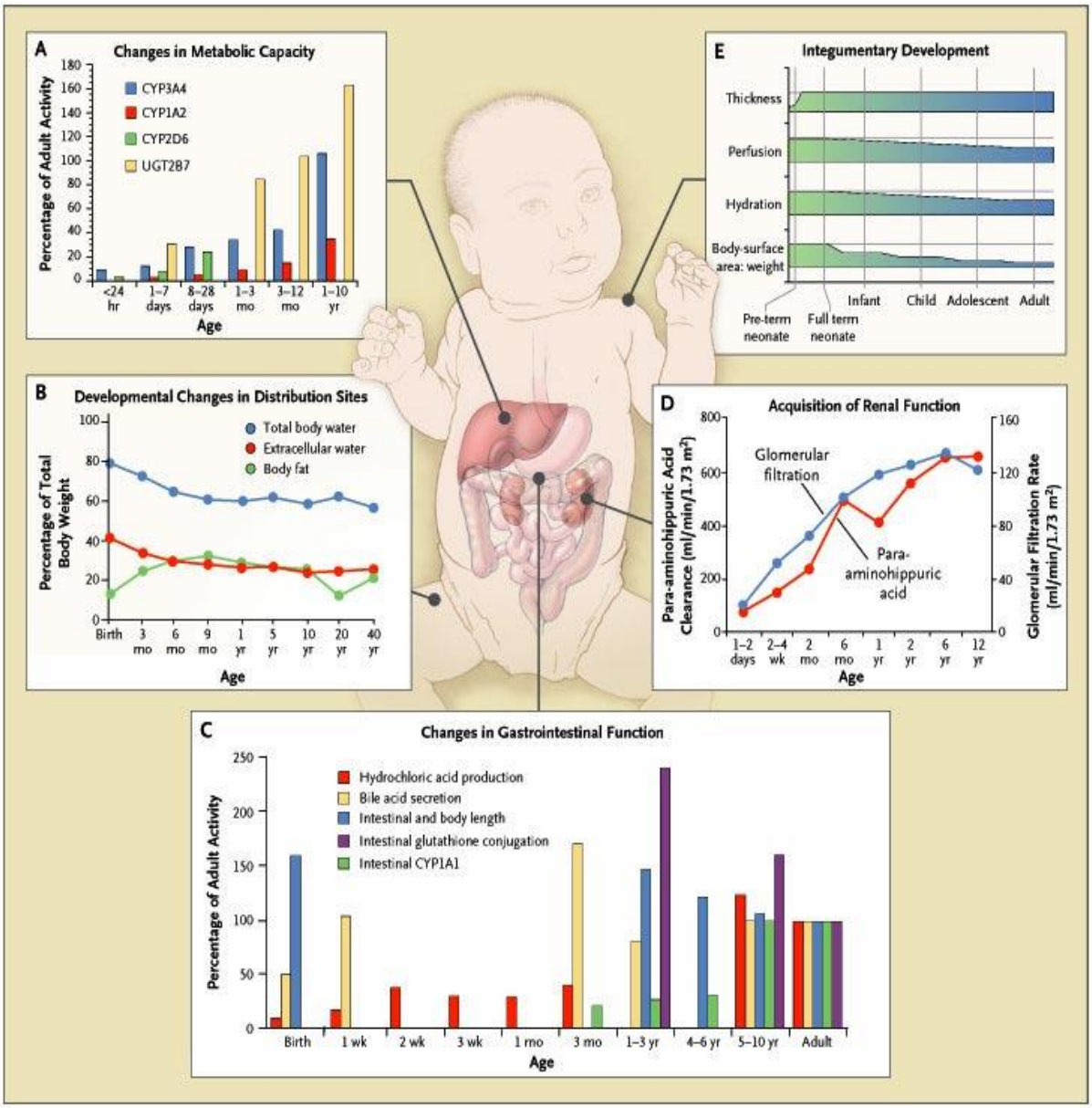
Annex 7.1.2: Regional causes of childhood deaths in 2010



Source: Liu L, Johnson HL, Cousens S, et al, for the Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012; 379: 2151–61.[4]

Annex 7.1.3: Developmental Changes in Physiology in Children



Source: Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental Pharmacology – drug disposition, action, and therapy in infants and children. N Engl J Med 2003;349:1157-1167.[35]

