CHAPTER 2

The European Pediatric Regulation: will it provide children with the medicines they need?

Submitted

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ABSTRACT

The EU Pediatric Regulation requires the pharmaceutical industry to plan clinical trials in children at an early development stage in adults. The aim of this study was to evaluate whether this initiative is likely to provide medicines that children need. We evaluated the drug classes for which pediatric development was either agreed for development or was waived by the EMA from 2007 until March 2012. We questioned if the scope of drug classes for which pediatric development was agreed reflects trends in Dutch pediatric usage and availability data, the relative distribution of drug classes included in the EMA Pediatric Needs Lists, or drug expenditure data. Dutch pediatricians were asked if they perceived these pediatric medicines as being necessary. Allergens were excluded from the analysis. Approximately two-thirds of the medicines were agreed for pediatric development; deferral was granted for 83% percentage of these medicines. The majority of medicines agreed for pediatric development belonged to the drug class antineoplastic and immunomodulatory drugs, anti-infectives for systemic use, and drugs that act upon the blood and blood-forming organs. The majority of agreed research and development occurred for drug classes for which drug expenditure is currently high (which reflected extensive adult use). For these drug classes, there appeared to be relatively little need for research and development based upon Dutch pediatric usage and availability data or based on the EMA Needs Lists. Dutch physicians working in pediatric healthcare were not convinced that medicines for which pediatric development was agreed were needed for clinical practice. Given the substantial public health investment and the potential negative effects of the Regulation on research in areas with bona fide needs, key improvements in the Regulation's implementation are recommended in order the ensure that the Regulation provides children with medicines they actually need.

Introduction

The Pediatric Regulation, introduced by the European Medicines Agency (EMA) in early 2007, changed the European regulatory environment for the development of pediatric medicines. One of the Regulation's strategies is to require industry to plan clinical trials in children in an early stage during drug development in adults or in case a new indication, formulation or administration route is investigated for adults for on-patent medicines. Marketing authorization applications for this type of medicines must contain the results of all previous studies and information described in the company's pediatric investigation plan (PIP) previously agreed by EMA's Pediatric Committee (PDCO). Prior to the Regulation's implementation, the lack of appropriate pediatric formulations in a large number of therapeutic areas[1] was an important reason for off-label and unlicensed drug use and was a major obstacle to the study of drugs in children. This situation was complicated further by a general lack of overlap between areas in which pediatric drug research was conducted and both pediatric therapeutic needs[2] and pediatric disease burden[3]. The Regulation – which is based upon unmet pediatric needs and establishes clear obligations and a system of incentives aimed at pharmaceutical companies – was expected to result in research more focused on children's needs and to drive fundamental changes in therapeutic options for treating pediatric patients[2]. In addition, the Regulation was expected to provide early access to newer, safer, more targeted treatments[4,5], and to lead to more options in terms of age-appropriate formulation types[6].

In July 2012, the EMA submitted a five-year interim report to the European Commission[7] in which they reflected on the experience acquired as a result of the Regulation. From 2008 through 2011, 13 new medicines, 30 new indications, and 9 new formulations of existing medicines were authorized for use in children based on PIPs that were agreed by the PDCO. Importantly, some pediatric therapeutic areas that predominantly affect children had been neglected in terms of pharmaceutical research[7]. However, the assessment of concordance between agreed pediatric drug development and pediatric needs was limited to determining the number of development plans by therapeutic area covered by the planned indication. In addition, some important issues were not considered in the report, including the Regulation's impact on the development of age-appropriate formulations, despite the specific emphasis placed upon this aspect by the Regulation.

Therefore, the objective of our study was to determine in further detail whether the initiative is likely to provide medicines that children need. First, we determined the drug classes and age groups for which pediatric development was either agreed or waived by the PDCO from 2007 until March 2012. We also evaluated whether the scope of drug classes for which pediatric development was agreed matched the trends in Dutch pediatric pharmaco-epidemiological prescription and availability data or drug expenditure data. Finally, we evaluated whether Dutch pediatricians believe that pediatric medicines developed and researched under the Regulation are actually needed.

