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Questionable Industry-Sponsored Postneonatal Pediatric Studies in Slovenia ☆

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ABSTRACT

Background: US and EU pediatric laws promote industry-sponsored pediatric studies, based on the therapeutic orphans concept that claims discrimination of children in drug treatment and drug development.
Objective: We investigated the medical validity of international pediatric studies with centers in Slovenia, an EU member state, and challenge their medical utility.
Methods: We analyzed international industry-sponsored pediatric studies with centers in Slovenia, listed in www.ClinicalTrials.gov, for their medical value.
Results: Most pediatric studies triggered by the US Food and Drug Administration and by the European Medicines Agency were/are without medical or scientific value. They were/are formally and regulatorily justified, but lack medical sense and thus were/are unethical. Several even harm children and/or adolescents with serious diseases by exposing them to placebo or substandard treatment.
Conclusions: Pediatric studies triggered by US and EU regulatory demands are a serious abuse of nonneonatal children and adolescents in Slovenia and worldwide. They are medically redundant at best and often deter patients from effective innovative personalized therapy. They also exclude young patients from reasonable studies. Institutional review boards/ethics committees should be alerted, should critically review all ongoing pediatric studies, should suspend those found to be questionable, and should reject newly submitted questionable ones.

Introduction

US and EU laws promote pediatric studies sponsored by pharmaceutical companies based on the concept that children are discriminated against in drug treatment and drug development.[1] The medical legitimacy of such studies has been challenged mainly because they define children administratively and claim that underage persons remain as immature and vulnerable as newborns until they reach age 17 or 18 years.[2–4] The aim of medical research is to improve prevention, diagnosis, and treatment.[5] Studies without the potential to answer scientifically or clinically relevant questions are unscientific and unethical. All medical journal editors are obliged by the International Committee of Medical Journal Editors only to consider publications of clinical studies that were registered before recruitment starts in a public trials registry.[6] These databases provide an overview over clinical studies performed currently or in the past. In our view, this information is undervalued in medical research, as is research into the origin of studies from the interaction between pharmaceutical companies and regulatory authorities. Herein we use such an approach to investigate pediatric studies listed on www.ClinicalTrials.gov, including at least 1 center in Slovenia. Comparable investigations have already been published for studies with centers in Switzerland,[2] the United States, Russia,[7] and China,[8] but not yet for a European Union member; Slovenia is an EU member state.

In some diseases, a child's body may respond differently to drugs; for example, in hypertension, where blood vessel elasticity decreases over time. Regarding most other diseases, a child's organs mature in the months after birth sufficiently to allow drug treatment with the same principles as in adults. For example,

☆ Core data of this study, specifically Table 2, were presented at the 7th Slovenian Pediatric Conference, September 27–29, 2018, Portorož, Slovenia.

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Table 1
Origins of the therapeutic orphans concept and US/EU pediatric legislation.

Timeline	Event
1956	Toxicities of antibiotics reported in preterm newborns[17]
1962	US law demands proof of S&E of new drugs by clinical studies,[18] and transfers jurisdiction over the advertising of prescription drugs from the FTC to the FDA[19]
From 1962 on	Companies put pediatric warnings into labels to prevent damage lawsuits
1968	Shirkey claims these warnings deny children the use of many new drugs[20]
1977	The AAP characterizes prescribing drugs not FDA-approved in children as experimental[21]
1979	The FDA defines children as from birth to age 16 y (21 CFR 201.57 (f)(9))[13]
1995	The AAP demands clinical testing of new drugs in all pediatric age groups[22]
1997	US law introduces voluntary PE to facilitate pediatric studies[1]
2001	First FDA pediatric report to congress[23]
2003	US law authorizes FDA to demand pediatric studies also without reward[1]
2006	The European Union makes PIPs mandatory for drug approval, defining children as from birth to age 18 y[1]
2012	Both US laws become permanent as FDASIA[3,24]
2016	Second FDA pediatric report to congress[25]
2016	EMA pediatric report to EU Commission[26]
2017	EU Commission pediatric report[27]