Annex 7.1.4: EMA Matrix – routes of administration/dosage form versus age

Route / Dosage Form	*Preterm newborn infants*	*Term newborn infants (0d-28d)*	*Infants and Toddlers (1m-2y)*	*Children (pre school) (2-5y)*	*Children (school) (6-11y)*	*Adolescents (12-16/18y)*
Peroral						
Solution/ Drops	2	4	5	5	4	4
Emulsion/ Suspension	2	3	4	5	4	4
Effervescent DF*	2	4	5	5	4	4
Powders/ Multiparticulates	1	2	2	4	4	5
Tablets	1	1	1	3	4	5
Capsules	1	1	1	2	4	5
Orodispersable DF	1	2	3	4	5	5
Chewable tablets	1	1	1	3	5	5
Nasal						
Solution	3	4	4	4	4	4
Semisolid DF	2	3	3	4	4	4
Rectal						
Suppositories	4	5	5	4	3	2
Rectal Enema	5	4	4	3	3	2
Rectal capsules	2	3	4	4	4	3
Topical/ transdermal						
Ointment, Cream, Gel	4	4	4	5	5	5
Liquid DF	4	4	4	5	4	4
Transdermal Patch	1	2	2	4	4	5
Parenteral						
i.v. Solution	5	4	4	4	4	3
i.m.	3	3	3	4	4	3
s.c.	4	4	4	4	4	3
Pump system	5	4	4	4	4	3
Pulmonary						
Nebuliser	2	3	4	5	4	3
MDI / Spacer	1	3	4	5	4	4
DPI	1	1	3	4	5	5
Ocular						
Eye drops	3	4	4	4	5	5
Semisolid DF	2	3	4	4	4	4

*DF: Dosage Forms

(1–not applicable, 2–applicable with problems, 3– probably applicable, but not preferred, 4– good applicability, 5 – best and preferred applicability)

Source: European Medicines Agency. Reflection Paper on Formulations of Choice for the Paediatric Population (EMEA/CHMP/PEG/194810/ 2005).[38]

Annex 7.1.5: Novel drug formulations for children

Dosage form	Brand product (manufacturer)
Multiparticulates	
Granules / Sprinkles / Pellets	Pankreatin Kreon® (Kali-Chemi Pharma), artesunate and mefloquine granules - Artequin® Pediatric (Mepha), methylphenidate granules – Medikinet® (Medice)
Mini-tablets	Pankreatin - Pankreatan® (Novartis) Cholspasminase ® (Merck) Enzym-Lefax® (Bayer) Cotazym® (UCB), Methylphenidate controlled release – Ritalin® pellets (Sandoz) Concerta® trilayer (J&JPRD)
Flexible dispersible formulations	
Dispersible tablets	ACT-Coartem® Dispersible (Novartis,MMV) Sinupret® Liquitabs® (Bionorica)
Oral lyophilisates	Cetirizine - Zyrtec® (Duncan)
Orally disintegrating tablets- lozenges	Sodium fluoride - Fluoretten® (Sanofi-Aventis)
Oral strips / Buccal wafers	Dextromethorphan, acetaminophen - Triaminic® (Novartis) Ondansetro - Setofilm® (Applied Pharma Research & Labtec & Monosol Rx)
Chewable tablets	Magnesium hydroxide gummy bears-Pedia Lax® (Fleet) Montelukast sodium – Singulair® (MSD)
Chewing gums	Dimenhydrinate - Superpep® (Hermes)
Medicated lollipop	Fentanyl citrate - Actiq® (Cephalon)
Orally disintegrating mini-tablets	Hydrochlorothiazide-Ludiflash®, Sodium stearylfumarate - Pruv® (JRS)

Sources: Stoltenberg I, Winzerburg G, Breitkreutz J. Solid oral forms for children – formulations, excipients and acceptance issues. Journal of Applied Therapeutic Research, 2010; 7(4): 141-146.[43]

Breitkreutz J. Nach der EU-Reform. Arzneiformen für Kinder. Pharm. Unserer Zeit 2009;38: 30-37.[45]

Annex 7.1.6: Novel drug devices for children

Dosage form	Brand product (manufacturer)
Novel dosing instruments for oral liquids	
Teat/Pacifier with reservoir	Nystatin suspension, Mykundex® (Bioglan)
Single-use spoon filled with medicine	Diphenhydramin solution,BenadrilTM® (Pfizer)
Dropper tube	Codeine drops (Stella / Abbott)
Dose sipping technology – straw with taste	Clarithromycin micropellets Clarosip® (Grünenthal GmbH)
Solid dosage pen	Carvedilol, salutas and metoprolol tartrate, microsinused as model drugs
Coated particles for oral administration	
Coated particles in suspension	Clarytromycin (Abbott)
Coated particles in tablets for preparing suspension	Roxithromycin (Infectopharm)
Coated particles on dosage spoon	Pre-dosed azithromycin spoon (Sandoz)
Needle-free injection devices	
Jet injectors	Subcutaneous administration of insulin, vaccines, growth hormone Saizen® (Bioject and Serono)
Microstructured transdermal systems for intradermal vaccines	
Novel devices for inhalation therapy	
Nebuliser with spacer/valved holding chamber and face mask	
Nebulisers with a vibrating mesh technology for aerosol generation	
Nebuliser with an electronic unit	For antibiotics e.g. tobramycine, Pari Boy® - electric nebuliser with compressor and face mask, AeroChamber® Plus (VHC) Ventolair Autohaler for beclomethasone dipropionate
Dry powder inhalers	Flutide Diskus® 50 with fluticasone propionate, (GSK) Inhalation-driven multidose dry powder inhaler with micronized budesonide (AstraZeneka), Pulmicort Resules® with micronised budesonide suspension for inhalation

Sources: Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. Exp Opin Drug Deliv 2007; 4:37–45.[39]