Methods

Drug classes with agreed or waived pediatric development

A publicly available database on the EMA website[8] was searched in March 2012 for PDCO opinions and EMA decisions on company proposals for PIPs, waivers or modifications for the pediatric development of active substances. The Regulation includes a system for waiving medicines that are unlikely to benefit children and for deferring the start or completion of measures in the PIP until after authorization for adults in order to ensure that medicines are tested in children only when safe and to prevent unnecessary delays in the authorization for adults. After the PDCO has agreed to the PIP, the PIP can be modified by the company at a later stage by adding new knowledge or if the company encounters difficulties with its implementation that render the plan untenable or no longer appropriate. In these situations, the company may propose changes to the PIP or may request a deferral or waiver – based on

specific grounds from the PDCO. The types of EMA decisions that are posted on the EMA website therefore include decisions that (1) agree on a PIP proposed by the company, either with or without a partial waiver and/or deferral ('P'); (2) grant a waiver proposed by the company in all age groups for the listed condition or conditions ('W'); (3) are based on an application by the company for modifying an agreed PIP ('PM'); (4) refer to a refusal of a PIP proposed by the company ('RP'); (5) refer to a refusal of a waiver requested by the company in all age groups for the listed condition or conditions ('RW'); and (6) refer to a refusal of an application by the company to modify an agreed PIP ('RPM'). In our analysis, active substances with one or more PIPs with a decision type P, PM, or RPM were considered as active substances for which pediatric development was agreed by the EMA (referred to hereafter as 'medicines with agreed pediatric development'). Active substances with one or more PIPs with a decision type W were considered as active substances for which the EMA agreed to waive pediatric development (referred to hereafter as 'medicines with waived pediatric development').

DATA RETRIEVAL

Data were extracted using a pre-established study database (in a Microsoft Excel workbook) and included PDCO decision number, active substance, condition, therapeutic area, pharmaceutical form(s), route(s) of administration, company name, decision type, the date of the initial decision or last updated decision in the case of a request for modification, the age range of the pediatric population covered by the PIP, the type and number of required studies, waiver type, deferral (yes or no), invented name (if available) and the PIP's expected completion date. The pharmaceutical forms under each PIP were categorized into: peroral, topical/transdermal, ocular, nasal, parenteral, auricular, rectal, pulmonary, and vaginal. The oral pharmaceutical form was further subdivided in: solution/drops, emulsion/suspension, powder/multiparticulate, tablet, chewable tablet, and capsule. The pediatric subset was categorized into: younger than 2 years of age (infants and toddlers), 2-11 years of age (children), and 12-18 years of age (adolescents). If the researched age range included ages that fell within a specific age subgroup, this subgroup was listed as 'yes'.

ATC CODE ASSIGNMENT

Generic names of active substances in the study database were searched in a searchable version of the World Health Organization Collaborating Centers (WHOCC) database[9]. If the generic name was not included in the PIP, Thomson Reuters' Integrity database[10] was searched for this information. The WHO Anatomical Therapeutic Chemical (ATC) Classification anatomical main group and therapeutic subgroup retrieved from the WHOCC database (2013) were added to each active substance in the study database using a standardized approach. Medicinal products are classified according to the main therapeutic use of the main active ingredient, on the basic principle of only one ATC code for each route of administration. For active substances with only one entry in the WHOCC database, this unique ATC code was included in the study database. A medicinal product can be given more than one ATC code if it is available in two or more strengths or administration routes with clearly different therapeutic uses. Pharmaceutical forms for topical and systemic use are also given separate ATC codes. For active substances with multiple entries in the WHOCC database, planned pediatric indication and formulation were taken into account while choosing the most appropriate code. Combination products contain two or more active ingredients. Fixed combination products (e.g., amlodipine/valsartan) have a unique ATC code. For other ATC combination levels, not all active ingredients are searchable in the WHOCC database, but ATC code is based on the code of the main ingredient. Unique ATC codes for combination products in the study database were added if present. If no unique ATC code could be identified, general WHO guidelines were followed, i.e., different combination products sharing the same main active ingredient are usually given the same ATC, or the ATC code of the main ingredient was included (as the classification of combination products is decided by the main therapeutic use).