AAP=American Academy of Pediatrics; CFR=code of federal regulations; FDASIA=Food and Drug Administration Safety and Innovation Act; FTC=Federal Trade Commission; PE=pediatric exclusivity; PIP=pediatric investigation plan; S&E=safety and efficacy.

monoclonal antibodies do not change their mode of action with administrative age limits. However, administrative age limits serve as inclusion criteria of many pediatric studies triggered by US and EU regulatory authorities. Such studies are currently accepted by the international clinical community and published in high-ranking medical journals.

Children's rights are codified in international conventions.[9,10] The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) insist on separate proof of efficacy for drug approval in underage patients and are authorized by laws to enforce studies in children.[1] These laws are based on the belief that children were/are discriminated in pharmaceutical treatment and drug development[1,11,12] and that children's physiology requires separate studies. The FDA defines children as age ≤16 years (ie, <17 years),[13] the EU defines children as age <18 years.[1] Table 1 outlines the origins of this concept and of US/EU pediatric laws.

The FDA and the EU also use the concept of extrapolation of adult study data to children (defined as age <17 years [FDA]/age <18 years [EU]). The FDA has in some clinical areas retreated from the therapeutic orphans concept; for example, in epilepsy.[14,15] The EMA has published a concept paper on extrapolation of efficacy,[16] but nonetheless continues to insist adamantly on separate proof of efficacy in pediatric populations, as shown unambigously by the numerous pediatric investigation plan (PIP)-triggered studies that are performed worldwide.[2–4,7,8]

FDA pediatric requests based on the first pediatric law from 1997 are voluntary. Companies decide if they want to perform the study/studies requested in an official written request; as a reward they get 6 months expanded market protection against generic competition (pediatric exclusivity); a later law, the Pediatric Research Equity Act, authorized the FDA to mandate pediatric studies without a reward, usually as a postmarketing requirement.[1] Pediatric studies can also be part of regular drug development when a drug is targeted for a predominantly pediatric disease.

Materials and Methods

We investigated international prospective clinical studies sponsored by pharmaceutical companies listed in www.ClinicalTrials.gov with at least 1 center in Slovenia in the age group from birth to 17 years. We excluded vaccination studies, retrospective studies, and studies that recruit children, adolescents, and adults together, because we focused specifically on pediatric studies. We retrieved regulatory documents related to the studies' origins from FDA and EMA websites to check if they were requested/demanded by FDA, EMA, or both as pediatric studies, or if they were performed as a routine part of drug development. Studies in www.ClinicalTrials.gov can be Internet-retrieved by the national clinical trial number; PIP decisions by the PIP number. FDA documents are referenced by their weblink. We analyzed the studies' design and rationale on the basis of developmental pharmacology, ethics and medical rationale, and practicality.

Results

We found 19 pediatric studies in Slovenia sponsored by international pharmaceutical companies (listed in Table 2).

Discussion

Individual studies

Tiotropium bromide is a long-acting anticholinergic bronchodilator used in chronic obstructive pulmonary disease and asthma. Study 1 (Table 2) tested tiotropium versus placebo on top of of maintenance therapy with an inhaled corticosteroid in adolescent patients. It was triggered by the tiotropium PIP (Table 3). The FDA written request for tiotropium bromide asked for a double-blind placebo-controlled study in children aged 6 to 11 years but not in adolescents.[28] The publication of study 1 does not mention its regulatory background; it confirms the well-known pharmaceutical effects of tiotropium in adolescents.[29] The authors report that this was the first placebo-controlled study of tiotropium Respimat SoftMist inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany) in adolescents with symptomatic asthma.[29] In the placebo group, this study withheld effective treatment.

