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The Challenges of Pediatric Drug Development

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ABSTRACT

Introduction and Background: "Pediatric Drug Development" is being used to describe not the development of drugs for children, but rather the planning & conducting separate efficacy and safety (E&S) studies requested/demanded by regulatory authorities designed to produce pediatric labels. Pediatric studies required for drug approval enroll "children"; defined as <17 years of age (US Food and Drug Administration [FDA])/ <18 years (European Union [EU]). The medical rationale for study designs was examined.

Material & Methods: International industry-sponsored pediatric E&S studies registered in www.clinicaltrials.gov were analysed along with the history of US/EU laws, published literature, internet-retrieved regulatory documents, and regulatory/ American Academy of Pediatrics (AAP) justifications for doing separate pediatric E&S studies.

Results: US/EU regulators utilize an official, but non-physiological definition of childhood based on an age limit of 17/18 years. This definition, which blurs the interface between medicine and law, emerged after clinical studies became required for drug approval in 1962 prompting drug manufacturers to insert pediatric warnings into product information. Intended largely as legal protection against liability, they were interpreted medically. Absorption, distribution, metabolism, excretion mature rapidly. Drug toxicities seen in newborns during the first months of life were cited by AAP/FDA in warnings of dangers of drugs in all "children" including in adolescents who are physiologically no longer children. Warnings were/are exaggerated, exploit/ed parents' protective instincts and fears, and increase/d pediatric clinical trial activity. Conflicts of interest created by this increased activity involve research funding, career status & advancement, commercial profits.

Discussion: FDA/EMA-requested/demanded "pediatric" studies were identified which lack medical sense at best, others actually harm young patients by impeding use of superior, effective treatments. Separate labels for different indications make medical sense; separate approval in persons above/below 17/18 years of age does not.

Conclusions: Pediatric medical research should be restricted to studies which meet important medical needs of all recruited young patients, which generate information that cannot be obtained by other study designs, and do not limit access to superior alternative therapies. Clinical centers, investigators, and IRBs/ECs should more carefully examine studies for unjustified regulatory demands, prevention of subjects' access to superior treatments, and undeclared COI's. Questionable studies should not be approved and ongoing ones should be suspended.

Introduction

Pediatric drug development (PDD) is a term being misused in the title of several books,[1,2] in US Food and Drug Administration (FDA)[3] and International Conference on Harmonisation[4] documents, in academic publications,[5–9] in articles by pharmaceutical industry employees,[10,11] and by regulatory authorities.[12,13] The term *pediatric development* is also being used with the same meaning.[14,15] PDD has fundamental political, economic, legal, and clinical dimensions and implications. The EU Commission estimates that the execution of a single Pediatric Investigation Plan (PIP) costs the industry roughly €20 million.[16] More than 1000 PIPs have been issued,[16] amounting to €20 billion. US patent extensions, granted since 1997, can be worth several hundred million US dollars.[17] Several US laws and 1 EU law have been introduced/reauthorized to promote PDD,[14] including 2 FDA pediatric reports,[3,18] a report from the European Medicines Agency (EMA),[15]

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and a report from the EU Commission.[16] PDD would seem to mean development of medicines for children. This meaning is used in statements that address the public. For the FDA, EMA, and the American Academy of Pediatrics (AAP), however, it means separate regulatory approval of medicines for minors and separate labels.[3,8,10,18,19] The FDA and the European Union define children chronologically (ie, age <17 years and age <18 years, respectively).[14,20] The AAP lists, on a regular basis, updates on FDA pediatric label extensions.

The idea is that because children are not a separate species, efficacy and safety (E&S) studies are not always required to allow rational pediatric drug use (or even labeling) and that decades of Western medicine's and society's focus on PDD, better medicines for children,[21] or pediatric development[14,15] is/was flawed.