The ATC code for combination products and active substances with multiple entries in the WHOCC database were assigned based on the consensus of two researchers (authors A.D.M. and L.S.). For active substances that did not have an entry in the WHO database, the temporary ATC code given at the 2013 meeting of the WHO International Working Group for Drug Statistics Methodology[11]

was used if available. For the remaining substances, a 'fictitious' ATC code was assigned based on the ATC of a reference drug with the same target and indication (if available) or based on the drug target, therapeutic group, product class listed in the Thomson Reuters' Integrity database[10] (accessed in March 2014), or indication. For these active substances, an additional pharmacist (author R.R.) reviewed all of the collected data and the ATC proposed by the first two authors and provided input; based on this input, a final ATC was chosen.

DATA MERGING

Pediatric development was analyzed for each active substance. All of the data from various PIPs for a given active substance were merged, except for allergen products. PIPs for allergen products were left out of the analysis, as the information in the Decisions and Opinions was not specific enough to distinguish different active substances or pediatric development. For all other active substances, if a therapeutic area was addressed by multiple indications for a given active substance, it was considered only once in the analysis. If the same formulation type was considered in multiple PIPs, it was counted only once. If the pharmaceutical form in the PIP was intended for several administration routes, was constituted in several different ways, or if the pharmaceutical form was packaged in several different delivery devices, the pharmaceutical form was counted twice.

The EMA's online database includes several duplicate applications that share pediatric development. EMA decisions can be split or merged, and until 2010, duplicate applications could be submitted by a company for a given active substance that had—or planned to have—more than one marketing authorization and for which the scope of the development was the same (e.g., the same conditions, route of administration, and/or formulation). For example, one marketing authorization holder can have two or more authorizations in order to have different trade names, and two pharmaceutical companies can be joint holds of a global marketing authorization. The EMA database also holds 'temporal' duplicate applications (e.g., an EMA decision regarding a refused waiver for a particular active substance that is later followed by an agreed PIP for the same indication). Currently, duplicate PIPs are not identified on the EMA website. Because duplicate PIPs share a single pediatric development, all PIPs were checked manually for duplicate status (by reviewing the conditions, subset of the relevant pediatric population, administration route, formulation, and agreed studies). In the event of a duplicate application, only one PIP was considered in our analysis. In the event of a temporal duplicate (waiver followed by agreed PIP for same indication), only the EMA's most recent decision was included in the analysis. The input from the EMA was sought in case of unclarity regarding duplicate status.

DATA ASSESSMENT

All medicines for which pediatric development had been agreed and all active substances for which development was waived were listed according to drug classes and therapeutic subgroups. The number of formulation types and number of formulations were assessed by drug class.

Drug classes with an established or potential pediatric need

Data extracted from the EMA Pediatric Needs Lists[12] (published through July 2012) included the active substance, therapeutic area, authorized indication, and specified needs. Needs were categorized as 'formulation only' (research need for an age-appropriate or disease-appropriate formulation only), 'pediatric studies only' (only need to expand the indication to other indications or age groups, need for study, or definition of age limit), or 'full pediatric development' (the need for age-appropriate formulations and studies). Medicines for which there was only a need for the availability of the indication or age-appropriate formulation in all EU member states were not included in the analysis. Medicines were listed by drug class and evaluated for their specified needs type.

Trends in the prevalence of drug use in Dutch children

Data were obtained from the PHARMO Database Network, a population-based network of healthcare databases that combines data from various healthcare settings within the Netherlands. These data sources are linked on a patient level using validated algorithms[13–15]. For this study, drug dispensing data from 2005 through 2011 extracted from the PHARMO Out-patient Pharmacy Database were used. The Out-patient Pharmacy Database includes healthcare products prescribed by a general practitioner or specialist and dispensed by an out-patient pharmacy (coded according to the WHO ATC Classification System). The dispensing records include the type of product, date, strength, dosing regimen, quantity, route of administration, the prescriber's specialty, and the cost. Within each year from 2005 through 2011, a separate patient selection was performed; accordingly, we selected all children who were 0-18 years of age in a given calendar year and had at least one drug dispensed from the PHARMO out-patient pharmacy database (excluding vitamin K, as this is given to all children who are breast-fed)[16]. For each calendar year, age was assessed by subtracting the year of birth from the calendar year. Patients were grouped into specific age groups (see above). For each year in the study period, the number of children for whom any drug was dispensed was measured and then extrapolated to the general population of the Netherlands. Specifically, we multiplied the number of children counted by the number of inhabitants in the Netherlands; we then divided by the number of residents in the PHARMO catchment area (standardized for calendar year, age, and gender). Prevalence of use was reported per 10,000 children and was stratified by calendar year and age group. In addition, we counted and extrapolated the number of children for whom different anatomical classes of the ATC classification scheme (first level ATC code) were dispensed.