Lacosamide, a third-generation antiepileptic drug was FDA-approved in 2008 as add-on drug for refractory partial onset seizures and in 2014 as monotherapy for partial onset seizures.[38] Studies 2 and 3 (Table 1) were triggered both by FDA postmarketing request and an EU PIP (Table 3). Since 2016, separate pediatric efficacy studies are no longer FDA-demanded for antiepileptic drugs in patients aged ≥4 years.[15,39] Thus, the FDA has for epilepsy partially abandoned the therapeutic orphans concept. Study 2 would now be considered obsolete even by FDA standards, as would study 3 regarding patients aged ≥4 years. Meanwhile, the EMA continues its demands for so-called pediatric studies, although the FDA has made concessions to medical wisdom. In the ongoing extension study 3, US centers continue participation. Study 2 withheld effective treatment in the placebo group.

Table 2
International industry-sponsored pediatric studies in Slovenia

Study	NCT#	Description	Sponsor	Patients/centers	Age	Status	Town
1	NCT01122680	DB R PC S&E tiotropium in asthma	BI	105/19	12–17 y	Completed 2010-2011	KLM
2	NCT01921205	Lacosamide vs placebo as add-on in POS	UCB	404/118	4–17 y	Completed 2013-2017	Lj
3	NCT01964560	Lacosamide in POS longterm ES	UCB	500/117	1 mo–17 y	Enrolling by invitation	Lj
4	NCT02201108	PC S&E, PK teriflunamide in MS	Genzyme	166/59	10–17 y	Active, NR since 2014	Lj
5	NCT00952380	Dalteparin for VTE in cancer patients	Pfizer	50/51	≤18 y	Recruiting since 2009	LLL
6	NCT02798471	R OL edoxaban vs. SoC in VTE	DS	274/171	≤17 y	Recruiting since 2016	Lj
7	NCT02616562	E&S daily vs. weekly GHT in GHD	Novo N	60/56	30 mo–10 y	Active, NR	Lj
8	NCT01973244	SD vs. daily dose GHT in GHD	Novo N	32/8	6–13 y	Completed 2013-2014	Lj
9	NCT00936403	GH NNC126-0083 in GHD	Novo N	31/21	6–12 y	Completed 2009-2010	Lj
10	NCT01947907	S&E,PK,PD daily vs weekly GHT in GHD	Ascendis	53/36	3–12 y	Completed 2013-2015	Lj
11	NCT00943501	PC S, T, PK, PD of liraglutide in DMT2	Novo N	21/20	10–17 y	Completed 2009-2011	Lj
12	NCT01835431	I degludec/aspart vs. I detemir in DMT1	Novo N	362/35	1–17 y	Completed 2013-2014	Lj
13	NCT00312156	S&E if I detemir vs. I NPH in DMT1	Novo N	347/42	6–17 y	Completed 2002-2003	Lj
14	NCT00723411	rhGAD65 in newly diagnosed DMT1	Diamyd	334/70	10–20 y	Terminated 2008-2011	Lj
15	NCT02130362	LT S&E of adalimumab in Crohn's D	AbbVie	1300/213	6–17 y	Recruiting since 2014	Lj
16	NCT00962741	Etanercept in JIA	Pfizer	127/42	2–17 y	Completed 2009-2013	Lj
17	NCT01421069	ES of etanercept in JIA	Pfizer	109/35	2–30 y	A, NR since 2011	Lj
18	NCT00652925	DB celecoxib vs. naproxen in JIA	Pfizer	225/58	2–18 y	Completed 2002-2005	Lj
19	NCT01261624	OL dose finding of givinostat in JIA	IF	16/13	2-17 y	Terminated	Lj

BI=Boehringer Ingelheim; D=disease; DB=double blind; DM=diabetes mellitus; DMT1=diabetes mellitus type 1; DMT2=diabetes mellitus type 2; DS=Daiichi Sankyo ES=extension study; E&S=efficacy & safety; GHD=growth hormon deficiency; GHT=growth hormone treatment; I=insulin; IF=Italfarmaco; JIA=juvenile idiopathic arthritis; KLM=Kamnik, Ljubljana, Maribor; Lj=Ljubljana; LLL=Lekarna-Ljubljana, Ljubljana; LT=long term; MS=multiple sclerosis; Novo N=Novo Nordisk; NPH=Neutral Protamin Hagedorn; NR=not recruiting; PC=placebo-controlled; PD=pharmacodynamics; PK=pharmacokinetics; POS=partial onset seizures; R=randomized; rhGAD65=recombinant human glutamic acid decarboxylase; SD=single dose; S&E safety & efficacy; SoC=standard of care; VTE=venous thromboembolism.