Modern drug development was part of the scientific and industrial revolution that followed the Middle Ages and Renaissance. The Renaissance (literal translation: rebirth) was not recovery of lost knowledge, but rather development of new visions, science, and technology that changed the world. World War II brought scientific and industrial breakthroughs, including radar and nuclear bombs, and industrially produced penicillin followed by other antibiotic agents.[22] Two major tragedies followed: sulfonilamide elixir in 1938 led to >100 deaths[5]; and thalidomide caused severe malformations in roughly 10,000 children worldwide between 1959 and 1961.[23] The resulting public uproar led in 1962 to a US law that established adequately controlled studies as the basis for drug approval. Today, this principle is accepted worldwide.[24]

In the 1950s, toxicity and death had been described in preterm newborns treated with antibiotic agents.[25,26] The 1962 law also gave regulatory oversight of drug advertising to the FDA.[27] Largely as a way to protect themselves from liability, US pharmaceutical companies inserted pediatric warnings into their product information. These warnings were interpreted medically by Shirkey[28] who characterized "infants and children" as "therapeutic orphans," claiming that such labels denied children the use of many modern drugs. Shirkey was the first chairman of the AAP Committee on Drugs.[28] During the following years, AAP and FDA developed—in close collaboration—the demand for separate E&S studies in children,[5] culminating in AAP guidelines on clinical studies in pediatric populations in 1977[29] and 1995.[30] In 1997, the first US pediatric law was passed that offered pediatric exclusivity; that is, a 6-month patent extension for patent-protected drugs, as a reward for conducting studies in pediatric populations.[5,14] Pediatric exclusivity is granted if a company voluntarily completes studies listed in an FDA-issued Written Request.[5,14] This first US pediatric law (renewed in 2002) was complemented in 2003 by a law authorizing the FDA to demand pediatric studies—but without any reward (Pediatric Research Equity Act [PREA]).[5,14] These US laws inspired the Euopean Union, which held its first pediatric meeting in 1997,[31] followed by 10 years of deliberation and, in 2006, the current EU Paediatric Regulation.[5,14]

Society's focus on children was not limited to medical treatment. In 1959, the United Nations adopted the Declaration of the Rights of the Child,[32] in 1989 the Convention on the Rights of the Child.[33]

Materials and Methods

This article describes the background of US and EU pediatric legislation and challenges these in view of key principles of developmental pharmacology. FDA/EMA-requested/demanded industry-sponsored international pediatric drug studies registered in www.ClinicalTrials.gov are used to illustrate problems with current legislation. A number of regulatory, Internet-retrievable documents are analyzed with respect to how they relate to the public's willingness to support PDD.

Results

Both the United States and European Union define children chronologically (age <17 years and age <18 years, respectively).[14,20] These age limits are administrative. They may be adequate for issuing a license to operate a motor vehicle, but not for pharmaceutical treatment. Shirkey's classification of children as therapeutic orphans[28] and the AAP's characterization of child treatment as experimental whenever not explicitely FDA-approved,[29] were exaggerated and alarmist. Absorption, distribution, metabolism, and excretion (ADME) functions in preterm newborn infants are immature.[34] Medical warnings are important for preterm newborns and, to a lesser degree, term newborns, but not for all children (ie, age <17 years/age <18 years).[35,36] Drug treatment should be governed by physiologic rather than regulatory and administrative age limits.

The introduction of clinical E&S trials as the new requirement for drug approval rocked the old and powerful professions of medicine and pharmacy. Two new major players emerged: pharmaceutical industry (initially still the chemical industry) and regulatory authorities. Evidence-based medicine[37] became a new mantra.[38] Whereas clinical trials are crucial in deciding whether a treatment is safe and effective, many other types of medical and pharmaceutical knowledge transfer exist. These include teaching in universities and in clinical practice, guidance and criticism from supervisors and colleagues, exchange of experience in hospital, discussions with colleagues at conferences and in publications, interactions with representatives from pharmaceutical companies, and reading/viewing drug labels. Even exposure to advertisements from and warnings about the pharmaceutical industry, both amply available in television, press, Internet, and social media, can be useful. Medical doctors and pharmacists do not rely predominantly on FDA/EMA-approval labels. The exaggerated emphasis on evidence-based medicine has been mockingly discussed in the suggestion that the efficacy of parachutes should be proven in double-blind, randomized, controlled trials.[39]

US and EU laws regarding pediatric health care are partly the result of the introduction of new principles of drug approval in the United States in 1962, which fundamentally changed the roles of the medical and pharmacology professions. Before World War II, most drugs were purchased in a pharmacy, including powder made from pulverized mummies, pain medications containing cocaine and/or opioids, and snake oil. Little was known about developmental physiology, apart from the centuries-old belief that babies only swallow liquids; knowlege that babies, children, and adolescents grow and are vulnerable; and assertion their legal status differed from adults. Superstitions were common; for example, charm amulets were trusted to help against epilepsy. Developmental aspects of ADME in young patients were unknown.

