

Questionable international pediatric studies with Swiss participation

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Summary

Drug development and clinical studies are today international. Several global pharmaceutical companies are headquartered in Switzerland, and Switzerland is well connected into international academic research networks. Swiss clinical centers also participate at many international clinical studies.

The concept of children as "therapeutic orphans" claims that children are denied the use of many drugs; United States (US) and European Union (EU) laws promote pediatric studies sponsored by pharmaceutical industry. These studies recruit worldwide, but their medical sense has been challenged; they define children by chronological age, not physiologically.

We analyzed exemplarily international industry-sponsored pediatric studies in oncology, rheumatology, dermatology and gastroenterology listed in www.clinicaltrials.gov with at least one center in Switzerland, respectively, for their medical value.

The organs of newborns and babies differ physiologically from adults, requiring separate pharmacokinetic (PK) and dose-finding studies where a potential therapeutic need in these patients exists. Most analyzed regulatory-demanded pediatric studies repeat(ed) proof of efficacy in adolescents and children and were/are medically of limited value. In these patients absorption, distribution, metabolism and excretion are physiologically sufficiently comparable to adults. For pharmaceutical treatment, children need PK- and dose-finding studies, not separate proof of efficacy. PK and dose-finding in adolescents is medically unnecessary. Most pediatric studies triggered by US and EU regulatory demands constitute an abuse of patients. Several oncology studies deny access to appropriate treatment and/or expose patients to arbitrary treatment.

It would be desirable for Switzerland to introduce pharmaceutical law that allows treatment of underage patients based on physiology, not on chronological age. Swiss ethics committees should suspend ongoing questionable pediatric studies and reject newly submitted questionable studies.

Key words: Pediatric Drug Development, Better Medicines for Children, Pediatric Legislation, Pediatric Investigation Plan (PIP), Pediatric Clinical Pharmacology, Pediatric Regulation, Pediatric Exclusivity

Introduction

Testing of new medicines in clinical studies is global today. Switzerland is part of many worldwide scientific networks and participates in numerous international studies. United States (US) and European Union (EU) laws promote pediatric studies [1]. The SwissMedic and the Federal Office of Public Health's websites express thoughts about medicines for children comparable to the justifications of US & EU pediatric laws [2,3]. However, the medical value of pediatric studies triggered by regulatory authorities has been challenged [4-6].

We investigated pediatric studies in which Swiss centers participate(d) and challenge the medical value of many of these studies. It might be necessary to re-assess the definition of children in the context of pharmaceutical treatment, to re-assess the need for separate pediatric adult-type drug approval, and to address hidden conflicts of interest of pediatric researchers worldwide, including Switzerland, and of both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). We also challenge the concept of children as "therapeutic orphans" [7]. In view of our findings, we outline herein the potential consequences for Swiss clinical research, Swiss pharmaceutical laws, and Switzerland's scientific standing.

Methods

We searched www.clinicaltrials.gov for international industry-sponsored studies with involvement of at least one Swiss center and with the terms 'malignancy', 'juvenile idiopathic arthritis (JIA)', 'gastrointestinal disorder' and 'dermatologic disease', narrowing the age range of participants to "children" (birth - 17 years). Many new effective medications were developed in these clinical areas recently; they offer a solid exemplary cross section to investigate the impact of the international discussion about pediatric drug development [8, 9] on Swiss study clinical centers. Studies that recruited adolescents & adults or children and those that recruited only adolescents & adults were disregarded to focus on truly pediatric studies; studies with predominantly children plus young adults (<30 years) were reviewed. Studies performed only in Switzerland and studies sponsored by non-profit organizations were disregarded. For the identified studies, FDA and EMA documents were searched on the internet, using google and the FDA/EMA

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websites. The medical rationale of the studies was analyzed regarding the background literature, pediatric clinical pharmacology, and value. Pediatric investigation plan (PIP) decisions and studies in www.clinicaltrials.gov are listed with their PIP/NCT-number, allowing document retrieval by google and/or www.clinicaltrials.gov.

