Pediatr Drugs (2017) 19:515–522
DOI 10.1007/s40272-017-0260-2

CURRENT OPINION

Do Paediatric Investigation Plans (PIPs) Advance Paediatric Healthcare?

Klaus Rose[1] · **Philip D. Walson**[2,3]

Published online: 9 September 2017

Abstract Since 2007, new drugs need a paediatric investigation plan (PIP) for EU registration. The PIPs' justifications can be traced back to concerns expressed by Shirkey that label warnings against paediatric use made children "therapeutic orphans", and the American Academy of Pediatrics' claim that all children differ considerably from adults. US legislation first encouraged, then also required, separate, adult-style safety and efficacy studies in all paediatric subpopulations. This triggered paediatric regulatory studies by the pharmaceutical industry. There were also negative outcomes, as a result of using the legal definition of childhood as a medical/physiological term. The "therapeutic orphans" concept became dogma that supported/expanded adult-style regulatory testing into all age groups even when poorly justified in adolescents or where other methods are available to generate needed data. PIPs are especially problematic because they lack the limitations imposed on the Food and Drug Administration's (FDA's) regulatory actions and more practical approaches used in the USA. Many PIP studies are medically senseless or even questionable and/or unfeasible with poor risk/benefit ratios. For example, physiologically mature adolescents have been exposed to treatments and doses known to be suboptimal in adults. Unfeasible PIP studies in rare diseases may harm patients by preventing their participation in more beneficence-driven studies. PIP-required studies can prevent effective treatment of allergic rhinitis during years of placebo treatment, exposing minors to the risk of disease progression to asthma. The PIP system should be revised; more should be done by key players, including institutional review boards/ethics committees, to ensure that all paediatric clinical studies are medically justified, rather than legislation driven, and can produce scientifically valid results.

Key Points

The "therapeutic orphans" dogma has had negative as well as positive effects.

Some paediatric studies required to market drugs are impractical, scientifically unjustified, or ethically questionable.

The methods designed and used to test new drugs in adults may not be appropriate or even needed in all minors in order to enable the safe and effective treatment of children and adolescents.

1 Introduction

Since 2007, when the European Union (EU) paediatric legislation came into force [1], new drugs need a paediatric investigation plan (PIP) accepted by the European Medicines Agency's (EMA's) Paediatric Committee (PDCO) for registration [2, 3]. PIPs must discuss the adult disease, its counterparts in children, and "propose" child-friendly formulations (e.g., syrup), juvenile animal studies, clinical studies, and more [1–3]. The aim of this article is to

✉ Klaus Rose
klaus.rose@klausrose.net

[1] klausrose Consulting, Pediatric Drug Development and More, Aeussere Baselstrasse 308, 4125 Riehen, Switzerland

[2] Walson Consulting, LLC, Seattle, Washington, USA

[3] Department of Clinical Pharmacology, University Medical Center, Göttingen, Germany

critically evaluate how well the EU paediatric legislation is achieving the stated goal of the PIP system: "to improve the health of the children of Europe" [3]. We analyzed the intellectual roots of the US paediatric legislation [4, 5], which preceded the EU legislation, especially key publications by Shirkey [6] and statements by the American Academy of Pediatrics (AAP) [7, 8], then analyzed the EU paediatric legislation (EUPL), PIP decisions and decision patterns for their effects on paediatric healthcare.