Label warnings about lack of studies and possible drug toxicities in children aged <17 or <18 years did not prevent improvements in adult and child health care over the past half century, as demonstrated by the advancements made in neonatology,[40] pediatric oncology,[41] pediatrics, and developmental pharmacology.[34] However, on a societal level conceptualization of the role of pharmaceutical treatment of young patients is frozen in the concept of 2 distinct human populations that require separate studies and drug approvals: Adults versus minors. This concept emerged after 1962, partially due to legitimate concerns for children's health when treated with modern drugs that had not been given to children before marketing. Legitimate concerns can be influenced by the self-interests of those doing the approving (ie, regulators and their consultants) or doing funded pediatric drug testing, including members of the AAP. Potential conflicts of interest have resulted from the fact that PDD has increased the administrative power of regulatory authorities.[42] Pharmaceutical drug development and

the E&S trial system upon which it is based have been very successful. Today, we have effective treatments for many diseases against which physicians were helpless just a few years ago. However, the concept that all off-label use is bad or that all children aged <17 or <18 years can benefit only when/if separate adult-style E&S trials are performed has occasionally become an obstacle to the most effective standard-of-care treatment for some young patients.

Two melanoma studies in adolescent patients, 1 requested by the FDA and both by EU PIPs, were terminated in 2016 because monotherapy with ipilimumab or vemurafenib had been replaced by more effective combination treatment. Five questionable studies in young patients with solid tumors, including children with melanoma, continue to recruit worldwide.[43,44] A number of questionable studies triggered by FDA/EMA requests/demands have been completed. Many more are recruiting worldwide in centers in Switzerland, the United States, Russia, and China.[45–47] These studies were identified because all clinical trials must today be registered in a publicly available registry, with www.ClinicalTrials.gov being the largest and most user-friendly. Without registration, publication in respected biomedical research journals is no longer possible.[48]

Off-label use of drugs and treatment of children

Drug labels are a legal construct at the interface of clinical care, commerce, and authorities. They are relatively new in history. Quality control of pharmaceuticals existed more than 1000 years ago in Baghdad (today's Iraq). However, only during the 20th century did 2 important new concepts evolve: proof of clinical efficacy of industrially produced medicines before they can be sold and differentiation of medicines for sale without restrictions (ie, over the counter) versus those physicians have to prescribe. These concepts require solid institutions, including organizations representating medical doctors and pharmacists, regulatory authorities, and society, accepting that treatment can be achieved without hocus-pocus.

Modern drug labels go back to 1906, when US law defined the terms *adulterated* and *misbranded*, and prohibited interstate commerce of misbranded and adulterated foods, drinks, and drugs. US federal laws focus on the supply of medical products. They ensure that pharmaceuticals do not reach the marketplace until they are examined and approved by the FDA. The federal laws are not intended to reach into the realm of physicians practicing medicine.[42] From 1938 on, US law demanded proof of safety of new drugs before marketing. Since 1962, US law has demanded proof of efficacy of new drugs by adequate clinical testing before approval.[14,24]

The term *off-label* emerged in 1988.[49,50] Off-label prescribing and off-label use are not regulated by the FDA. Off-label promotion is heavily constrained. US federal law does not prohibit such promotion verbatim, but a drug is considered misbranded when its label lacks adequate directions for using it safely and for the intended purposes. Statements by manufacturers that promote their drug for an off-label use can be interpreted as an intended use, which creates a misbranding event. Manufacturing, delivering, receiving, or introducing drugs into US interstate commerce that are misbranded is unlawful.[42] In 2012, the US federal government negotiated $4.5 billion in criminal and civil settlements for off-label promotion by 2 manufacturers.[42] The ban of promotion of off-label use can be seen as a contradiction to the First Amendment to the US Constitution. In 2017, the FDA modified its view of intended use. Arizona now allows manufacturers to communicate about off-label uses.[51]

The FDA's position against off-label promotion of drugs was/is based on concerns that physicians and/or the public might be misled about a drug's safety or efficacy. So far, no differentiation is made between off-label use in children compared with off-label use in adults. Differentiation between adults and children in terms of ADME functioning is appropriate for preterm newborns, but not for older children. During the first 6 months of life, ADME function matures dramatically.[32] The consensus against off-label use of drugs in children (defined administratively, not physiologically) is a relic from the 1960s when clinical studies as the basis of drug approval altered medicine, pharmacy, and pharmacology.