Walsh J,Bickmann D, Breitkreutz J, Chariot-Goulet M, on behalf of the European Paediatric Formulation Initiative (EuPFI). Delivery devices for the administration of paediatric formulations: Overview of current practice, challenges and recent developments. International Journal of Pharmaceutics 2011;415:221– 231. [51]

Annex 7.1.7: Paediatric products prequalified up to 2012

- Abacavir (as sulfate) 60 mg
- Lamivudine/Nevirapine/Stavudine 60 mg/100 mg/12 mg
- Lamivudine/Nevirapine/Stavudine 30 mg/50 mg/6 mg
- Lamivudine/Nevirapine/Zidovudine 30 mg/50 mg/60 mg

- Isoniazid/Pyrazinamide/Rifampicin 30 mg/150 mg/60 mg
- Artemether/Lumefantrine 20 mg/120 mg
- Lamivudine – 30 mg - Dispersible tablets
- Lamivudine – 30 mg – Tablets
- Zidovudine – 100 mg - Tablets
- Isoniazid/Rifampicin – 60 mg/60 mg - Dispersible tablets
- Abacavir (as sulfate)/Lamivudine – 60 mg/30 mg – Tablets
- Nevirapine 50 mg/5 ml - Oral suspension
- Lopinavir/Ritonavir 100 mg/25 mg - Tablets
- Abacavir (as sulfate)/Lamivudine/Zidovudine 60 mg/30 mg/60 mg - Tablets
- Lamivudine/Zidovudine 30 mg/60 mg - Tablets

Source: World Health Organization. Prequalification Programme, A United Nations Programme managed by WHO. 2011; Available at: http://apps.who.int/prequal/. Accessed May 2, 2013.[64]

Annex 7.1.8: List of centrally authorised medicinal products for which the therapeutic indication was extended or amended to the paediatric population.

Trade name	Active substance (INN)Inn	Date of EU DC	Subject of extension	MAH	Requirement to fulfil Article 8 of Paediatric Regulation Yes/No
Keppra	Levetiracetam	04/01/2007	Extension of the indication to include adjunctive therapy in the treatment of primary generalised tonic-clonic (PGTC) seizures in adults and adolescents from 12 years of age with idiopathic generalized epilep	UCB Pharma SA	No
Prevenar	Pneumococcal saccharide conjugated vaccine, adsorbed	09/03/2007	Extension of the indication to include new information on efficacy against disease caused by Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23F in otitis media.	Wyeth Lederle Vaccines S.A.	No

Trade name	Active substance (INN)Inn	Date of EU DC	Subject of extension	MAH	Requirement to fulfil Article 8 of Paediatric Regulation Yes/No
Prevenar	Pneumococcal saccharide conjugated vaccine, adsorbed	02/04/2007	Extension of indication from active immunisation against bacteraemic pneumonia to active immunisation against pneumonia.	Wyeth Lederle Vaccines S.A.	No
Remicade	Infliximab	30/05/2007	Extension of indication to include treatment of severe active Crohn's disease in children aged 6 to 17 years.	Janssen Biologics B.V.	No
Aranesp	Darbepoetin alfa	30/08/2007	Extension of indication for CRF patients, which currently restricts the use of Nespo to paediatric subjects >/= 11 years of age	Amgen Europe B.V.	No
Telzir	Fosamprenavir	13/09/2007	Extension of indication of Telzir in combination with ritonavir for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults in combination with other antiretroviral medicinal products to include paediatric populations.	ViiV Healthcare UK Limited	No
Combivir	Lamivudine / zidovudine	13/11/2007	Extension of indication to include paediatric patients and replacement of film coated tablets by scored film coated tablets.	ViiV Healthcare UK Limited	No
Aerius	Desloratadine	31/03/2008	Extension of indication from 'chronic idiopathic urticaria' to 'urticaria'.	Merck Sharp & Dohme Ltd.	No
Apidra	Insulin glulisine	20/06/2008	Extension of indication to include 6 years old and older children based on the results of 2 paediatric studies.	Sanofi-aventis Deutschland GmbH	No
Gardasil	Human papilloma virus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	10/07/2008	Extension of indication to include the prevention of high-grade vaginal dysplastic lesions (VaIN 2/3).	Sanofi Pasteur MSD, SNC	No

Trade name	Active substance (INN)Inn	Date of EU DC	Subject of extension	MAH	Requirement to fulfil Article 8 of Paediatric Regulation Yes/No
Humira	Adalimumab	25/08/2008	Extension of indication to include treatment of active polyarticular juvenile idiopathic arthritis in adolescents from 13 to 17 years of age.	Abbott Laboratories Ltd.	No
Cancidas	Caspofungin	26/11/2008	Extension of the indication to include the paediatric population.	Merck Sharp & Dohme Ltd.	No
Enbrel	Etanercept	22/12/2008	Extension of indication to include the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.	Pfizer Ltd.	No
Zavesca	Miglustat	26/01/2009	Extension of indication to include the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease.	Actelion Registration Ltd.	No
Protopic	Tacrolimus	26/02/2009	Extension of indication to 'maintenance treatment' further to completion of one study in adult patients and one in paediatric patients.	Astellas Pharma Europe B.V.	No
Aptivus	Tipranavir	23/06/2009	Extension of indication to include the treatment of HIV-1 infection in highly pre-treated adolescents 12 years of age or older with virus resistant to multiple protease inhibitors.	Boehringer Ingelheim International GmbH	No
Xolair	Omalizumab	27/07/2009	Extension of indication to children from 6 to <12 years of age as add-on therapy to improve allergic asthma control.	Novartis Europharm Ltd.	No
Abilify	Aripiprazole	21/08/2009	Extension of indication to include treatment of schizophrenia in adolescents 15 years and older.	Otsuka Pharmaceutical Europe Ltd.	No
Keppra	Levetiracetam	02/09/2009	Extension of indication to include the adjunctive treatment of partial seizures with or without secondary generalisation in children from 1 month to <4 years old.	UCB Pharma SA	No