2 Children as "Therapeutic Orphans"

Since the 1962 amendments to the US pharmaceutical law, drugs have needed proof of safety and efficacy (S&E) from clinical studies [4, 5]. These amendments were introduced in response to the thalidomide catastrophe. Gradually, most countries introduced comparable legislation. Regulatory authorities became a third pillar of the healthcare system, alongside the medical profession and industry. To avoid liability lawsuits, manufacturers emphasized whenever their respective drug had not been investigated in children. Shirkey in 1963 concluded that this denied children the use of new medications and made them "therapeutic orphans" [6]. The AAP took up Shirkey's concerns. It stated in 1977 that use of drugs not labeled for children created a dilemma for physicians—avoid them and deprive children of potential benefits, or prescribe them despite the lack of Food and Drug Administration (FDA) certification for children—and that it was "unethical to adhere to a system which forces physicians to use therapeutic agents in an uncontrolled experimental situation virtually every time they prescribe for children" [7]. In 1995 AAP claimed, "There is a moral imperative to formally study drugs in children so that they can enjoy equal access to existing as well as new therapeutic agents" [8], that "When drugs have been administered to children without sufficient pharmacology studies to identify the optimal therapeutic approach, children have occasionally suffered severe toxic effects, including death" [8], and "Growth, differentiation, and maturation can alter the kinetics, end organ responses, and toxicities of drugs in the newborn, infant, child, or adolescent as compared to the adult" [8].

In fact the 1962 US pharmaceutical law did not distinguish between children and adults; it addressed "human beings" [4, 5]. Paediatric disclaimers had limited legal weight. They protected manufacturers in lawsuits and were sometimes used by insurance companies as a reason to not pay, but neither labels nor the FDA could forbid the drugs' use in children [9]. Drugs with paediatric disclaimers could not be advertised for children because after 1962 the FDA controlled drug advertising [10]. Shirkey's claim that children were denied the use of many new drugs was misleading: the 1962 amendments did not specifically restrict drug use in children [9] and the AAP's 1977 warning about toxic effects and death (repeated in 2010 [11]) referenced only two publications on antibiotics in *premature babies* [8]. These publications did not prove there were different "kinetics, end organ responses, and toxicities of drugs" in *all age groups*.

In fact, AAP documents on off-label use emphasized repeatedly physicians' right to prescribe what helped. The AAP supported knowledge-based, off-label treatment of children: "Evidence, not label indication, remains the gold standard from which practitioners should draw when making therapeutic decisions for their patients" [12]. Yet the AAP also saw paediatric labels as the path towards optimal clinical care for children.

Additionally, both Shirkey and the AAP used "children" in its contemporary sense, i.e., persons below the age of majority. There was a lack of appreciation that a legal rather than a physiological definition for "children" was used. Endorsed and amplified by AAP statements that toxicity and death are risked by treatment of those who are legally minors, the "therapeutic orphans" concept resulted in the AAP and FDA concluding that minors needed separate proof of S&E studies. This has contributed to the development of paediatric clinical pharmacology, to US paediatric pharmaceutical legislation, and other positive outcomes, but has also become a dogma that needs critical reassessment.

3 Progress in Child Healthcare and Labels

Many diseases with high under-five mortality were gradually prevented by vaccination, better housing, sanitation, nutrition and other improvements; others became treatable. Paediatric oncology evolved with systematic use and investigation of adult cytotoxics in children [13, 14]. It did not focus on labels. Many paediatric subspecialties successfully used new drugs when they became available, including neonatology [15] and paediatric cardiology [16]. Children were not "therapeutic orphans". The call for them to benefit more from pharmaceutical progress is justified and well-intended, but real-world observations show that their healthcare is not necessarily or exclusively linked to paediatric labels.

4 Paediatric Clinical Pharmacology, US Paediatric Legislation, and the FDA

Absorption, distribution, metabolism and excretion (ADME) are clearly different in newborns and infants [17]. Since 1997 US paediatric legislation has offered patent extension in exchange for doing FDA-requested (usually industry-suggested) paediatric studies. This resulted in

many regulatory paediatric studies done by industry [2, 18]. However, the ADME differences between adults and children are most pronounced in newborns and infants; differences become less with increasing age [17]. The upper age limit for "children" for the FDA is 16 years. In 2014 the FDA explained its current view of evidence needed for paediatric labeling [19]: (1) paediatric clinical studies in an indication different from the adult one; (2) paediatric studies in the same indication as the adult one; and (3) adult studies plus additional information in the specific paediatric population. Point (3) is a departure from the therapeutic orphans dogma. Indeed, in 2016 the FDA expanded the indication for partial onset seizures for antiepileptic drugs down to 4 years [20], in 2017 it approved avelumab down to 12 years, based on only additional population pharmacokinetic (PK) data [21], and recently approved ivacaftor for further cystic fibrosis mutations, based only on in vitro studies [22].