Clinical caregivers required a framework for drug use in children, specifically in the view of the reported toxicities,[25,26] and pediatric warnings were therefore inserted into product information.[28] The FDA and the AAP established a close collaboration[5] that today needs critical re-evaluation. It served as a catalyst for increased funding of pediatric research, augmented first by US pediatric legislation in 1997, and then by the EU Paediatric Regulation.[14] There were at least 2 motivations to advocate for increased pediatric drug research: concern for children's health and the desire for knowledge from research in pediatric populations. However, increased drug research also created potential conflicts of interest related to issues such as funding, promotion, status, and infrastructure.

Today's medical care relies to a relevant degree on off-label drug use.[42] Additionally, not all labels are based on science. The first oral contraceptive in Germany, for example, was approved for menstrual dysfunction. For contraception, the label restricted prescription to married women.[50] Medically, this doesn't make sense, but it reflected the conundrum of parents who faced criminal charges of procuration if their daughter's boyfriend stayed overnight and somebody noticed/denounced this.

Clinical justifications of separate pediatric drug approval and regulatory coding

The EU Paediatric Regulation was preceded and accompanied by academic publications that alleged high risks of off-label drug use in minors. For example, that "off-label use doubles the frequency of adverse drug reactions, which are sometimes life-threatening."[52] The authors of this claim cite 2 studies as support. One was a prospective study done within UK pediatric wards that classified administered drugs as on- or off-label and recorded adverse drug reactions (ADRs). The incidence of ADRs was comparable to other studies, but more occurred in the intensive care unit. The factor most highly related to the risk of an ADR was the number of drugs given to a patient. Roughly half the ADRs occured with opiates. There were nominally more ADRs after off-label than on-label use.[53] This shows that complex clinical conditions are more difficult to handle than simple ones. The other study analyzed prescriptions from office-based pediatricians in France. Half the ADRs occurred in infants, half in children, none in adolescents. More ADRs were observed in children with indications not covered by the respective label, but the authors concluded: "The risk of ADRs could be acceptable if the therapeutic benefit is largely greater."[54] Neither article justifies the claim of a double frequency of ADRs with off-label use.

The EMA claims that pediatric off-label use is always harmful, but does not address lifesaving, almost universal off-label drug use in neonatology and oncology.[55] The entire field of pediatric oncology evolved off-label (in its early years the term *off-label* did not exist).[50]

Several dimensions should not be confused. If an inexperienced physician prescribes drugs to seriously ill patients of any age, this can be dangerous. In the 1940s and 1950s, little was known of newborns' ADME function. Developmental pharmacology stepwise elucidated ADME in infants. Treatment errors were reported to prevent repetition of mistakes. There is a fundamental difference

between justified warnings and exaggerated warnings that children of all ages need separate E&S studies.[30]

Confusion about how to best treat children is not the result of a conspiracy. Genuine therapeutic intentions pushed the use of modern drugs in children, including antibiotics in newborns and treating pediatric cancer with chemotherapy agents developed for adults. When toxicities in newborns were observed and industry protected itself against damage lawsuits, industry unconsciously contributed to the emergence of appropriate warnings about toxicities in newborns. However, they also contributed to inappropriate warnings that the risk of toxicity is increased in all children aged <17 years treated off-label.

The rapid maturation of the organs responsible for ADME functions was not yet known.[34] There were genuine concern for children's health, but this developed its own dynamic, influenced by conflicts of interest including regulators (eg, FDA and EMA), professional organizations (eg, AAP), industry (eg, pharmaceutical and contract research organizatons), health care providers, and investigators.

The International Committee of Medical Journal Editors acknowledges conflicts of interest exist beyond financial ones.[56] PDD creates many potential conflicts of interest, not all of which are always revealed or considered by institutional review bords/ethics committees or journal editors, including institutional rivalry, the influence of research funding and publications on career advancement, and regulatory opposition to physicians' freedom to prescribe.

FDA and EMA reports about PDD are easier to more critically review once a reader is alerted to their use of code words. For example, the EMA describes PDD as a clinical challenge in a recently uploaded video.[57] Yet the EMA claims of progress are based on exclusively regulatory end points.[15] The FDA proposed in 2001 a number of clinical parameters to measure the outcomes of the US pediatric legislation in their statement: "Superior drug treatment information is expected to permit quicker recoveries from childhood illnesses, with fewer attendant hospital stays, physician visits and parental work days lost."[3] In 2016, these end points were skipped and replaced by regulatory end points.[18] The success of PDD should not be judged on how many studies/subjects, but rather on how many studies produced useful information and improved patient outcomes.