Trends in Dutch pharmaceutical expenditure

Drug volume consumed and drug prices for the years 2007 through 2011 were extracted by drug class from the GIP (*Genees- en hulpmiddelen Informatie Project*; in English: the Medicines and Aiding Devices Information Project) databank[17], an information system used by the Dutch Healthcare Insurance Board. Drug classes were listed by expenditure data (both overall and per user).

Survey of Dutch physicians working with children

All medicines for which a development plan was agreed by March 2012 were listed by EMA therapeutic area using an online survey that included information regarding agreed clinical studies in children. Fifty medical specialists and residents in the fields of pediatrics or child and adolescent psychiatry completed one or more surveys in which they were asked to indicate whether they need the medicine in their practice ('yes' or 'no'); if 'yes', would they (intend to) use the drug in their practice for treating the study population described in the clinical study and do they find the information obtained from the trials useful; if 'yes', would they prescribe the medicine.

Data analysis

Descriptive data were analyzed using Microsoft Excel 2007. Data from the PHARMO Database Network were analyzed using SAS programs organized within SAS Enterprise Guide version 4.3 (SAS Institute Inc., Cary, NC, USA) and conducted under UNIX using SAS version 9.2.

Results

Research and development under the Pediatric Regulation

765 EMA decisions were extracted from the EMA database, of which 117 decisions concerned allergens (which were excluded from the analysis). Of the remaining decisions, 9% were (temporal) duplicates. Thus, a total of 590 EMA decisions were included in our analysis. Consensus regarding ATC was reached

for anatomical main group for each medicine that did not have a unique entry in the WHOCC database. For two medicines (Eritoran and Clazosentan), no therapeutic subgroup could be assigned.

Pediatric development was agreed for 358 medicines and waived for 173 medicines (Figure 1). Antibacterials for systemic use, antihemorrhagic agents, antineoplastic agents, drugs used in diabetes, immunosuppressants, systemic antivirals, and vaccines accounted for half of all medicines for which pediatric development was agreed. In all drug classes, fewer medicines were researched in infants and toddlers than in older age groups, with the exception of antiparasitic agents, which was an extremely small drug class in the analysis. Medicines were researched at the same frequency in children and adolescents for nearly all drug classes, with the exception of drugs that act on genitourinary system and sex hormones, which were studied more frequently in adolescents. Deferral of one of the measures described in the PIP was granted for 83% of medicines with agreed pediatric development.

The majority of medicines were formulated for parenteral (48%) or oral (43%) use (allergens not considered). Oral formulation types are shown in Figure 2. Multiple dosage formulations were listed for 124 medicines, covering a range of 2-7 dosage formulations. Age-appropriate formulations were considered for 210 medicines for infants and toddlers, for 327 medicines for young children 327, and for 331 medicines for adolescents.

Drug classes with an established or potential pediatric need

A total of 323 active substances in 51 different therapeutic subgroups had a recognized need for pediatric research or development; full pediatric development was indicated for half of these active substances (Figure 3). Drugs used in diabetes, drugs for cardiac therapy, antineoplastic agents, immunosuppressants, anesthetics, analgesics, antiepileptics, psycholeptics and drugs for obstructive airway disease accounted for half of all medicines for which a need for pediatric research or development was recognized.

Trends in the prevalence of drug use in Dutch children

From 2005 through 2011, the prevalence of using any medicine was highest among adolescents, infants, and toddlers. Whereas the prevalence increased in adolescents, the use of medicines in infants and toddlers decreased after 2008. Use in children remained relatively stable in any calendar year after an initial increase from 2005 to 2006. The prevalence of medication use per age group is shown in Figure 4.