Trade name	Active substance (INN)Inn	Date of EU DC	Subject of extension	MAH	Requirement to fulfil Article 8 of Paediatric Regulation Yes/No
PegIntron	Peginterferon alfa-2b	11/11/2009	Extension of indication of the combination therapy peginterferon alfa-2b and ribavirin to include treatment of the paediatric population.	Schering-Plough Europe	Yes
Rebetol	Ribavirin	11/11/2009	Extension of indication of the combination therapy peginterferon alfa-2b and ribavirin to include treatment of the paediatric population.	Schering-Plough Europe	Yes
Orencia	Abatacept	20/01/2010	Extension of indication to include the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs including at least one TNF inhibitor.	Bristol-Myers Squibb Pharma EEIG	Yes
Reyataz	Atazanavir sulphate	05/07/2010	Extension of indication for Reyataz capsules to include the treatment of HIV-infected children and adolescents above the age of 6 in combination with other antiretroviral medicinal products.	Bristol-Myers Squibb Pharma EEIG	No
M-M-RVAXPRO	Measles, mumps and rubella vaccine (live)	06/09/2010	Extension of indication to include administration to healthy children from 9 months of age.	Sanofi Pasteur MSD, SNC	No
Inomax	Nitric oxide	17/03/2011	Extension of indication to include the treatment of pulmonary hypertension peri- and post heart surgery in children.	INO Therapeutics AB	Yes
Humira	Adalimumab	18/03/2011	Extension of indication to include treatment of active polyarticular juvenile idiopathic arthritis in the paediatric population aged from 4 to 12 years.	Abbott Laboratories Ltd.	Yes
Viread	Tenofovir disoproxil fumarate	24/03/2011	Amendment of indication based on the 48-week results of a safety and efficacy study GS-US-104-0321 in treatment-experienced adolescents aged 12 to 18 years old.	Gilead Sciences International Ltd.	Yes

Trade name	Active substance (INN)Inn	Date of EU DC	Subject of extension	MAH	Requirement to fulfil Article 8 of Paediatric Regulation Yes/No
Invega	Paliperidone	08/04/2011	Extension of indication to include treatment of psychotic or manic symptoms of schizoaffective disorder.	Janssen-Cilag International N.V.	Yes
Revatio	Sildenafil	02/05/2011	Extension of indication in paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension.	Pfizer Ltd.	Yes
Kiovig	Human normal immunoglobulin (ivig)	27/07/2011	Extension of indication to include treatment of multifocal motor neuropathy (MMN). Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT) in adults and children.	Baxter AG	Yes
Roactemra	Tocilizumab	01/08/2011	Extension of indication to include treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.	Roche Registration Ltd.	Yes
Synflorix	Pneumococcal polysaccharide conjugate vaccine (adsorbed)	05/08/2011	Extension of indication to increase the upper age limit of infants and children from 2 years to 5 years.	GlaxoSmith Kline Biologicals S.A.	Yes
Enbrel	Etanercept	24/08/2011	Extension of indication to include lower age range for polyarticular juvenile idiopathic arthritis (JIA) "from the age of 4 years" to "from the age of 2 years".	Pfizer Ltd.	Yes
Enbrel	Etanercept	24/08/2011	Extension of indication to include lower age range for paediatric plaque psoriasis from "from the age of 8 years" to "from the age of 6 years".	Pfizer Ltd.	Yes

Trade name	Active substance (INN)Inn	Date of EU DC	Subject of extension	MAH	Requirement to fulfil Article 8 of Paediatric Regulation Yes/No
Levemir	Insulin detemir	24/10/2011	Extension of indication as add-on therapy to liraglutide treatment.	Novo Nordisk A/S	Yes
Levemir	Insulin detemir	24/10/2011	Extension of indication to children aged 2-5 years	Novo Nordisk A/S	Yes
Soliris	Eculizumab	24/11/2011	Extension of indication to include atypical haemolytic uremic syndrome (aHUS). Additional vaccination and antibiotic prophylaxis recommendation have also been added in section 4.2 for treatment of aHUS in adults and children.	Alexion Europe SAS	Yes
Cervarix	Human papilloma virus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	05/12/2011	Extension of indication to children from 9 years.	GlaxoSmith Kline Biologicals S.A.	Yes

Source: European Medicines Agency with its Paediatric Committee. 5-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation. EMA/428172/2012 2012; Available at: http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf. Accessed May 2, 2013.[69]

Annex 7.1.9: List of medicinal products and companies that have benefited from the 6-month extension of the supplementary protection certificate.