Table 3
Regulatory origin of pediatric studies

Compound	EMA Pediatric investigation plan No.	FDA
Tiotropium	EMEA-000035-PIP02-09-M02	–
Lacosamide	EMEA-000402-PIP02-11-M04	PMR[30]
Teriflunamide	EMEA-001094-PIP01-10-M04	PMR[31]
Dalteparin	EMEA-000081-PIP01-07-M09	–
Edoxaban	EMEA-000788-PIP02-11-M06	–
GH Norditropin	–	RRR[32]
GH Ascendis	–	RRR[33]
Givinostat	EMEA-000551.PIP01-09	
Insulin degludec/aspart	EMEA-000479-PIP01-08-M03	PMR[34]
Insulin detemir	EMEA-000412-PIP01-08-M01	PMR[35]
Liraglutide	EMEA-000128-PIP01-07-M08	PMR[36]
rhGAD65	EMEA-000609-PIP01-09	–
Adalimumab	EMEA-000366-PIP01-08-M06	–
Etanercept	EMEA-000299-PIP01-08-M03	–
Celecoxib	–	WR[37]

EMA=European Medicines Agency; FDA=US Food and Drug Administration; PMR=postmarketing requirement, based on the Pediatric Research Equity Act; rhGAD65=recombinant human glutamic acid decarboxylase; RRR=regular regulatory requirement; WR=written request.

Separate efficacy studies in patients with multiple sclerosis aged ≤17 years are regulatorily justified. However, exposing patients with multiple sclerosis of any age to placebo treatment withholds effective treatment and can cause irreparable damage to the central nervous system. The course of pediatric multiple sclerosis differs from adult multiple sclerosis, but the underlying process is inflammatory.[40,41] Teriflunamide, FDA-approved for multiple sclerosis treatment, works equally before and after the 18th birthday.[42] In the placebo group in study 4, (Table 2) effective treatment is witheld as is flexible treatment with combination therapy in underage and vulnerable patients.[43] It was both FDA- and EMA-triggered (Table 3). Preadolescent and adolescent multiple sclerosis patients need dose finding, not placebo-controlled randomized proof-of-efficacy studies once efficacy in human beings has been established. Dose finding can and should be performed in 1 or a few centers. Some physicians will use their medical wisdom and judgment and prescribe adequate treatment in underage patients[41]; others will hesitate because of concerns with off-label treatment.

Dalteparin, a low-molecular-weight heparin, is used for prophylaxis and treatment of venous thromboembolism. Study 5 (Table 2) was PIP-triggered (Table 3). Red and white blood cells and thrombocytes have the same size, weight, and function in humans of all ages, from the moment that blood cells emerge in the embryo,[44] dalteparin works in children, adolescents, and adults. This study confirmed the pharmaceutical properties of dalteparin in underage patients. It was regulatorily imposed, wasted medical resources, but did not harm patients.

Edoxaban, a novel oral anticoagulant works in all nonneonatal patients. Today, treatment with novel anticoagulants is standard of care.[45,46] Study 6 (Table 2) exposes underage patients to traditional standard of care, which today should be regarded as substandard. The sponsoring company is forced to undertake this study by an EU PIP (Table 3).

Studies 7 through 10 (Table 2) investigated the use of different growth hormones in children. Children with growth hormone deficiency experience retardation of growth. These studies demonstrate that there is a market for treatment of childhood diseases. None of these studies were triggered by a PIP or an FDA request based on pediatric legislation.