Trends in pharmaceutical expenditure data

Pharmaceutical expenditure for all drug classes was generally stable in the Netherlands from 2007 through 2011. Notable exceptions included a clear decrease in the cost of cardiovascular drugs, a clear increase in the cost of antineoplastic and immunomodulating drugs, and varying costs for neurological agents and drugs that act on the alimentary tract. The per-user and the total (volume times per-user) costs are shown in Figure 5.

Survey of Dutch physicians working with children

The majority of respondents (19 out of 32 who provided basic information) worked (at least part-time) at a non-academic center. The survey related to ophthalmology was the only one not completed once. Incomplete surveys included surveys with a large number of medicines, for example the survey related to cardiovascular disease. Surveys completed by at least 10% of respondents included those related to neonatology/pediatric intensive care, cardiovascular diseases, diagnostics, anesthesiology, and pain. These surveys included a total of 36 different active substances, five of which (chloroprocaine, perflubutane, fentanyl citrate, morphine, and dopamine) were perceived as useful by all respondents. In most cases, if the respondents identified the medicine as being useful, they also found research to be useful and would use the

medicine in clinical practice. Another 13 active substances were perceived as not useful by all of the respondents for the proposed indication, nearly all of which were listed for treating cardiovascular disease.

Discussion

More than five years have passed since the Pediatric Regulation was implemented; in this period, the EU budget's contribution to operational costs totaled more than 39 million euros, in addition to the contribution of resources in-kind by European national competent authorities[18]. Despite this substantial public health investment, it is unlikely that (future) pediatric authorizations will be focused more on pediatric needs. Drug classes and therapeutic subgroups with a high need for pediatric research and development on the EMA Needs Lists (including drugs that act on the cardiovascular or nervous system and drugs for treating obstructive airway disease) or for which a pressing pediatric need has been expressed in the literature (e.g., ophthalmological agents[19]) are either researched rarely or often waived from pediatric development. In addition, despite the diversity of therapeutic subclasses listed on the Needs Lists, pediatric research agreed under the Regulation was dominated by seven therapeutic subgroups (allergens not considered).

Ideally, drug research in children should be prioritized based on current trends in medication use[20] and frequent pediatric use of medicines that are not readily available or age-appropriate may indicate an important unmet pediatric need[1]. Our analysis of Dutch outpatient pediatric use revealed that the use of any medicine was highest among Dutch adolescents, infants, and toddlers, which suggests a shift in the highest use of medication towards adolescents, as previous studies found the highest prevalence of medication use among younger children[16,21]. Consistent with this notion, adolescents were rarely waived from pediatric development under the Regulation. In 2009, the percentage of medicines that were authorized and commercially available for use in Dutch children was highest for anti-infectives, respiratory drugs, and antiparasitic agents, and lowest for genitourinary drugs, sex hormones, dermatologicals, and cardiovascular drugs[1]. Although future studies should attempt to determine whether the low availability of these drug classes for children is a problem in clinical practice[1], combining these availability data with our outpatient usage data suggests the possible presence of an unmet pediatric need for research and development of dermatological agents in all ages and genitourinary drugs and sex hormones in adolescents; although these medicines are frequently prescribed to these age groups, they are not always readily available. Unfortunately, these drug classes are researched relatively rarely under the Regulation. Based on prescription and availability data, there is no apparent pediatric need for anti-infectives (which are prescribed frequently and are readily available), a drug class that is researched frequently under the Regulation. However, current availability data may not be the best indicator of the potential need for anti-infectives, as the need for drug availability may exceed regulations in the near future due to microbial (antibiotic resistance) and viral (pandemic flu) threats. Therefore, the development of new anti-infectives for use in children should not lag behind the development for use in adults.

The need to develop more age-appropriate formulations for younger age groups[1] appears to be addressed by the Regulation, as infants and toddlers are considered with respect to more than 200 medicines. In contrast to expectations[6], in most cases only one formulation type will be developed. Despite the inclusion of younger age groups, there seems to be no shift in the types of formulations that may be available for children following the implementation of the Regulation; similar to the situation in 2009[1], most pediatric medicines that are developed are intended for oral (mostly tablets) or parenteral administration.