Background

A claim that children are discriminated against in drug treatment and drug development evolved after US law established the principle of clinical trials as the basis for regulatory drug approval, a principle today recognized worldwide [10]. The US law of 1962 didn't differentiate adults from children [11], but transferred jurisdiction over prescription drug advertising to the FDA [12]. In the 1950's, drug toxicities in newborns had been reported [13]. Drug developers soon included pediatric warnings into drug labels to avoid lawsuits. Due to the new FDA judicial authority, these drugs could not be advertised for children. Shirkey claimed this denied children the use of drugs and characterized children as "therapeutic orphans" [7]. The American Academy of Pediatrics (AAP) claimed that drug prescription for children without explicit FDA certification was experimental [14], and that children needed separate pharmacological evaluation of new drugs for all age groups [13]. FDA and AAP lobbying resulted in a 1997 law that rewarded pediatric studies with voluntary "pediatric exclusivity": additional six months protection against generic competition [1]. The company submits a proposal; if the FDA agrees, it issues a "Written Request" (WR). After study report submission and FDA scrutiny, pediatric exclusivity is granted [15]. A second law authorized the FDA to mandate pediatric studies without reward (pediatric research equity act, PREA, [1]). Both US laws are now permanent [16].

The US legislation inspired the EU to develop its own pediatric regulation, now in force since 2007 [1,6,17]. Without PIP, new drugs cannot get adult EU-approval, unless the targeted disease is PIP-exempted [5,6]. PIPs must address juvenile animal studies, formulations (e.g. tablets vs. syrup), pediatric studies, & more. The EMA issued more than 1000 PIPs [18].

The toxicities the AAP referred to in 1995 had been reported in *newborns* [13]. The AAP warnings "extrapolated" potential toxicities from *physiologically immature newborns* to all children, but in this "extrapolation" it used not the physiological, but the legal definition of children [5]. Pediatric laws responded to the AAP's "*moral imperative to formally study drugs in children so that they can enjoy equal access to existing as well as new therapeutic agents*" [13]. In our opinion, this does not reflect science, but an emotional appeal to protective instincts the word "child" triggers. US and EU pediatric laws define children not physiologically, but administratively: FDA <16 [19], EU <18 years [6,8].

Assuming fundamental differences between children and adults, the regulatory authorities require separate, repeated proof of safety & efficacy (S&E) in underage patients. Regarding efficacy, extrapolation from adults is deemed acceptable at various degrees, but already the term "extrapolation" suggests fundamentally different physiologies between adults and children, a flawed assumption with the

exception of newborns and babies. Regulatory standard requirements usually include separate pediatric proof of efficacy (or extrapolation), studies on pharmacokinetics (PK) and pharmacodynamics (PD), and dose finding studies for either 2-18 years olds, or sub-populations, e.g. 6-11 and 12-17 years olds, or further divided subpopulations [5, 20].

Results

Oncology

Table 1 lists international industry-sponsored pediatric studies with at least one Swiss center. All studies in table 1 are PIP-related, the respective PIP # is given in the 2nd column. Talimogene is a genetically modified viral oncolytic for local injection into unresectable recurrent melanoma after initial surgery [21], venetoclax a medication for chronic lymphatic leukemia [22]. There is also an FDA WR for atezolizumab [23], but the WR document is not on the internet.

Gastroenterology

Studies 1-3, table 2 correspond to the first three studies requested in the FDA pediatric pantoprazole WR [24]. The FDA requested pantoprazole pediatric studies both in the WR and under PREA; the clinical pharmacology of all pediatric studies is discussed in the FDA pediatric clinical pharmacology review [25]. The FDA granted pantoprazole pediatric exclusivity in 2009 [24]. These studies are reported and discussed in several papers [26-29].

Study 4, table 2 corresponds to the clinical study required in the tobramycin PIP.

Juvenile Idiopathic Arthritis (JIA)

The naproxen study (study 1, table 3) corresponds to neither a specific PIP nor a specific FDA WR. The FDA issued a naproxen WR, demanding a PK study and an S&E study in patients with juvenile rheumatoid arthritis [30]; today, the term "juvenile idiopathic arthritis" (JIA) is preferred. The canakinumab studies correspond both to FDA canakinumab registration studies [31,32] and to the studies required in the canakinumab PIP, see table 4.