Liraglutide (study 11 in Table 2) is a human glucagon-like polypeptide-1 analogue approved for type 2 diabetes mellitus in several countries.[47] Both FDA and EMA demanded a separate study in patients with type 2 diabetes mellitus aged 10 to 17 years despite the fact that glucagon-like polypeptide-1 has the same mechanism of action before or after the 10th or 17th birthday. Because this study was placebo-controlled, it withheld effective treatment from the control group.

Studies 12 and 13 (Table 2) compared safety and efficacy of different insulin types in children and adolescents. Insulin does not change its mode of action with administrative age limits. Consequently, dose finding is medically justified but separate comparisons of different insulin types in underage patients is not. Nonetheless, both studies 12 and 13 were demanded by EU PIPs.

Study 14 (Table 2) investigated recombinant human glutamic acid decarboxylase in patients aged 10 to 20 years. Study 14

(Table 2) was terminated because the primary end point at 15 months was not met. This compound has not been approved in any country. The PIP demands 5 double-blind placebo-controlled so-called pediatric studies (Table 3): 1 in patients aged 10 to 18 years, 2 in patients aged 10 to 20 years, 1 in patients aged 4 to 9 years, and 1 in patients aged 1 to 3 years. To recruit patients into study 14 was premature.

Study 15 (Table 2) investigates adalimumab in Crohn's disease. Adalimumab, a tumor necrosis factor inhibitor, is FDA-approved for Crohn's disease for patients aged 6 years and older.[48] Study 15 is a registry study that will recruit >1000 patients in 213 centers worldwide. Because it is noninterventional, it will not harm patients. But in our opinion does not make medical sense and will not contribute practical information.

Etanercept is a tumor necrosis factor inhibitor with well-known anti-inflammatory characteristics, which are the same before and after the 18th birthday of patients. Studies 16 and 17 (Table 2) were open-label. They confirmed etanercept's anti-inflammatory characteristics. They did not harm patients but the study wasted medical resources and time as well as failed to contribute new information.

Celecoxib and naproxen are nonsteroidal anti-inflammatory drugs. Celecoxib is COX-2 selective. Study 18 (Table 2) was triggered by an FDA request. The study confirmed both celecoxib's and naproxen's anti-inflammatory characterics.[49] The sponsor of the study was rewarded by 6 months US patent extention for celecoxib[37] (Table 3).

Givinostat is a histone deacetylase inhibitor with anti-inflammatory potential still in clinical development.[50] Study 19 (Table 2) was the first of 2 PIP-demanded clinical studies (Table 3). The study was terminated due to lack of recruitment.[50]

Discussion

Today's medical progress depend upon clinical studies. Their role has become so crucial that a strong emphasis on methodology has emerged. Medical research should always help us "to understand the causes, development, and effects of diseases and improve preventive, diagnostic, and therapeutic interventions."[5] This is best exemplified by an ostensibly serious review of (nonexisting) randomized controlled trials to prove efficacy of parachutes that concludes that there are only 2 options: accept "that, under exceptional circumstances, common sense might be applied when considering the potential risks and benefits of interventions," or "continue our quest for the holy grail of exclusively evidence-based interventions and preclude parachute use outside the context of a properly conducted trial."[51] When Shirkey[20] in 1968 coined the term therapeutic orphans, most of his contemporary pediatricians simply ignored the pediatric warnings in the new US drug labels and used medications in children based on their medical judgment of what was best for the patient. We claim that these colleagues showed common sense (or medical wisdom) as was discussed in the parachute study.[51] They did not intellectually challenge these warnings, which were written by lawyers, not physicians, to prevent damage lawsuits in the litigious

United States. Nonetheless, Shirkey interpreted them as medical warnings. In our view, the time has come to challenge Shirkey's interpretation. He disregarded the fact that the FDA had/has no right to tell a physician how to use a drug and that off-label use of medications has gone on for the benefit of patients for many decades.[52] The therapeutic orphans concept is a blur at the interface of administration, law, and medicine.[2–4,53–55]