The Regulation may lead to newer, safer, or more targeted treatments, as our study database included several novel drug types which may also become available for use in children, including tissue transglutaminase inhibitors[22], soluble guanylate cyclase activators[23], and toll-like receptor 4 receptor antagonists[24]. In addition, several protein-based drugs have agreed pediatric

development plans and may provide additional options for meeting unmet pediatric needs[25]. It remains to be seen whether these drugs will be developed successfully for children, as some developments have already been discontinued[10]. In addition, as more than 80% of the medicines in our database had at least one deferred measure in the agreed development plans, children are likely to have late rather than early access to new medicines. As a result, it is possible that no effect of the Regulation will be seen regarding the total off-label use in the pediatric population – even though this is one of the Regulation's intended aims – as has been demonstrated for triptans, which were labeled for pediatric use with delay; pediatric treatment remained dominated by off-label use, despite labeling the product in an age-appropriate formulation for the most relevant age group[26].

Finally, relatively few medicines in the fields of neonatology/pediatric intensive care, cardiovascular disease, diagnostics, pain, and anesthesiology were considered to be needed by a small contingent of Dutch physicians working in pediatric healthcare.

It is not surprising that the drug classes in our evaluation with the lowest number of medicines with agreed pediatric development have the lowest pharmaceutical expenditure. Under the Regulation, only medicines for which the adult indication also exists in children and for which no important reason exists to waive pediatric development will be considered for pediatric development. It has been argued that many children are denied access to innovative medicines because of this 'adult-driven' approach, for example in the field of oncology[27]. It has therefore been argued that implementation of the Regulation should be guided instead by the biology of pediatric tumors and the medicine's mechanism of action. We argue that this approach should be expanded beyond pediatric oncology, as this approach is relevant to other therapeutic areas as well. Indeed, in a recent publication, the PDCO explained that it tends to ask for research based on the medicine's mechanism of action[28]. However, whether this request for additional research will be voluntary or mandatory is currently unclear. In addition, new incentives should be considered for first-in-children indications.

It should be noted that our evaluation was limited by the cross-sectional nature of the collected data, as agreed PIPS may have been modified after our search. In addition, some data in the EMA database cannot be readily used for scientific analyses such as our study. For example, although duplicate applications and shared pediatric development among PIPS cannot be identified easily, this information is important for reliably assessing the impact of the Regulation on pediatric research and development. Our evaluation of the perceived usefulness of medicines researched under the Regulation among Dutch physicians working in pediatric healthcare should be regarded as preliminary, as it included fifty physicians only. In addition, it may be valuable to evaluate the perceived usefulness in expert groups as well.

In conclusion, progress has been made regarding the (planned) inclusion of adolescents in pediatric research and the development of more age-appropriate formulations for younger age groups. However, the Regulation's key strategy does not necessarily lead to the increased pediatric development of drug classes for which there may be a unmet pediatric need and physicians are unlikely to have more options in terms of formulation types for the majority of pediatric medicines. Instead, the Regulation's output is in line with expenditure data, most likely as a result of the 'adult-driven' approach. Pediatric research in actual needs areas may be hampered as a result of the Regulation, as the number of agreed pediatric development plans is high and the number of children available for research is low. Given the substantial public health investment and the potential negative effects of the Regulation on research in actual needs areas, important refinements in implementation are needed in order to ensure that the Regulation will provide children with the medicines they actually need.

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FIGURE 1 Number of active substances per drug class for which pediatric research and development was agreed (with or without deferral of one of the measures in at least one development plan) or waived under the Pediatric Regulation, based on published EMA decisions through March 2012. Octocog alfa (B02), cyclosporin (S01), budesonide (R03), ulipristal acetate (G03), everolimus (L01, L04), and afamelanotide (D02) had agreed as well as waived pediatric development plans. Antineoplastic agents, immunosuppressants, antihemorrhagic drugs, antiviral agents for systemic use, and vaccines were the largest therapeutic subgroups for which pediatric development was agreed (each subgroup contained >20 active substances). In the main drug classes for which pediatric development was waived, drugs that act on the renin-angiotensin system, lipid-modifying drugs, antineoplastic drugs, drugs used in diabetes, sex hormones and modulators of the genital system, and ophthalmological drugs were the largest therapeutic subgroups (each subgroup contained >10 active substances).