Abatacept was assessed in a three-part study including an open-label extension in JIA patients 6-17 years [33]. The FDA demanded abatacept studies in a WR [34] and by PREA [35]. Two abatacept PIPs (EMA-00118-PIP01-07-M01, for i.v. infusion; EMA-000118-PIP02-10-M02 for subcutaneous administration) are for poliarticular JIA (pJIA), one (EMA-00118-PIP03-15) for systemic lupus erythematoses. The abatacept study in table 3 corresponds both to the FDA PREA study and to the abatacept PIP EMA-00118-PIP01-07-M01

Dermatology

Study 1, table 5 corresponds to the first clinical study demanded in the secukinumab PIP.

Study 2, table 5 corresponds to study 4 in the canakinumab PIP EMA-000060-PIP01-07-M03. Study 3, table 5 was the follow-up study to study 2, corresponding to study 5 in the same PIP.

Discussion

Oncology

Genomic analysis shows that "conventional" melanoma is the same in adolescents and adults, while Spitz nevi, Spitzoid melanomas, and melanomas arising within giant congenital melanocytic nevi are different [36]. Talimogene is a drug for local injection into unresectable recurrent melanoma [21]. www.clinicaltrials.gov lists 32 talimogene studies in various cancer types. If a primary endpoint is reached, Amgen will ask for approval for another indication. Study 1 [table 1](#) plans to recruit 18 patients worldwide in 17 centers with different cancer types. The only common element of these patients is their age and that they have cancer. In our opinion, there is no medical rationale

for this study. Amgen is committed to this study because without PIP the EMA would have blocked talimogene approval.

Three combination systemic treatments for metastatic melanoma are now FDA-approved. Study#2, [table 1](#) (paclitaxel) is one of four monotherapy studies that currently is recruiting worldwide different solid tumors in underage patients, including melanoma [4,5,37], although superior combination treatment is available. These four studies in our estimation should be suspended. Melanoma patients should receive combination treatment, perhaps combined with talimogene injection. Patients with cancer should be offered the best treatment available, particularly adolescents for whose neoplasms approved therapy exists.

Table 1: International industry-sponsored pediatric studies in Malignancies with Swiss centers

#	NCT# / PIP#	Abbreviated study description	Sponsor	Age	Patients/ centers	Status	Swiss centers
1	NCT02756845 / EMEA-001251-PIP01-11-M03	S&E of talimogene laherparepvec in advanced non-CNS tumors	Amgen	12-21 y (P1) 2-11 y (P2)	18/ 17	Recruiting	Basel, Zuerich
2	NCT01962103/ EMEA-001308-PIP01-12-M01	DF & PE of paclitaxel in R/R solid tumors	Celgene	6 mo-17 y (P1) 2-24 y (P2)	107/ 20	Active NR	Zuerich
3	NCT02393859 / EMEA-000574-PIP02-12-M01	Blinatumomab E, S, T as consolidation therapy vs. conventional consolidation chemotherapy with HR first relapse B-precursor ALL	Amgen	<17 y	320/ 76	Recruiting	Basel, Zuerich
4	NCT02187354 / EMEA-000574-PIP02-12-M01	Blinatumomab expanded access in R/R B-precursor ALL	Amgen	<17 y	?/ 19	Available	Zuerich
5	NCT03236857 / EMEA-002018-PIP02-16	S & PK of Venetoclax in R/R malignancies	AbbVie	<25 y	135/ 25	Recruiting	Zuerich
6	NCT02541604 / EMEA-001638-PIP01-14-M01	Atezolizumab in previously treated solid tumors	Roche	<30 y	100/ 58	Recruiting	Zuerich
7	NCT02197416 / EMEA-000081-PIP01-07-M09	Dabigatran Etexilate for Secondary Prevention of Venous Thromboembolism	BI	<18 y	100/ 76	Recruiting	Lausanne, Zuerich
8	NCT02447666 / EMEA-001272-PIP02-13-M01	Azacitidine PK, PD, S, A, & comparison to historical control in AMDS or JMML before HSCT	Celgene	1 mo – 18 y	55/ 39	Recruiting	Zuerich