Developmental pharmacology and PDD

A key publication outlines how ADME function matures in children. After age 8 years, ADME of children and adolescents approximate that of young adults, although in younger children dosing needs to be adjusted. Dosing recommendations per kilogram bodyweight are given for gentamicin, ceftazidime, clindamycin, carbamazepine, phenytoin, phenobarbital, theophylline, digoxin, captopril, and ranitidine. The doses in adults were adjusted for an average ideal adult body weight of 70 kg, the pediatric doses reflected average ranges recommended in a widely used pediatric handbook.[34] Analyses of international industry-sponsored clinical studies in various clinical areas, including leukemias,[58] melanoma,[43,44] psoriasis,[59] multiple sclerosis,[60] and international industry-sponsored clinical trials with centers in Switzerland, the United States, Russia, and China[45–47] show that most FDA/EMA-requested/demanded studies request/demand separate proof of efficacy in various pediatric age groups instead of dose-finding in young children. An overview, coauthored by developmental pharmacologists and FDA employees ignores this alternative. It uses the sulfanimide elixir (1938) and the thalidomide (1959-1961) catastrophies to justify the alleged need for pediatric labels and the cascade of US pediatric laws, without discussing physiological maturation vis-à-vis drug treatment.[5]

International pediatric clinical studies

Regulatory requirements resulted in many international pediatric studies. FDA Written Request, PREA-demanded studies and the >1000 PIPs[16] result(ed) in mostly international studies that recruit young patients worldwide. Of the 346 studies conducted following FDA requests/demands for 130 products in 2007 to 2011, 229 were efficacy and safety, 57 pharmacokinetic parameters/safety, 15 pharmacokinetic/pharmacodynamic parameters, 34 safety, and 11 other study types.[61] Most were E&S studies, rarely in neonates.

International pediatric studies have become a business that requires logistics, infrastructure, manpower, and offers jobs, themes for conferences, networking, careers, publishing, and more. Costs are eventually paid by consumers and taxpayers, through US patent extensions, by the threat of non-EU-approval of new drugs, or by EU-funded initiatives like Global Research in Pediatrics,[62] the European Network of Pediatric Research at the EMA,[63] or the Paediatric Medicines Regulators' Network with annual meetings, reports, and more.[64] Many triggered pediatric studies are medically senseless at best. Some even harm patients by withholding standard-of-care treatment[36,43,44] and/or by placebo treatment.[36] They contribute to consolidating the concept that there are 2 separate human species: adults (aged >17 or >18 years) and minors (aged <17 or <18 years). Pediatric research groups and multistakeholder groups support this by consensus reports, publications, meta-analyses, conference reports, and more.[7,65–69]

Pediatric oncology

Most melanomas observed in adolescents are adult-type melanomas.[43,70,71] Several reports of pediatric melanoma describe adult-type melanomas in young patients.[72,73] The FDA approved combination treatments in malignant melanoma. There is no acceptable justification to withhold such treatment from adolescents. Even clinicians and multistakeholder-groups now advocate to include adolescents into adult pivotal studies of new anticancer compounds.[74,75] There are more cancer types where efficient treatment is available, including vemurafenib for Erdheim-Chester disease, which rarely occurs in young patients.[76] The FDA recently approved tisagenlecleucel for relapsed/remitting acute lymphatic leukemia in patients aged ≤25 years,[77,78] rendering PIP-demanded pediatric studies of relapsed/remitting acute lymphatic leukemia obsolete.

A PIP-triggered study (NCT00643565, EMEA-000056-PIP01-07-M02) treated patients with rhabdomyosarcoma (RMS) and non-RMS soft tissue sarcomas (NRSTS) with bevacizumab plus standard chemotherapy.[79] RMS affects predominantly patients younger than age 14 years, NRSTS affects predominantly adolescents and young adults.[80] Bevacizumab showed no added efficacy. The PIP justifications for this study were regulatory, not science-based. The study report does not discuss the study's medical sense.[79] There is no scientific rationale that bevacizumab should help patients aged <18 years with RMS/NRSTS. Researchers profited from this study by networking, investigators' meetings, presentations at international conferences, and maintanance of research infrastructures. The same researchers defend the PIP system[69] and ask for its expansion.[68,74]