No.	INN of medicine to which patent applies	Marketing authorisation holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
1	Abatacept (Orencia)	Bristol-Myers Squibb Pharma	Austria (year not reported possibly 2011) Denmark (21	Bulgaria (2011) Greece (2010) Lithuania	Hungary Italy (SPC granted)	Romania (no SPC) Slovak Republic

No.	INN of medicine to which patent applies	Marketing authorisation holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
		EEIG	June 2010) Estonia (17 October 2011) Finland (13 September 2011) France (10 December 2010) Germany (16 August 2010) Ireland (30 June 2010) Luxembourg (23 December 2010) The Netherlands (31 August 2010) Portugal (2 November 2010) Slovenia (16 November 2011) Sweden (21 November 2011) United Kingdom (6 January 2011)	(2011) Luxembourg (2011) Romania (2011) Spain (2010)		
2	Anastrazole (Arimidex and associated names)	AstraZeneca AB	Austria (2010) Belgium (2010) Denmark (2010 Finland (2 March 2010)	Romania (2010, 2011; *SPC granted after appeal*)	Greece Portugal Spain	Bulgaria Greece Hungary Portugal Slovak Republic Slovenia *(no*

No.	INN of medicine to which patent applies	Marketing authorisation holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
			France (11 June 2010) Germany (19 July 2010) Ireland (29 June 2010) Italy (16 March 2010) Luxembourg (27 July 2010) The Netherlands (1 April 2010) Sweden (27 April 2010) United Kingdom (10 June 2010)			*SPC)*
3	Atorvastatin (Sortis and associated names)	Pfizer	Austria (year not reported, possibly 2011) Denmark (02 May 2011) Germany (11 August 2011) Ireland (28 June 2011) Italy (17 May 2011) Luxembourg (27 June 2011) Sweden (14 April 2011) The Netherlands (12 April 2011) United	France (2010)	Denmark Finland Greece Ireland Portugal Romania	Bulgaria *(appeal procedure after decision for termination of the procedure for SPC granting)* Germany Greece Hungary Luxembourg Portugal Romania *(no SPC)* Slovak Republic Slovenia *(no SPC)* Spain *(SPC denied)*

No.	INN of medicine to which patent applies	Marketing authorisation holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
			Kingdom (23 June 2011)			
4	Caspofungin (Cancidas)	Merck Sharp and Dohme	Austria (31 May 2010) Belgium (21 December 2010) Finland (14 September 2011) Greece (24 November 2010) Italy (13 July 2010) Portugal (12 March 2010) Slovenia (18 May 2010) Denmark (2009) France (2009) Germany (2009) Ireland (2009) The Netherlands (2009) Sweden (2009) United Kingdom (24 August 2009)	Bulgaria (2010) Czech Republic (2010, 2011) Hungary (2010, 2011) Poland (2011) Romania (2010, 2011) Slovak Republic (2010, 2011) Spain (2010)		Luxembourg
5	Clopidogrel (Plavix and associated names)	Sanofi BMS	Denmark (23 January 2012) Finland (9 November 2011)	Ireland (2011) Italy (2011) The Netherlands (2011)		

No.	INN of medicine to which patent applies	Marketing authorisation holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
			Germany (30 November 2011) Portugal (8 November 2011) Sweden (13 October 2011)	United Kingdom (2011)		
6	Latanoprost (Xalatan and associated names)	Pfizer	Austria (year not reported, possibly 2011) Denmark (07 March 2011) Finland (12 May 2011) Germany (30 March 2011) Ireland (1 March 2011) Italy (20 February 2011) Luxembourg (15 July 2011) Portugal (21 January 2011) Sweden (17 March 2011) The Netherlands (27 January 2011) United Kingdom (10 May 2011)	Spain (2010)	France Finland Greece Ireland Romania	Bulgaria *(SPC refused)* Germany Greece Hungary Romania *(no SPC)* Slovak Republic Slovenia *(no SPC)*
7	Losartan (Cozaar and associated	Merck Sharp & Dohme BV	Austria (12 February 2010) The	Cyprus (2010)	Greece Portugal Romania Spain	Bulgaria Greece Hungary Portugal

No.	INN of medicine to which patent applies	Marketing authorisation holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
	names)		Netherlands (2009) Germany(2009) Denmark (2009) Finland (2009) France (2009) Ireland (2009) Italy (2009) Sweden (2009) United Kingdom (2009) Luxembourg (2009)			Slovak Republic Slovenia *(no SPC)*
8	Montelukast (Singulair)	Merck Sharp & Dohme	Denmark (23 January 2012) Ireland (28 November 2011) Slovenia (16 November 2011) Sweden (15 September 2011) The Netherlands (21 September 2011) United Kingdom (03 January 2012)	Germany (2011) Italy (2011) Luxembourg (2011) The Netherlands (2011)		
9	Nevirapine (Viramune)	Boehringer	Denmark (23 January 2012) Portugal (2 December	Italy (2011) Luxembourg (2011)		