Abbreviations in alphabetic order: ALL Acute Lymphoblastic Leukemia; AMDS advanced myelodysplastic syndrome; BI Boehringer Ingelheim; CH Confoederatio Helvetica = Switzerland; CNS central nervous system; HSCT Hematopoietic Stem Cell Transplantation; JMML juvenile myelomonocytic leukemia; NR not recruiting; P1 Phase 1; P2 Phase 2; Roche Hoffman-La Roche = Genentech/Roche; R/R relapsed or refractory; S&E safety & efficacy

Table 2: International industry-sponsored pediatric studies in gastrointestinal disorders

#	NCT# / PIP#	Abbreviated study description	Sponsor	Age	Patients/ centers	Status	Swiss Centers
1	NCT00868296	Pantoprazole in presumed GERD	Wyeth*	<12 mo	58/71	Completed 2006-2008	Zuerich
2	NCT00362609	Pantoprazole in GERD	Wyeth*	<28 days	59/71	Completed 2006-2007	Zuerich
3	NCT00259012	Pantoprazole in GERD	Wyeth*	1-11 mo	67/31	Completed 2005-2008	Zuerich
4	NCT01082367 / EMEA-000184-PIP02-14	R DB PC S&E study of inhaled tobramycin for treatment of early infections of p. aeruginosa in CF	Novartis	3 mo-6 y	50/19	Completed 2010-2015	Zuerich

Abbreviations: GERD gastro-intestinal reflux disease; PK pharmacokinetics; S&E safety & efficacy; R randomized; DB double-blind; PC placebo-controlled; CF cystic fibrosis
Explanations: *Wyeth is today part of Pfizer

Table 3: International industry-sponsored JIA studies with Swiss centers

#	NCT# / PIP#	Abbreviated study description	Sponsor	Age	Patients/ centers	Status	Swiss Centers
1	NCT00807846	Effects of celecoxib or naproxen on blood pressure in JIA	Pfizer	2-17 y	201/ 39	Completed 2009-2012	Lausanne, Zuerich
2	NCT00886769 / EMEA-000060-PIP02-08-M06	R DB PC canakinumab study in JIA	Novartis	2-19 y	84/ 91	Terminated 2009-2011	Bern, Lausanne, Zuerich
3	NCT00889863 / EMEA-000060-PIP02-08-M06	Flare prevention of canakinumab in JIA	Novartis	2-19 y	177/ 73	Completed 2009-2011	Bern, Lausanne, Zuerich
4	NCT00891046 / EMEA-000060-PIP02-08-M06	OL canakinumab JIA extension study	Novartis	2-19 y	270/73	Completed 2009-2014	Lausanne
5	NCT00095173 / EMEA-00118-PIP01-07-M01	Abatacept R withdrawal S&E study in active polyarticular JIA	BMS	6-17 y	214/ 36	Completed 2003-2011	Lausanne

Abbreviations: JIA juvenile idiopathic arthritis; BMS Bristol Myers Squibb; JIA juvenile idiopathic arthritis; R randomized; DB double-blind; PC placebo-controlled; OL open label

What is the value of testing blinatumomab separately in minors vs. standard chemotherapy (table 1, studies 3-4)? This kind of study offers little value and prevents innovative treatment, e.g. tisagenlecleucel [38]. There is little expectation that underage patients with various tumors will benefit from venetoclax or atezolizumab (table 1, studies 5-6). Medically, separate proof of S&E of dabigatran in minors should not be required (table 1 study#7). Studying PK of azacitidine in patients <1 year makes medical sense, but not in patients <18 years (table 1 study 8).

Gastroenterology

Clinical investigation of pantoprazole in newborns and babies aged up to 12 months (table 2, studies 1-3) is appropriate. However, it is not appropriate to undertake a pantoprazole study on pantoprazole PK and safety in children and adolescents from 6-16 years [39] that was performed outside of Switzerland: PK investigation in very young children is valid, but separate PK investigation in adolescents is not.

There was no medical need for the double-blind placebo-controlled study to prove S&E of inhaled tobramycin in children with cystic fibrosis (table 2 study 4). Children with cystic fibrosis are similar to adults with this disease. Dose-finding in children would have been appropriate, but not placebo-controlled separate proof of S&E. Novartis had to perform this study because the EMA forced them into this commitment without which, EU approval would have been blocked.