5 EU Views of Off-Label Use

Some European publications on paediatric off-label use were pragmatic [23], some conceded that adverse drug reactions might be balanced by increased therapeutic efficacy [24], and some were accusatory, e.g., "Children and infants deserve the same right to treatment as adults" [25]. The latter was not supported by data, but was based on a *moral argument*, similar to the AAP's 1995 statement [8].

5.1 EU Debate and Paediatric Legislation

A 1998 EMA report warned that a "lack of appropriate dosage recommendations for children" resulted in frequent off-label use in children [26]. But paediatric dosing recommendations *did* exist. Paediatricians and physicians were trained to use them. Children were treated based on their doctors' best knowledge and opinion. Adjustment of practice in the light of new findings is a normal process in medicine. But instead *regulatory* studies in children of all age groups were required [27], without differentiating between subpopulations or considering whether studies mirroring those for adult approval are necessary for all minors.

A 2004 EMA paper characterized off-label use in children as dangerous without mentioning paediatric oncology, neonatology, other paediatric subspecialties, or differentiating between beneficial and potentially dangerous off-label use [28]. The EU arguments were and are formal, often biased and ignore many pathways of knowledge transfer. Physicians first study and receive clinical training, then gain experience through patient care and continuing medical education. The clinical impact of drug labels depends on physician and setting. Paediatric oncology and neonatology are practiced in specialized centers where label changes will change little. In contrast, label changes can be expected to impact general practitioners more.

5.2 The EU Law

Recital 3 and the definition of the "paediatric population" in article 2(1) of the EUPL are shown in Table 1. These reflect AAP statements discussed above, and do not differentiate between paediatric subpopulations. Not all minors below their 18th birthday need separate adult-style S&E studies. The 18th birthday is a legal, not a physiological border.

5.3 Positive Impact of PIPs, and PIP Shortcomings

US and EU paediatric legislation have both improved understanding of and support for paediatric studies in academia, industry, regulatory bodies, governments and the public. This has increased the number of investigators, industry experts, regulators, legislators, parents and patients who are interested in as well as capable of making meaningful contributions to our understanding of what studies need to be done and how better to do them.

Some examples of problematic outcomes of the PIP system follow.

5.3.1 PIP-Required Clinical Studies

PIPs are required at the end of phase 1, when no efficacy data exist yet. PIPs must address the targeted adult disease, corresponding childhood diseases, and "propose" juvenile

Table 1 EUPL recital 3 and article 2(1)

Recital 3	Problems resulting from the absence of suitably adapted medicinal products for the paediatric population include inadequate dosage information which leads to increased risks of adverse reactions including death, ineffective treatment through under-dosage, non-availability to the paediatric population of therapeutic advances, suitable formulations and routes of administration, as well as use of magistral or officinal formulations to treat the paediatric population which may be of poor quality
Article 2(1)	'Paediatric population' means that part of the population aged between birth and 18 years

animal studies, formulation development (e.g., syrup), clinical studies, and more [3]. PIPs do not prioritize even when multiple drugs are being developed for the same adult disease that has a vanishingly low incidence in children. The feasibility of any single drug's PIP is based on the assumption that the entire paediatric population with a given disease would be available to recruit for that drug. Studies of other drugs being studied or even already approved in other countries for the same disease or indication are not considered. The EMA PDCO decides about PIPs even though final authority about drug registration rests with another EMA committee. If the PDCO judges "proposals" to be insufficient, the PIP is rejected and adult approval is blocked. Thus, sponsors can be pressured to make study "proposals" that they feel are impractical, unnecessary or even undoable. The system rewards "proposing" such studies with permission to proceed with drug development, while discouraging reasoned dissent. PIP decisions are published on the EMA website and can be googled using the PIP number. The PIP system requires studies in the "paediatric population" (Table 1, [1]) that mirror adult registration studies.