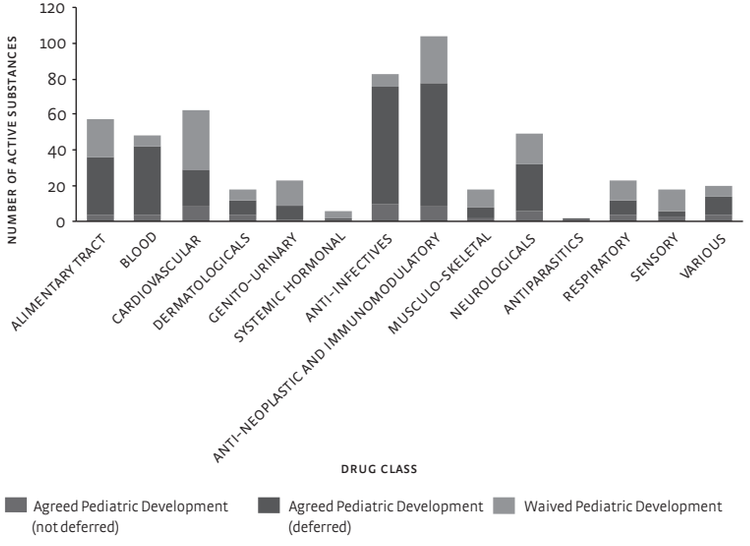

FIGURE 2 Oral formulation types developed or researched under the Pediatric Regulation, based on published EMA decisions through March 2012.

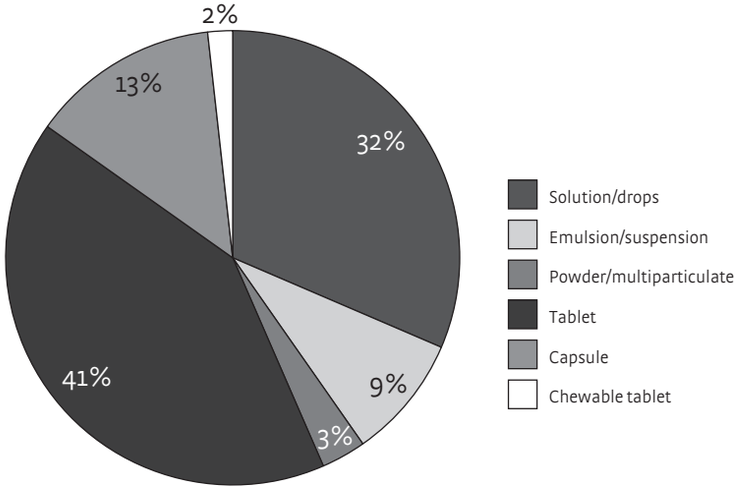

FIGURE 3 Number of active substances per drug class listed in the Pediatric Needs Lists published through July 2012 for which a pediatric need for research was indicated. For three neurological agents, no specific need was specified on the Neurology Needs List. Drugs that act on the sensory organs were not included in any of the Pediatric Needs Lists. Drugs that act on the sensory organs were not included in any of the Pediatric Needs Lists. Most of the active substances with a need for pediatric research or development were drugs used in patients with diabetes, antithrombic agents, cardiac therapy drugs, diuretics, anti-viral agents for systemic use, antineoplastic agents, immunosuppressants, anesthetics, analgesics, anti-epileptics, psycholeptic agents, and drugs for treating obstructive airway disease (each therapeutic subgroup contained 10-38 active substances).