A separate article[81] discusses dose finding of moleculary targeted agents in 19 pediatric studies, but does not discuss that only 2 of those studies were limited to patients aged <18 years; most included patients up to age 18, 20, 21, and 22 years old (ie, legally adults). Recruiting young adults into allegedly pediatric studies is dishonest. The authors do not address this.[81] Most reports concluded that findings in children matched those in adults.[81]

Does monotherapy testing of biologics make sense in all cancers in all age groups? For bevacizumab, avelumab (EMEA-001849-PIP02-15-M01), nivolumab (EMEA-001407-PIP01-12-M01), and pembrolizumab (EMEA-001474-PIP01-13-M01) the EMA demands studies in patients aged <18 years for different malignant neoplasms. There is no solid rationale for thinking that monoclonal antibodies should work differently in minors with malignancies.

No apologies were published for the terminated studies in adolescents with melanoma.[35,43, 44,75]

A recent article on pediatric studies in atopic dermatitis defines children as ages >3 months to <18 years and takes the regulatory framework for granted.[82] The Declaration of Helsinki states the purpose of medical research as to understand diseases and improve prevention, diagnostics, and treatment.[83] The article does not mention that the FDA approved crisaborole in patients aged 2 to 79 years without separate pediatric studies.[84]

Many publications confirm the antiinflammatory effect of monoclonal antibodies and nonsteroidal antiinflammatory drugs in patients aged <16 years.[45,47,85–88] Why should they not work in young patients? These studies are published in prestigious journals, lack medical sense, but advance careers.[85–88]

A recent article[66] reports on pediatric cardiovascular drug development. Sponsored by pharmaceutical companies, the panel did not discuss drug development, but regulatory approval of antihypertension, antidislipidemia, pulmonary antihypertension, antiheart failure, and anticoagulant drugs in young patients. The usual mantras are repeated. The article includes accolades for both US and EU pediatric laws.[66]

FDA and EMA demand separate studies for insulin subtypes in children.[89] Diabetes is not a disease that changes its characteristics on a patient's 17th or 18th birthday.[36,45,47]

Discussion

Prevention of promoting unproven use of a drug in other indications makes sense. Otherwise, companies could register a niche indication and promote use for other indications. Use or promotion of off-label use in minors should no longer be equated with general use or promotion of off-label use. The problem of how to deal with labeling for children was created by the incomplete separation between law and medicine that originated with the medical interpretation of pediatric warnings.[90] The AAP has continuously supported both the contradictory FDA requirements for separate pediatric labels and the pragmatic (and correct) support for the appropriate off-label use by pediatricians. The AAP has not opposed the FDA's demands for pediatric studies in physiologically mature young patients; perhaps because the AAP uses age ≤21 years (age ≤25 years in patients with special needs)[91] as limits for treatment by pediatricians. These age limits may be appropriate for clinical care, but not for deciding when adult drug treatment is or is not appropriate.

The European Union amplified the demands for pediatric studies by extending the definition of children to age <18 years. PDD could and should refer to development of drugs specifically for use in children. There are many diseases that exist predominantly or exclusively in children, but PDD is being used to justify separate regulatory approval in patients aged <17 or <18 years. Claims by FDA and EMA and even by eminent consulting researchers should not be unquestioningly accepted as scientific. The concerns outlined above are real and deserve serious consideration, especially because there are often superior, alternative ways to generate pediatric dosing information. It is especially important that all potential conflicts of interest be exposed and explored by anyone who demands, designs, funds, conducts, or publishes PDD trials.

The US pediatric law of 1997 rewarded industry with 6 months of patent extension for patent-protected drugs. Only young patients and their families did not benefit from these studies. Pediatric oncology was a courageous young discipline half a century ago. Today, practitioners in the field treat all young cancer patients. Some pediatric oncologists regard it as justified to subject young patients to questionable studies. Roche/Genentech sponsored the pediatric bevacizumab study because of PIP EMEA-000056-PIP01-07-M02. Without this PIP, registration in adults would have been blocked. Bevacizumab is profitable—for the company this was a business decision. Were patients and families informed that the study lacked medical sense? This is not addressed in the study report.[79]

The rewards for industry changed with the EU legislation. A patent extension is possible toward the end of the patent life, but companies must submit PIPs early. Without an EMA-approved PIP, registration is blocked. The representative bodies of US and EU research-based pharmaceutical industry emphasize that they support the aims of the pediatric laws.[92,93] This is a weak strategy. Industry still needs to digest the AAP's moral imperative.[30]

The reasons that misuse of the term *PDD* has continued unchallenged for many years include the public's high trust in institutions, the hierarchical organization of medicine, peer reviewers and junior editors who reject publication of thoughts outside of commonly accepted mantras, and science that struggles to conceptualize our increasingly complex world.