No.	INN of medicine to which patent applies	Marketing authorisation holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
			2011) Sweden (16 November 2011)			
10	Rizatriptan (benzoate) (Maxalt and associated names)	Merck Sharp & Dohme		Portugal (2012)		
11	Valsartan (Diovan and associated names)	Novartis Pharma AG	Austria (10 December 2010) Denmark (1 November 2010) Finland (22 October 2010) France (10 December 2010) Germany (13 January 2011) Ireland (22 December 2010) Italy (05 November 2010) Luxembourg (23 December 2010) The Netherlands (7 October 2010) Portugal (16 December 2010) Sweden (30	Spain (2010)	Greece Hungary Romania Slovenia	Bulgaria Greece Romania (no SPC) Slovak Republic

No.	INN of medicine to which patent applies	Marketing authorisation holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
			September 2010) United Kingdom (11 January 2011)			
12	Zoledronic acid (Zometa and associated names)	Novartis	Austria (year not reported possibly 2011) Denmark (6 April 2010) France (11 June 2010) Finland (14 September 2011) Germany (27 May 2010) Ireland (28 June 2010) Italy (13 July 2010) Luxembourg (22 December 2010) The Netherlands (3 March 2010) Portugal (15 March 2010) Slovenia (19 March 2010) Sweden (27 April 2010) United Kingdom (30 June 2010)	Cyprus (2010) Greece (2010) Hungary (2010, 2011) Romania (2010, 2011) Spain (2010)		Bulgaria Slovak Republic

Source: European Medicines Agency with its Paediatric Committee. 5-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation. EMA/428172/2012 2012; Available at: http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf. Accessed May 2, 2013.[69]

Annex 7.1.10: Funded off-patent medicine projects (start up to 1 January 2010) and agreed PIPs, if available.

No.	Acronym	Year start	Objectives (active substance[s] in bold)	Agreed PIP
1	KIEKIDS	2011	To develop an innovative, age-adapted, flexible and safe paediatric formulation of **ethosuximide** for the treatment of absence and of myoclonic epilepsies in children	NA
2	NEO-CIRC	2011	To provide safety and efficacy data for **dobutamine**, to perform pre-clinical studies, to develop biomarker of hypotension and to adapt a formulation for newborns	NA
3	TAIN	2011	To develop a neonatal formulation of **hydrocortisone** for the treatment of congenital and acquired adrenal insufficiency and for use in oncology (brain tumours and leukaemia)	NA
4	DEEP	2010	To evaluate PK & PD of **deferiprone** in in 2-10 years old children in order to produce an approved Paediatric Investigational Plan to be used for regulatory purposes	EMEA-001126-PIP01-10
5	HIP Trial	2010	Evaluates the efficacy safety, PK, PD of **adrenaline** and **dopamine** in the management of neonatal hypotension in premature babies and to develop and adapt a formulation of both suitable for newborns in order to apply for a Paediatric Use Marketing Authorisation (PUMA)	EMEA-001105-PIP01-10
6	TINN2	2010	To evaluate PK & PD of **azithromycin** against urea plasma and in BPD in neonates.	NA
7	NEMO	2009	Evaluates the efficacy safety, PK, PD, mechanisms of action of **bumetanide** in neonatal seizures, including the effect on neurodevelopment and to develop and adapt a bumetanide formulation suitable for newborns in order to apply for a Paediatric Use Marketing Authorisation (PUMA).	NA
8	NeoMero	2009	European multicentre network to evaluate pharmacokinetics, safety and efficacy of **meropenem** in neonatal sepsis and meningitis	EMEA-000898-PIP01-10
9	PERS	2009	Focuses on two indications, the use of **risperidone** in children and adolescents with conduct disorder who are not mentally retarded, and the use of risperidone in adolescents with schizophrenia	EMEA-001034-PIP01-10
10	EPOC	2008	To evaluate pharmacokinetics and pharmacodynamics of	NA

No.	Acronym	Year start	Objectives (active substance[s] in bold)	Agreed PIP
			doxorubicin	
11	LOULLA & PHILLA	2008	Development of oral liquid formulations of **methotrexate** and 6-**mercaptopurine** for paediatric acute lymphoblastic leukaemia (ALL).	NA / NA
12	NeoOpioid	2008	Compares **morphine** and **fentanyl** in pain relief in pre-term infants	EMEA-000712-PIP01-09
13	NEUROSIS	2008	Efficacy of **budesonide** (BS) in reducing bronchopulmonary dysplasia (BPD)	EMEA-001120-PIP01-10
14	O3K	2008	Oral liquid formulations of **cyclophosphamide** and **temozolomide**	EMEA-000530-PIP02-11 / NA
15	TINN	2008	Aims to evaluate PK & PD of **ciprofloxacin** and **fluconazole** in neonates	NA

NA = Not available

- HEALTH.2011.2.3.1-1 Investigator-driven clinical trials of off-patent antibiotics