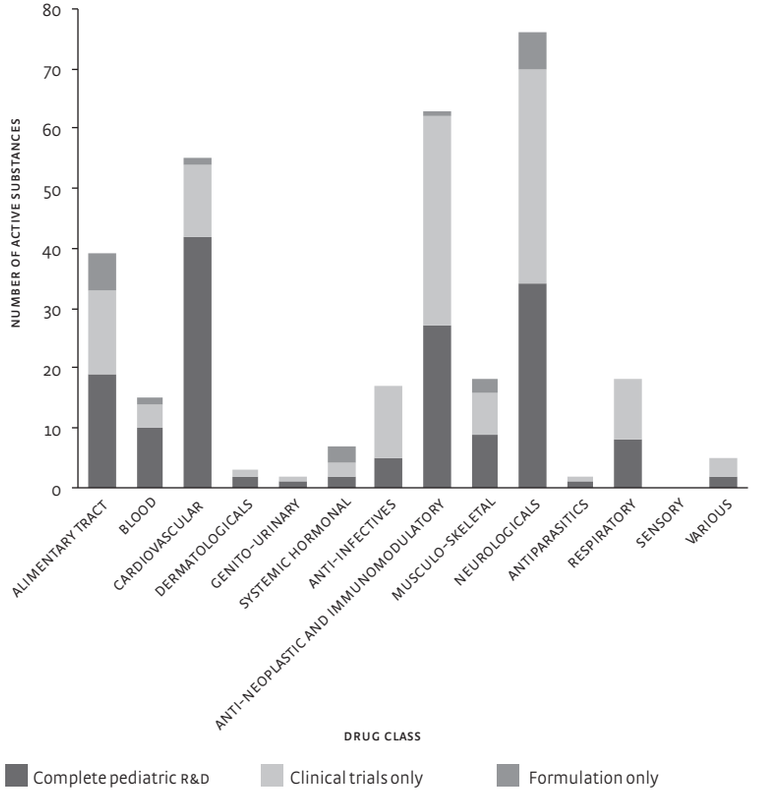

FIGURE 4 Average number of users per 10,000 children by anatomical class and age group from 2005 through 2011. In all pediatric age groups, the most frequently used medications were drugs that act on the alimentary tract, dermatologicals, anti-infectives for systemic use, and respiratory drugs. With respect to infants and toddlers, drugs that act on the sensory organs were also used frequently; among adolescents, drugs that act on the genitourinary system and sex hormones were used frequently (predominantly among females). In all pediatric age groups, a decrease in prevalence was observed with respect to the use of anti-infectives, and an increase in prevalence was observed with respect to drugs that act the alimentary tract and dermatological agents. Among children and adolescents, an increase in the use of neurological agents was observed, with the largest increase among antidepressants (including antidepressants combined with psycholeptics) and stimulants. Among adolescents, an increase in the use of respiratory drugs and drugs that act on the genitourinary system was also observed.

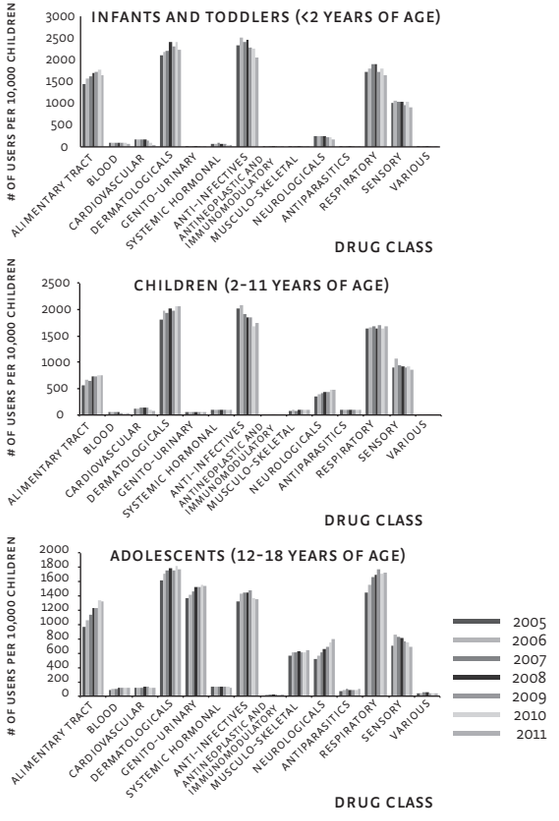

FIGURE 5 Total pharmaceutical expenditure data of active substances per drug class from 2007 through 2011; data were retrieved from the GIP databank and are expressed as the fraction of total costs of all drug classes for overall medicinal costs (total medicinal costs) and per user (individual medicinal costs).