5.3.2 *Questionable Studies in Adolescents*

PIPs routinely require S&E studies either in adolescents alone or in both adolescents and children.

Several PIPs request studies in "children" between the body's maturity and 18th birthday, maturity being defined by sexual puberty or by closure of the growth plates:

- EMEA-001264-PIP01-12 (chondrocytes for joint repair) requires a study in children between closure of growth plates and the 18th birthday.
- EMEA-000250-PIP01-08-M02 and EMEA-000658-PIP01-09 (contraceptives) require PK comparisons between young women after menarche and before their 18th birthday versus women 18–50 years old.
- EMEA-001492-PIP01-13 (trifarotene, anti-acne) requires one study of different trifarotene concentrations versus placebo in "children" versus adults, and one of trifarotene versus vehicle, again in "children" versus adults; "children" are defined as "from puberty to less than 18 years of age".

Clinical studies in older adolescents or young adults can make sense, such as studies of some psychiatric drugs, but they need not be done exclusively in adolescents, or they could be done using opportunistic study designs. However, the examples above and studies that include doses already shown to be sub-therapeutic in young adults (see Sect. 5.3.3) are unlikely to produce therapeutically relevant findings and could be considered unethical [29].

5.3.3 *Unfeasible Studies*

In 2007 the EMA established a list of PIP-exempted diseases ("class waivers"). These were diseases where paediatric studies were judged to be either unfeasible or unnecessary. Some waivers were soon revoked [30], including for melanoma in children >12 years of age, resulting in the initiation of unfeasible studies. The EMA claimed that enough adolescents with melanoma exist for clinical trials. Twelve melanoma PIP trials were approved [31]. Six company-sponsored international studies were initiated either for minors only with melanoma or with one of a number of malignant tumors including melanoma [31–37]. Two were terminated in 2016 due to slow recruitment [31–33]; four are ongoing [31, 34–37]. Six adolescents with metastasized melanoma were enrolled in a vemurafenib "dose escalation" trial that included treatment below the FDA-approved dose [31, 32].

PIPs routinely require paediatric studies for all new compounds that target predominantly adult diseases; even when the diseases only very rarely occur in minors. In addition to melanoma [31, 38, 39], the same approach has been used for leukemia subtypes [14], multiple sclerosis [40] and psoriasis [41]. In 2015 the EMA again revised its class waivers, making PIPs mandatory for diseases even more rare in children, including liver cancer [42].

5.3.4 *Questionable Trials in a Frequent Disease*

Based on a standard allergen PIP developed by the EMA and the Paul-Ehrlich-Institute, 58 double-blind, 5-year, placebo-controlled studies of specific immunotherapy (SIT) should enroll many thousands of children and adolescents with allergic rhinitis into PIP-required studies scheduled until the end of 2031. These PIP-required studies would prevent effective treatment of allergic rhinitis during years of placebo treatment, exposing some minors to progression of disease to asthma as a result of the "atopic march" [43]. Switzerland, however, simply allowed retroactive approval of SIT allergens [44].

5.3.5 *The EMA's 10-Year Paediatric Reported "Successes"*

The "successes" mentioned in this report [45] are misleading at best. The "increasing numbers of medicines becoming available to children" (page 4 of the report) refers to the number of drugs with new paediatric labels rather than to drugs made available by the EUPL. The higher percentage of trials that include children is also given as evidence of success (Figure 2 on page 6 of the report), irrespective of what percentage of trials failed to produce meaningful data or whether or not the trials made

scientific or clinical sense. Some of the successes listed are of limited clinical importance. For example, two oncology "successes" are reported: a new asparaginase now "available" for acute lymphoblastic leukemia (ALL), and dinutuximab for neuroblastoma. ALL has been successfully treated for decades using asparaginase-containing regimens, with survival rates approaching 90%. Asparaginase was available for adults and children without a PIP. Additionally, neuroblastoma occurs only in paediatric patients. Dinutuximab did not need a PIP to be developed. In the USA, for example, studies of new oncology drugs are approved only by the Oncology Division of the FDA. Even in the EU, oncology marketing authorization decisions are made by the EMA, not by the PDCO. The PIP system is redundant and unnecessary for drugs used exclusively in a paediatric population.