Rheumatology

The separate efficacy studies in minors with autoinflammatory diseases have not resulted in significant findings (table 3). Antiinflammatory compounds like canakinumab or abatacept work in patients before and after the 16th/18th

birthday. For PK, the study of prepubertal patients would have been sufficient.

Two canakinumab studies that were the basis of the FDA systemic JIA approval (study 2-3, table 3) corresponded both to the FDA systemic JIA registration studies (FDA studies 1&2, table 4) and to the PIP studies#2-3 (table 4). Study#4, table 3 corresponds to PIP study 4. These studies had to prove efficacy separately in minors. In our opinion there is no medical rationale for an abatacept S&E study (table 3, study #5) in patients 6-17 years. The patients' bodies are not altered on their 18th birthday. Such studies are performed for two reasons. The regulatory authorities insist on separate data in the two patient populations, adult vs. pediatric, and pediatric rheumatologists further their career by fulfilling this requirement with resultant publications [40-45].

Neither FDA WR nor PIP-demanded placebo-controlled studies in JIA or other autoinflammatory diseases are needed. There is no doubt that abatacept has antiinflammatory characteristics before and after the 18th birthday. These FDA and EMA JIA pediatric study demands are not based on science, but on the flawed "therapeutic orphans" concept.

Dermatology

There is no medical sense in a separate randomized etanercept-controlled secukinumab study in patients 6-17 years (table 5 study 1). Secukinumab as well as canakinumab are antiinflammatory before and after the 18th birthday.

Conclusions

Clinical trials have become global. US/EU pediatric laws have contributed to and foster an international network of pediatric researchers that perform unnecessary pediatric studies, including "pediatric" studies in physiological adults. The flow of money that oils this international "pe-

Table 4: Regulatory-demanded clinical canakinumab SJIA studies

FDA SJIA registration studies [31]	1. Randomized, double-blind, placebo-controlled, single-dose 4-week study assessing the short term efficacy of canakinumab in 84 patients randomized to receive a single subcutaneous dose of 4 mg/kg ILARIS or placebo. Primary objective: show superiority of canakinumab vs. placebo in the proportion of patients with at least 30% improvement in an adapted pediatric American College of Rheumatology (ACR) response criterion 2. Randomized, double-blind, placebo-controlled, withdrawal study of canakinumab flare prevention in patients with active SJIA. The study consisted of 2 major parts: 177 patients received 4 mg/kg canakinumab s.c. every 4 weeks in Part I; 100 of these patients continued into Part II to receive either canakinumab 4 mg/kg or placebo s.c. every 4 weeks.
FDA post-marketing requirement 2013 [32]	1. A long-term safety study in 100 pediatric patients 2 to 17 years of age with systemic JIA (SJIA) treated with canakinumab to evaluate for the risks of serious infections, neutropenia, thrombocytopenia, severe injection site reactions, and MAS. The study should include a control group of SJIA patients not receiving canakinumab. Patients should be followed for 5 years. Final Protocol Submission October 2013; Study Completion June 2022; Final Report Submission: June 2023
PIP EMEA-000060-PIP02-08-M06	1. Multi-centre, open label, repeated dose range finding study to evaluate the safety, tolerability, immunogenicity and pharmacokinetics of s.c. canakinumab in paediatric subjects with active systemic juvenile idiopathic arthritis. 2. Randomized, double-blind, placebo controlled, single-dose study to assess the efficacy of canakinumab in patients 2 - 19 y with SJIA and active systemic manifestations. 3. Randomized, double-blind, placebo controlled, withdrawal study of flare prevention of canakinumab in patients 2 - 19 y with SJIA and active systemic manifestations. 4. Open-label extension study in patients with SJIA and active systemic manifestations.