In some areas, the FDA has become less dogmatic. It accepts patients into pivotal dermatology studies who are aged 2 to 79 years.[84] For antiepileptic agents, it accepts extrapolation of efficacy from adults to young patients down to age 4 years.[94] In oncology, however, FDA recommends "an amendment of PREA to require certain drugs (including biological products) developed for adult cancer indications to be evaluated for a pediatric cancer indication."[18] Additional pediatric labels for antimelanoma drugs are clinically worthless, as are FDA/EMA-requested/demanded pediatric studies. The FDA's position that allows extrapolating efficacy from adults and accepts patients aged 2 to 79 years in pivotal studies, but wants additional pediatric studies for new anticancer drugs is contradictory. The FDA is not monolithic, but the EMA is thoroughly dogmatic. Even where the FDA no longer demands separate pediatric studies, the EMA continuously issues PIPs, including for epilepsy and dermatology treatments already shown to be effective.

Most supporters of PDD act in good faith, convinced they advance child health care. Confronted with facts, many will listen, unless strong conflicts of interest block unprejudiced opinion making. In evaluating how the term *PDD* has been and is being used, the hardest task has been to differentiate the appearantly caring and noble facade of PDD from its hidden, less-palatable, and profane interests: the desire for research funds, maintenance and advancement of careers, rivalry of spheres of interest, and dogmatism that blocks innovative thinking in the field of pediatrics.

The goal of this and other reviews is to facilitate next steps,[36,44,90] including mobilizing harmed patients and parents, appealing to the medical profession's honor and code of ethics, appealing to industry's desire to develop better and profitable products instead of sponsoring pseudoscientific studies and emphasizing that we all share the same motivation, and better alignment of regulatory activities with the real needs of patients and society.

The relationship between decades of pediatric legislation and improvement of child health care is neither direct nor clear. Child health care improved by new medicines, devices, and lessons learned. At least some, if not many, regulatorily demanded pediatric studies have diverted away attention from real PDD challenges. Innovation has been rapidly changing mankind for more

than a century. The lives of patients with diabetes, cystic fibrosis, multiple sclerosis, and many other diseases have improved, but many unfulfilled medical needs still exist. Some of these patients survive, others not yet. Instead of encouraging innovation, FDA and EMA have have diverted pediatric therapeutic research into an inappropriate regulatory framework, which lessens attention to true challenges, and limits researchers from addressing reasonable research questions.

The global epidemic of questionable studies in young patients might be the largest abuse of patients in clinical research in history, dwarfing inhumane studies of the past.[95,96] PDD might be the largest corruption of medical professions since the American Medical Association stopped taking money from the tobacco industry.[97]

Conclusions

Medical journals should reject manuscripts that describe studies that fail to acknowledge that regulatory decisions triggered sponsoring by industry. Editors need training to scrutinize submitted manuscripts, as do institutional review boards/ethics committees, children's hospitals, and research centers. All should be encouraged to examine each trial to determine whether or not there are other, scientifically valid ways to obtain either the necessary information or regulatory approval. Those studies that are found to be scientifically/morally unjustified should be rejected and ongoing scientifically/morally unjustified studies should be suspended. Medical students and other health care professionals need to learn early about the interplay of clinical care, drug/device development, and regulatory approval. Globally, representative bodies of health care professionals, including pediatricians, should discuss PDD at conferences and distance themselves officially from questionable studies. The International Committee of Medical Journal Editors should consider expanding its recommendations to deal with any poorly justified FDA/EMA-triggered studies. The lay press and the social media will hopefully soon address the challenges of PDD. The strength of free societies is to accept errors and correct them. US and EU laws need revision.

Potential Conflicts of Interest

Dr. Rose consults on pediatric drug development, teaches, organizes scientific conferences, edits books, and publishes. The author has indicated that he has no other potential conflicts of interest regarding the content of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2019.01.007.

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