6 Discussion

Shirkey, the AAP and FDA noted that more information on drugs and their interaction with the child's body (and vice versa) were needed for improved pharmaceutical treatment, specifically in small children. The AAP and FDA concluded that the "therapeutic orphan" should be fixed by more paediatric labels based on separate S&E trials in all age groups, almost as if they were another species. Since then, paediatric clinical pharmacology has expanded, attitudes about clinical studies in children have changed, paediatric research infrastructure and training has improved dramatically, and industry has performed many paediatric regulatory studies. Today, our understanding of the developing body is much greater than half a century ago. But the term "therapeutic orphans" also ignored the difference between small children and adolescents and the positive effects of some "off-label" treatments. This was amplified when the AAP extrapolated dangers, including death, from use of antibiotics in premature newborns to the entire paediatric population and claimed that ADME are different from adults in children of all age groups [7, 8, 11]. This dogma also initially resulted in the FDA requiring only adult-style S&E studies for paediatric labeling. Recent FDA decisions such as extrapolation of efficacy for antiepileptic drugs [20] and the anticancer compound avelumab [21] suggest a rethinking. The EMA has not shown comparable willingness to change its approach.

The EU paediatric legislation has certainly advanced awareness that clinical research in children is needed. But defining the "paediatric population" as everyone under age 18 (Table 1) and routinely requiring S&E studies that mirror the adult testing paradigm is not science-based and can harm patients enrolled in questionable studies. The adolescents enrolled in the vemurafenib "dose escalation" trial [31, 32] should have been treated as adults. Instead, they became a commodity required for drug approval. This PIP-requested trial lacked common sense and exposed patients to unjustified risks/harm [31, 38, 39]. The more compounds are developed for liver cancer [42], the more rare underage patients with liver cancer will be searched for to enroll in PIP-required studies that cannot enroll sufficient numbers for meaningful results. These rare diseases patients deserve treatment driven by therapeutic beneficence [29], not by dogma.

With the exception of psychiatric drugs and perhaps a few others, adult doses can be used in adolescents. In school-age and younger children, dose estimation using modeling and simulation is possible with confirmation by small PK/pharmacodynamic (PD) studies or with opportunistic PK/PD sampling of adolescents and children treated off-label [31, 46–48].

There are a number of limitations to the reach of paediatric regulatory authority in the US paediatric legislation that do not exist in the EU paediatric legislation. Thus, there are no mandatory paediatric studies for orphan diseases, mandatory studies are required only in the same disease as adults, and there are no additional requirements for drugs developed solely for paediatric diseases. Minors do not need just more studies, but rather reasonable approaches to obtain the information needed for effective and safe treatment.

Doing unnecessary or unfeasible global studies that are terminated because they fail to recruit represents considerable, unjustified costs. So far, industry has accepted this as bearable and necessary for adult development and registration. Such studies, however, have negative impacts on both the cost of medicines and on enrolled patients.

7 Conclusions and Alternatives

The FDA, AAP and EMA have claimed that the best way for children to benefit from pharmaceutical progress is more paediatric labeling. Labels provide important information, but responsible physicians will always use what they consider as the best available treatment, including off-label. There are also ways to develop useful paediatric dosing information other than adult-style S&E studies. Examples include the use of registry data and opportunistic use of PK/PD data collected in children receiving off-label treatments. Additional improvements to the EU paediatric legislation are beyond the scope of this manuscript, but would include exempting drugs being developed for purely paediatric, rare or orphan diseases from the PIP process; allowing for prioritization when multiple drugs are being developed for the same rare disease or condition; and delaying the PIP until at least some adult efficacy and

toxicity data are available. Other concrete suggestions for change include improved external oversight/review of PIP decisions, as well as regularly scheduled, very clearly described, more clinically meaningful outcomes for the PIP system. Examples include the number of studies that resulted in statistically valid results or meaningful changes in practice or dosing rather than just the number of PIP studies done.