Abbreviations: SJIA systemic juvenile idiopathic arthritis

Table 5: International industry-sponsored pediatric studies in dermatology

#	NCT#/ PIP#	Abbreviated study description	Sponsor	Age	Patients/centers	Status	Swiss Centers
1	NCT02471144/ EMEA-000380-PIP01-08-M03	R DB active-controlled secukinumab in severe plaque psoriasis	Novartis	6-17 y	169/ 58	Recruiting	St. Gallen, Zuerich
2	NCT01302860 / EMEA-000060-PIP01-07-M03	E, S, T of canakinumab in CAPS	Novartis	1-5 y	17/ 12	Completed 2010-2014	St. Gallen, Zuerich
3	NCT01576367 / EMEA-000060-PIP01-07-M03	Canakinumab CAPS extension study	Novartis	1-4 y	17/12	Completed 2012-2015	St. Gallen, Zuerich

Abbreviations: R randomized; DB double-blind; E efficacy; S safety; T tolerability; CAPS cryopyrin-associated periodic syndromes

diatric research" machinery is channeled from drug-developing pharmaceutical companies by FDA/EMA decisions into the pediatric research networks. For academic researchers, study participation allows networking, investigators' meetings, publications, and career advancement. Not all studies are performed in Switzerland. The decision of pharmaceutical companies to include or not include one or several Swiss centers depends on many factors including academic "marketing" for participation. The scientific and ethical integrity of most international multicenter industry-sponsored pediatric studies triggered by FDA- and EMA requests/demands is questionable.

So far, representatives of pediatric oncology and pediatric rheumatology have been strongly supportive of pediatric legislation [46,47]. There are strong conflicts of interest hidden behind emotional but misleading appeals to allegedly improve children's health through clinical studies. The conflicts of interest have so far not been addressed in the literature. These studies cause delays in therapy being made available to children and are part of the reason new medications are so expensive.

The majority of medically questionable pediatric studies performed in Switzerland were and are triggered by EU PIPs. US PREA does not apply to orphan designations. Furthermore, the EMA has constantly removed diseases from the list of PIP-exempted diseases. From 2018 on, PIPs will be required for drug submissions in hepatic cancer, Parkinson and amyotrophic lateral sclerosis [48], which rarely occur in minors. Compared to the number of PIP-studies, WR-triggered studies are fewer.

The discussed questionable studies are not performed in orphanages, remote Alabama regions like Tuskegee, or concentration camps [49], but in clean, well-organized hospitals that are committed to the highest standards of medical ethics. They are orchestrated by regulatory authorities that are caught in the flawed dogma of children as pediatric orphans. The PIP-triggered paclitaxel study, enforced by the EMA pediatric committee, exposes young melanoma patients to an arbitrary monotherapy, that lacks beneficence [50]. In our opinion the EMA pediatric committee is obsessed with promoting pediatric studies, most of which are medically unnecessary, and of which many, specifically in lethal diseases like cancer, potentially harm patients. The "therapeutic orphans" dogma is a blur at the interface of medicine and law [5] in our increasingly complex global society. It would be in pharmaceutical companies' own interest to defend pediatric patients against regulatory authorities.

The "therapeutic orphans" concept evolved with the entry of regulatory clinical trials into the world of clinical medicine, drug development and drug approval. Pediatric legislation in both the US and the EU intended to improve child healthcare. Clinical centers worldwide that participate in pediatric clinical trials, that in our opinion are questionable, perform high quality medical care on a daily base and also participate in scientifically justified clinical studies. Most clinicians that participate in questionable trials are unaware of the regulatory background of modern drug development and welcome the opportunity for international networking, publishing, and exchange of ideas. The "therapeutic orphans" concept was not invented by intentionally dishonest pediatricians. It was a construct born in a time where drug development was in its early stages, when the

world was still shocked by the horror of the thalidomide tragedy, and when the thought of children's rights and well-being began to play a major role in societal thinking. Half a century after its conception, it is time to challenge the "therapeutic orphans" concept that has become a regulatory dogma that exposes children to unnecessary clinical studies worldwide, including Switzerland.

It would be desirable for Switzerland to introduce a pharmaceutical law that would allow adaption of drug treatment to the physiological maturity of the patient, not his/her chronological age.

Disclosure statement

Klaus Rose worked 20 years within pharmaceutical industry in clinical development and medical affairs. Being independent since 2011, he provides consultation on paediatric drug development issues, teaches and organises conferences, as well as publishes and edits books. He receives annual royalties from Springer publishers for a book on paediatric formulations that he co-edited. He still owns shares of his former employers Roche/Genentech and Novartis. His clients are small, medium-sized, and large pharmaceutical companies and academic institutions. In addition, he is the father of a daughter with a rare syndrome and is thus biased against empty governmental promises. Jane M. Grant-Kels declares no competing interests.

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