Table 25: Investigator-driven clinical trials of off-patent antibiotics

No.	Acronym	Year start	Objectives (active substance[s] in bold)	Agreed PIP
1	MAGICBULLET	2012	Optimisation of treatment with off-patent antimicrobial agents of ventilator-associated pneumonia (VAP)	NA
2	AIDA	2011	Assessment of clinical efficacy by a pharmacokinetic / pharmacodynamic approach to optimise effectiveness and reduce resistance for off-patent antibiotics	NA

NA = Not available

Source: European Medicines Agency with its Paediatric Committee. 5-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation. EMA/428172/2012 2012; Available at: http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf. Accessed May 2, 2013.[69]

Information available on the website page: http://bit.ly/wUpuOb and http://bit.ly/xTshyn. Accessed May 3, 2013.

Annex 7.1.11: Therapeutic needs in the paediatric population according to the survey of all paediatric uses (EMA/794083/2009) and projects addressing the needs

Paediatric therapeutic area	Paediatric use	Active substance / class of substances	Addressed by (FP6, FP7, PIP etc.)	Comments
Infectious diseases	Treatment of bacterial infections in very young children	• Macrolides • Betalactamines plus beta-lactamase inhibitors • Carbapenems	• No PIP • No PIP • Doripenem (EMEA-000015-PIP01-07)	PIPs agreed for quinolones
Cardiovascular diseases	Treatment of hypertension (primary and seconddary)	• Renin-angiotensin inhibitors • Beta-blocker	• Aliskiren (EMEA-000362-PIP01-08), Alizisartan (EMEA-000237-PIP01-08), Candesartan (EMEA-000023-PIP01-07) • No PIP	
Cardiovascular diseases	Treatment of arrhythmia	• Antiarrhythmics	• No PIP	
Gastroenterology	Treatment of reflux disease	• Proton pump inhibitors • H2-receptor antagonists	• Rabeprazole (EMEA-000055-PIP01-07), esmeprazole (EMEA-000331-	

Paediatric therapeutic area	Paediatric use	Active substance / class of substances	Addressed by (FP6, FP7, PIP etc.)	Comments
			PIP01-08) • No PIP	
Pulmonology / respiratory medicine	Treatment of asthma	• Antiasthmatics (including montelukast, salbutamol)	• Montelukast (EMEA-000012-PIP01-07) • Tulobuterol (EMEA-000763-PIP01-09)	PIPs agreed for long acting beta agonists
Psychiatry	Treatment of depressive disorder	• Selective serotonin reuptake inhibitors • Serotonin-norepinephrine reuptake inhibitors • Tricyclic antidepressants	• No PIP • Desvenlafaxine (EMEA-000523-PIP01-08, waiver) • No PIP	Others: LUAA21004 (EMEA-000455-PIP02-10)
Dermatology	Treatment of atopic eczema	• Glucocorticosteroids, topical use	• No PIP	
Endocrinology	Prevention of pregnancy	• Oral contraceptives	9 unique PIPs agreed (EMEA-000148-PIP01-07, EMEA-000305-PIP01-08, EMEA-000475-PIP01-08, EMEA-000474-PIP01-08, EMEA-000250-PIP01-08-M01, EMEA-000518-PIP01-08, EMEA-000526-PIP01-08, EMEA-000546-PIP01-09, EMEA-000606-PIP01-09, EMEA-000658-PIP01-09, EMEA-000305-PIP01-08-M01, EMEA-000250-PIP01-08-M02, EMEA-000305-PIP01-08-M02)	
Endocrinology	Various uses	• Dexamethasone, systemic use	• No PIP	
Endocrinology	Not specified	• Multivitamin preparations	• No PIP	

Source: European Medicines Agency with its Paediatric Committee. 5-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation. EMA/428172/2012 2012; Available at: http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf. Accessed May 2, 2013.[69]

Annex 7.1.12: Projects on use of paediatric medicines funded by the Sixth and Seventh Framework Programme (FP6, FP7), excluding off-patent funded projects, presented in Annex 7.1.8

No	Project name	Period	Objective
FP6			
1	PRIOMEDCHILD	2007-2010	Coordination of research on priority medicines for children
2	EUROSTEC	2007-2011	Soft tissue engineering for congenital birth defects in children: new treatment modalities for spina bifida, urogenital and abdominal wall defects
3	KIDSCANCERKINOME	2006-2010	Selecting and validating drug targets from the human kinome for high risk paediatric cancers
4	CHILDHOPE	2006-2010	Chimaeric T-cells for the treatment of paediatric cancers
5	TEDDY	2005-2010	Optimise paediatric use of current drugs and promote the development of new drugs, by incorporating pharmacogenetic applications and implementing guidance/tools to perform paediatric research.
FP7			
1	DIRECT	2008-2010	Disseminate research funded by EC for improving treatment options for children suffering from cancer
2	GRIP	2011-2015	Coordinate knowledge management efforts and integrate existing research capacity for development and safe use of medicine in children, work closely with families to provide children with safe and effective medicines.
3	CUREHLH	2008-2011	Establish earlier diagnosis, learn about pathophysiology, and develop less toxic treatments for the rare disease haemophagocytic lymphohistiocytosis
4	RESPECT	2008-2011	Clarify expectations and needs of children and families to participation in clinical trials, empower and motivate children in future clinical trials research.
5	PHARMACHILD	2011-2014	Study pharmacovigilance for adverse effects in childhood arthritis from treatment with immune modulatory drugs
6	PANCARESURFUP	2011-2016	Collect data on long-term complications of cancer treatments, create European cohort for early identification and management of complications to improve health and quality of life and maximise use of health services
7	STOP	2011-2014	Assess and monitoring of Medication-Related Suicidality in children and adolescents in three paediatric observational trials (risperidone in conduct disorder; fluoxetine in depression, and montelukast in bronchial asthma)
8	ADDUCE	2010-2015	Investigate long-term adverse effects of methylphenidate on growth, neurological system, psychiatric states and cardiovascular system in children and adults
9	ENCCA	2011-2014	Establish European network for cancer research in children and adolescents, define research strategy facilitate clinical trials to introduce the new generation of biologically targeted drugs