US and EU paediatric legislation has treated all paediatric subpopulations the same. With few exceptions, adolescents with an adult body should receive adult doses. If reimbursement institutions refuse to pay, this is a legal, not a medical problem. *Legal* challenges should not be fixed with *medical* actions. New pharmaceutical legislation should explicitly allow physiologically adult adolescents to receive appropriate drugs and doses based on the treating physician's educated opinion.

Today's industrial and scientific revolution offers an increasing number of new medications for both adult and paediatric diseases. For adult diseases that rarely also affect children, there are better ways to make treatment available than blindly enforcing adult-type regulatory trials in all paediatric subpopulations, especially when multiple drug studies compete for the same very small number of rare paediatric patients; this is being done by four ongoing studies recruiting minors with melanoma or other solid tumors [31, 34–37].

The potential benefits of mandatory consideration of children in drug development should neither be ignored nor overestimated. Legislation can offer a useful framework for drug development, but cannot replace scientific progress. Asking for child-friendly formulations is reasonable; juvenile animal studies routinely requested by the EMA/PDCO while of questionable value do not harm children. Indiscriminately requiring undoable, unjustified or poorly designed paediatric studies can.

Companies who resist doing such studies risk being criticized for being against "better medicines for children". In the short-term it can be easier to accept the requirement to conduct a study even when management feels the study makes no sense or is likely to fail to recruit. But companies have both a moral and fiduciary responsibility to protect children against unrealistic or irrational EMA/PDCO requirements. They can seek help in doing so from institutional review boards (IRBs) and ethics committees (ECs). When they consider EMA/PDCO requests to be irrational, unethical or unfeasible, they should say so in writing, even if later during the PIP procedure, based on the written EMA feedback, they must "propose" such studies. Otherwise EMA/PDCO can refuse their PIP and block approval. If this happens, companies should then share their concerns with IRBs/ECs who are asked to approve the studies and to document when this occurs.

It is hoped that this paper will provide the clinicians and members of IRBs/ECs who are involved in paediatric trials a better understanding of the PIP system so that questionable PIP-required studies can be more easily identified. Additionally, researchers should continue to develop and test improved, alternative ways to collect dosing and efficacy data in all age groups and lobby for their use.

A statement on off-label use from the European Academy of Paediatrics (EAP) comparable to the AAP's [12] could also be helpful. Bodies representing European paediatricians and other physicians who treat children should also support indicated revisions of the PIP system.

Compliance with Ethical Standards

No actual trials were done or subjects recruited/involved in this Opinion paper. Therefore no IRB/EC review was requested or done.

Conflict of interest Dr. Rose has worked for 20 years in the pharmaceutical industry in drug development and medical affairs. Independent since 2011, he consults on pediatric drug development, teaches, organizes scientific conferences, edits books, and publishes. His main clients are small, medium-size and large pharmaceutical companies. He is also father of a daughter with a rare disease and is biased against governmental empty promises. Dr. Walson reports potential conflicts with his private consulting company (Walson Consulting LLC) that has provided fee for service consultation to the pharmaceutical industry and contract research organizations as well as to US and EU not-for-profit governmental funded research organizations (e.g., Eunice Kennedy Shriver National Institute of Child Health and Human Development, FP7 health projects, and the Innovative Medicines Initiative) and paid participation in numerous conferences devoted to pediatric clinical trials and drug development.

Funding No grants or funds have been involved in the authorship of this article. The authors declare no other conflicts of interest in this work.