Funds from pharmaceutical companies into regulatorily justified pediatric studies have created a strong conflict of interest in pediatric academic research. Participation in international studies offers networking opportunities, publications, participation at investigators' meetings, and presentations at conferences. The local institutional review boards/ethics committees of >500 study centers listed in Table 2 approved these studies. Formally, these studies appear to be well substantiated, with protocols, scientific justifications, and demanded by regulatory authorities. In our opinion, many of the studies performed in Slovenia and other centers worldwide lack(ed) medical sense and are/were thus in breach of the Declaration of Helsinki. Patients with asthma, epilepsy, multiple sclerosis, type 2 diabetes mellitus, and in danger of venous thromboembolis are/were exposed to substandard treatment (studies 1, 2, 4, 6, and 11). All these studies recruit(ed) internationally.

It is futile to speculate about the motivation of past persons involved in pediatric drug development, which over the years has become a powerful international movement.[53,54] The previously detected toxicities from medications given to preterm newborns required appropriate additional focus on pediatric clinical pharmacology. Worldwide pediatricians and institutions promoted a greater focus on children's rights.[9,10] The turning point came when separate pediatric labels were believed to be the solution of the perceived therapeutic orphans challenge. Pediatric oncology has over decades established public trust. Participation in a clinical oncology study is regarded as standard-of-care. Historically the studies originally performed by the pediatric oncology clinical networks were not focused on labels, but on patients. When the FDA defined children as patients younger than age 17 years and was authorized to reward studies for that population, the studies it rewarded were no longer patient-centric, but label-centric. The European Union has taken up this approach, has expanded it by defining children as age younger than 18 years, and has with the PIP system established a procedure that in many areas even goes beyond FDA demands. We have shown for studies that recruited in Slovenia and many other countries that for those underage patients with serious diseases, some of these studies withheld known efficacious treatment to those in the placebo control group or the control group was given a treatment, that by today's standards, is outdated and hence substandard.

The therapeutic orphan and pediatric drug development concepts are clashing increasingly with the speed of modern drug development. In our view, it is undefendable to deny young patients with multiple sclerosis, asthma, epilepsy, autoinflammatory diseases, or other serious ailments effective standard-of-care treatment. It is time for institutional review boards/ethics committees worldwide to update training in pediatric drug development.[2–4,7,8,53–55]

The original good intentions of the pediatric laws are obvious in the FDA report to US Congress in 2001: The incentives provided by the newly authorized pediatric exclusivity should lead to significant advances in pediatric medicine. Superior drug treatment information is expected to permit quicker recoveries.[23] In contradistinction, the 2016 report states: "Integration of pediatric planning and exclusivity requests has become a regular part of product development. This has led to enormous progress in obtaining pediatric studies and has permitted new pediatric labeling of more than 600 products."[25] Comparing the 2001 and 2016 statments reflects the shift from expected clinical outcomes toward regulatory activism. Children and adolescents do not need as many studies as possible, but studies with the potential to improve treatment.

Conclusions

Scientific publications should be expected to ethically outline the regulatory background of reported studies. These research articles are the outcome of executive orders by bureaucracies that have become powerful, but insensitive to medical ethics. Slovenian institutional review boards/ethics committees should be encouraged to analyze each pediatrics-focused study for its medical

worthiness. Those found to be without merit or unethical should be suspended; questionable newly submitted studies should be rejected. institutional review boards/ethics committees worldwide need training in developmental pharmacology and physiology to prevent the future approval of questionable studies. US and EU pediatric legislation need to be revised to spare children and adolescents from being recruited into unnecessary and potentially harmful studies.

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Potential conflicts of interest

Dr. Rose consults on pediatric drug development, teaches, organizes scientific conferences, edits book, and publishes. The other authors have indicated that they have no potential conflicts of interest regarding the content of this article.

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