Source: European Commission. CORDIS (Community Research and Development Information Centre) European R&D Projects funded under FP6 and FP. http://cordis.europa.eu/projects/home_en.html Accessed May 2, 2013.[74]

Annex 7.1.13: WHO/INRUD prescribing indicators by health facility ownership

Figure 4.6: WHOINRUD prescribing indicators by health facility ownership (prescribing by physicians, nurses, paramedics)

Indicator and category	Sample Size	Median	25th %ile	75th %ile
% Medicines from EML or Formulary				
Public	104	88.0	74.3	94.0
Private, for profit	19	52.6	38.0	67.0
Private, not for profit	8	77.0	58.9	84.0
% Medicines Prescribed by Generic Name				
Public	131	60.6	36.1	80.0
Private, for profit	24	13.3	7.8	50.4
Private, not for profit	10	62.5	52.0	75.5
% Patients with an Antibiotic Prescribed				
Public	223	48.4	37.0	57.1
Private, for profit	39	47.5	32.0	58.0
Private, not for profit	14	45.9	34.0	70.8
% Patients with Injection Prescribed				
Public	173	20.0	10.0	32.7
Private, for profit	34	19.4	7.0	38.0
Private, not for profit	11	37.0	19.0	63.1
% Treated According to Clinical Guidelines				
Public	146	39.3	21.5	59.0
Private, for profit	12	27.5	14.0	37.5
Private, not for profit	2	14.7	11.3	18.1
Average Number of Medicines per Patient				
Public	236	2.4	2.0	2.9
Private, for profit	51	3.0	2.4	3.7
Private, not for profit	14	3.0	2.4	3.3

WHO- World Health Organization, INRUD - International Network for the Rational Use of Drugs EML – Essential Medicines List

Source: World Health Organization. Medicines use in primary care in developing and transitional countries: Fact book summarizing results from studies reported between 1990 and 2006. WHO/EMP/MAR/2009.3. WHO Geneva, 2009. Available at: http://www.who.int/medicines/publications/primary_care_8April09.pdf. Accessed May 2, 2013.[120]

Annex 7.1.14: WHO/INRUD prescribing indicators by prescriber type

Indicator and category	Sample Size	Median	25th %ile	75th %ile
% Medicines from EML or Formulary				
MD	63	73.0	47.0	90.8
Paramedic or Nurse	86	87.4	68.0	94.0
Pharmacy Staff, Other, or Unspecified	20	64.5	44.0	83.0
% Medicines Prescribed by Generic Name				
MD	84	37.9	15.4	68.0
Paramedic or Nurse	100	64.4	49.3	80.8
Pharmacy Staff, Other, or Unspecified	15	48.0	36.0	71.6
% Patients with an Antibiotic Prescribed				
MD	134	48.6	30.6	62.3
Paramedic or Nurse	175	48.0	38.0	55.0
Pharmacy Staff, Other, or Unspecified	45	37.0	19.7	46.7
% Patients with Injection Prescribed				
MD	90	17.3	7.8	34.9
Paramedic or Nurse	161	21.9	11.0	34.1
Pharmacy Staff, Other, or Unspecified	31	23.0	11.0	30.0
% Treated According to Clinical Guidelines				
MD	42	37.2	19.5	51.6
Paramedic or Nurse	135	39.2	21.0	59.3
Pharmacy Staff, Other, or Unspecified	29	13.5	3.0	42.8
Average Number of Drugs per Patient				
MD	158	2.6	2.2	3.2
Paramedic or Nurse	180	2.4	2.0	3.2
Pharmacy Staff, Other, or Unspecified	45	2.2	1.4	2.8

WHO - World Health Organization, INRUD - International Network for the Rational Use of Drugs EML – Essential Medicines List

Source: World Health Organization. Medicines use in primary care in developing and transitional countries: Fact book summarizing results from studies reported between 1990 and 2006. WHO/EMP/MAR/2009.3. WHO Geneva, 2009. Available at: http://www.who.int/medicines/publications/primary_care_8April09.pdf. Accessed May 2, 2013.[120]