References

1. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. Official Journal of the European Union, 27.12.2006, L 378/1 - L 278/19. http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf. Accessed 26 May 2017.
2. Rose K. Pediatric pharmaceutical legislation in the USA and EU and their impact on adult and pediatric drug development. In: Bar-Shalom D, Rose K, editors. Pediatric formulations—a roadmap. AAPS & Springer: New York; 2014. p. 405–20 (Chapter 28).
3. Mentzer D. Progress review of the European Paediatric Regulatory Framework after six years of implementation. Int J Pharm. 2014;469:240–3.
4. Hilts PJ. Protecting America's health: the FDA, business, and one hundred years of regulation. Chapel Hill: University of North Carolina Press; 2004.
5. Kefauver-Harris amendments revolutionized drug development. https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm322856.htm. Accessed 26 May 2017.

6. Shirkey H. Therapeutic orphans. Pediatrics. 1999;104:583–4. (Reprint of the original article from 1968)
7. American Academy of Pediatrics. Committee on Drugs. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Pediatrics. 1977;60:91–101.
8. Committee on Drugs, American Academy of Pediatrics. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Pediatrics. 1995;95:286–94.
9. Blumer JE. Off-label uses of drugs in children. Pediatrics. 1999;104:598–602.
10. Donohoe J. A history of drug advertising: the evolving roles of consumers and consumer protection. Milbank Q. 2006;84:659–99.
11. AAP. Clinical report—guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Pediatrics. 2010;125:850–60.
12. Frattarelli DA, Galinkin JL, Green TP, Johnson TD, Neville KA, Paul IM, et al. Off-label use of drugs in children. Pediatrics. 2014;133:563–7.
13. Adamson PC. Improving the outcome for children with cancer: development of targeted new agents. CA Cancer J Clin. 2015;65:212–20.
14. Rose K, Walson PD. The contributions of the European Medicines Agency and its pediatric committee to the fight against childhood leukemia. Risk Manag Healthc Policy. 2015;8:185–205.
15. Philip AG. The evolution of neonatology. Pediatr Res. 2005;58(4):799–815.
16. Noonan JA. A history of pediatric specialties: the development of pediatric cardiology. Pediatr Res. 2004;56:298–306.
17. 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;349:1157–67.
18. Food and Drug Administration Modernization Act Of 1997. [[Page 111 STAT. 2296]]. Public Law 105–115. 105th Congress. https://www.gpo.gov/fdsys/pkg/PLAW-105publ115/pdf/PLAW-105publ115.pdf. Accessed 26 May 2017.
19. FDA 2014. General clinical pharmacology considerations for pediatric studies for drugs and biological products. Guidance for industry. http://www.fda.gov/downloads/drugs/guidances/ucm425885.pdf. Accessed 26 May 2017.
20. FDA 2016. FDA Update: anti-epileptic drug efficacy in adults can be extrapolated to pediatric patients. http://www.aappublications.org/news/2016/04/06/FDAUpdate040616. Accessed 26 May 2017.
21. FDA 2017. Avelumab prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761049s000lbl.pdf. Accessed 26 May 2017.
22. FDA expands approved use of Kalydeco to treat additional mutations of cystic fibrosis. Laboratory evidence used to support efficacy. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm559212.htm. Accessed 26 May 2017.
23. Stephenson T. Medicines for children—the last century and the next. Arch Dis Child. 2001;85:177–9.
24. Chalumeau M, Tréluyer JM, Salanave B, Assathiany R, Chéron G, Crocheton N, et al. Off label and unlicensed drug use among French office based paediatricians. Arch Dis Child. 2000;83:502–5.
25. Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatr. 1999;88:965–8.
26. EMA 1998. Report on the experts round table on the difficulties related to the use of new medicinal products in children held on 18 December 1997. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/09/WC500003759.pdf. Accessed 26 May 2017.
27. Choonara I, Dunne J. Licensing of medicines. Arch Dis Child. 1998;78:402–3.
28. EMA 2004. Evidence of harm from off-label or unlicensed medicines in children. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004021.pdf. Accessed 26 May 2017.
29. The Belmont Report. Office of the Secretary. Ethical principles and guidelines for the protection of human subjects of research. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. April 18, 1979. http://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/. Accessed 26 May 2017.
30. EMA 2011: EMA Decision CW/1/2011 on a class waiver on condition(s) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council. www.ema.europa.eu/docs/en_GB/document_library/Other/2011/12/WC500119981.pdf. Accessed 26 May 2017.
31. Rose K, Walson PD. Do the European Medicines Agency (EMA) decisions hurt pediatric melanoma patients? Clin Ther. 2017;39:253–65.
32. BRIM-P. A study of vemurafenib in pediatric patients with stage IIIC or stage IV melanoma harboring BRAFV600 mutations. https://clinicaltrials.gov/ct2/show/NCT01519323. Accessed 26 May 2017.
33. Phase 2 study of ipilimumab in children and adolescents (12 to <18 years) with previously treated or untreated, unresectable stage III or stage lV malignant melanoma. https://clinicaltrials.gov/ct2/show/NCT01696045. Accessed 26 May 2017.
34. A study of pembrolizumab (MK-3475) in pediatric participants with advanced melanoma or advanced, relapsed, or refractory PD-L1-positive solid tumors or lymphoma (MK-3475-051/KEYNOTE-051). https://clinicaltrials.gov/ct2/show/NCT02332668. Accessed 26 May 2017.
35. A study to determine safety, tolerability and pharmacokinetics of oral dabrafenib in children and adolescent subjects. https://clinicaltrials.gov/ct2/show/NCT01677741. Accessed 26 May 2017.
36. To find a safe dose and show early clinical activity of weekly nab-paclitaxel in pediatric patients with recurrent/refractory solid tumors. https://clinicaltrials.gov/ct2/show/NCT01962103. Accessed 26 May 2017.
37. A phase I/II, multicenter, open-label, dose-escalation study of the safety and pharmacokinetics of cobimetinib in pediatric and young adult patients with previously treated solid tumors. http://www.clinicaltrialsregister.eu/ctr-search/search?query=2014-004685-25. Accessed 26 May 2017.
38. Rose K. European Union pediatric legislation jeopardizes worldwide, timely future advances in the care of children with cancer. Clin Ther. 2014;36:163–77.
39. Rose K, Senn. Drug development: EU paediatric legislation, the European Medicines Agency and its Paediatric Committee—adolescents' melanoma as a paradigm. Pharm Stat. 2014;13:211–3.
40. Rose K, Mueller T. Children with multiple sclerosis should not become therapeutic hostages. Ther Adv Neurol Disord. 2016;9:389–95.
41. Rose K, Happle R. The impact of regulation on pediatric psoriasis drug approvals: the challenge of the European Union (EU) pediatric investigation plans (PIPs). Pediatr Dermatol. 2017;34:e154–9. doi:10.1111/pde.13097.
42. European Medicines Agency decision CW-0001-2015 of 23 July 2015 on class waivers in accordance with Regulation EC No 1901-2006 of the European Parliament and of the Council. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/07/WC500190385.pdf. Accessed 26 May 2017.

43. Tsilochristou OA, Douladiris N, Makris M, Papadopoulos NG. Pediatric allergic rhinitis and asthma: can the march be halted? Pediatr Drugs. 2013;15:431.
44. Rose K, Kopp MV. Pediatric investigation plans for specific immunotherapy: questionable contributions to childhood health. Pediatr Allergy Immunol. 2015;26(8):695–701.
45. 10-Year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation. http://ec.europa.eu/health//sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf. Accessed 26 May 2017.
46. Laughon MM, Benjamin DK Jr, Capparelli EV, et al. Innovative clinical trial design for pediatric therapeutics. Expert Rev Clin Pharmacol. 2011;4:643–52.
47. Gonzalez D, Melloni C, Yogev R et al. Use of opportunistic clinical data and a population pharmacokinetic model to support dosing of clindamycin for premature infants to adolescents. Clin Pharmacol Ther. 2014;96(4):429–37. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4169790/pdf/nihms609415.pdf.
48. Pediatric Trials Network. http://pediatrictrials.org/. Accessed 26 May 2017.