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Questionable Industry-Sponsored Pediatric Studies in China Triggered by United States of America (US) and European Union (EU) Regulatory Authorities

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Abstract

Background

Characterizing children as "therapeutic orphans" alleges that children were/are denied the use of many drugs. Both the United States (US) and the European Union (EU) issued laws based on this concept, promoting industry-sponsored pediatric studies that recruit worldwide. We challenge their medical usefulness.

Methods

We analyzed pediatric studies with Chinese centers sponsored by international pharmaceutical companies listed in www.clinicaltrials.gov for their medical value.

Results

Some studies have medical significance, but the majority are without medical value. Adolescents' bodies are physiologically mature. For children, pharmacokinetic and dose-finding studies are sufficient. Only newborns/babies are so different that separate proof of efficacy is medically justified. The identified questionable studies are formally regulatorily justified, but are medically futile and unethical. A fraction of international pediatric academia is corrupted by industry funds channeled via regulatory decisions into medically pointless studies. Compared to other countries, the portion of studies sponsored by international pharmaceutical companies in China is limited, but China has been involved nonetheless.

Conclusions

Pediatric studies triggered by regulatory demands are a serious abuse of young patients worldwide. They are medically redundant at best and deter patients with serious potentially life-threatening diseases from access to effective innovative therapy. They have the potential to jeopardize public trust in science and research. Also Chinese Institutional Review Boards (IRBs)/ ethics committees (ECs) should be alerted, suspend questionable pediatric studies, and reject newly submitted ones. Innovative Chinese legislation that bases pharmacological treatment on the body's physiology, not the date of birth, is recommended.

Keywords

Pediatric Drug Development; Pediatric Legislation; Pediatric Investigation Plan (PIP); Better Medicines for Children; Pediatric Clinical Pharmacology; Pediatric Pharmaceutical Laws

Abbreviations

AAP: American Academia of Pediatric
ADME: Absorption, Distribution, Metabolism, Excretion
EC: Ethics Committee
EMA: European Medicines Agency
ENPR-EMA: European Network of Pediatric Research at the EMA

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EU: European Union
FDA: US Food and Drug Administration
GRiP: Global Research in Pediatrics
IRB: Institutional Review Board
MRI: Magnetic Resonance Imaging
MS: Multiple Sclerosis
NCT Number: National Clinical Trials registration number in www.clinicaltrials.gov
OTC: Over the Counter
PK: Pharmacokinetics
PIP: Pediatric Investigation Plan
PREA: Pediatric Research Equity Act
S and E: Safety and Efficacy
US: United States of America
WHO: World Health Organisation
WR: FDA Pediatric Written Request

Introduction

The United States of America (US) and the European Union (EU) promote pediatric clinical studies sponsored by pharmaceutical industry [1-3], but the medical value of these studies is now being increasingly challenged [4-8]. We analyzed to what degree pediatric studies that were/are performed in China and were/are sponsored by international pharmaceutical companies were triggered by requests from US and EU regulatory authorities, and we investigated to what degree these studies correspond to the primary aim of medical research as defined in the declaration of Helsinki, i.e. "to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments)" [9].

The theory that children are discriminated in drug development and drug treatment [10] evolved after US law established in 1962 clinical trials as the basis for regulatory approval [11], a principle now recognized worldwide [12]. The same law also transferred jurisdiction over prescription drug advertising to the FDA [13]. In the 1950's, drug toxicities in preterm newborns had been reported [14, 15]. In follow-up, drug manufacturers inserted pediatric warnings into labels to avoid potential litigation. Due to the new FDA judicial authority, such drugs could no longer be advertised for children. Shirkey stated this denied children the use of drugs and characterized them as "therapeutic orphans" [10]. The American Academy of Pediatrics (AAP) took up Shirkey's position. In 1977, it claimed that that drug prescription for children without explicit FDA certification was experimental [16], and in 1995, that for children of all age groups separate pharmacological evaluation of new drugs were necessary [17]. FDA and AAP lobbying resulted in 1997 in US law that rewarded industry-sponsored pediatric studies with voluntary "pediatric exclusivity": an additional six months protection against generic competition [1]. The company first submits a proposal; if this is accepted by the FDA, it issues a "Written Request" (WR). Once the report of the requested study/studies has been submitted, examined and accepted, the FDA grants pediatric exclusivity [1]. The financial worth of such a pediatric exclusivity can be substantial [18]. Later, the "Pediatric Research Equity Act" (PREA), a second law, authorized the FDA to mandate pediatric studies without reward [1, 19].

The US pediatric laws inspired the EU to establish its own pediatric regulation, which has been operational since 2007 [1, 20]. Without PIP, new drugs can no longer be approved for adults in the EU, unless the targeted disease is PIP-exempted [1, 21, 22]. PIPs must propose juvenile animal studies, child-friendly formulations (e.g. liquids vs. tablets), clinical studies, and more. The PIP negotiation takes approximately one year from initial submission to EMA for approval. The EMA has so far issued >1000 PIPs [21]. In response to a recent paper that critically reviewed the PIPs [7], EMA employees published a counter-position [2], which might be useful for any reader who wants to compare the arguments of both sides.

The toxicities the AAP referred to were reported in premature newborns [14, 15]. The AAP warnings extrapolated potential toxicities from immature newborns to all children. Furthermore, this extrapolation used the legal, not the physiological term of children [17]. US and EU pediatric laws responded to the AAP's "moral imperative to formally study drugs in children" [17], which was not based on science, but was an emotional appeal to protective instincts the word "child" triggers in most civilized persons. US and EU pediatric laws define children not physiologically, but administratively: <16 (FDA)/ <18 years (EU) [1, 20, 24].

Methods

We identified in www.clinicaltrial.gov pediatric studies sponsored by international pharmaceutical companies in 0-17 year old patients. We disregarded studies that involved either adolescents and adults or children as well as those involving adolescents and adults in an effort to focus on truly pediatric studies, but we included studies recruiting patients up to 21 years old. We

also excluded vaccination studies. We retrieved related US Food and Drug (FDA)/ European Medicines Agency (EMA) documents from the internet. We examined if these studies were justified by the principles of medical research as defined by the declaration of Helsinki [9], and further key documents that define the ethics of human research [25-27]. We also analyzed the studies‘ design, justification and main endpoints with the background of what is now known regarding developmental pharmacology [28]. EMA pediatric investigation plan (PIP) decisions and studies in www.clinicaltrials.gov are given by the respective PIP/ NCT-number, allowing immediate internet-retrieval.

Results

Table 1 contains the pediatric studies listed in www.clinicaltrials.gov with study centers only in China (studies 9, 10, 11, 13, 19) or centers in China and other countries, sponsored by international pharmaceutical companies. The column "PIP#/WR" indicates if the respective study was triggered by an EMA-issued PIP (studies 3, 4, 11, 14, 15, 17-21), by FDA written requests (WRs) (studies 1, 2, 6-8), by FDA PREA demands (study 16), or was/is sponsored for other reasons. Cetaphil Restoraderm (study 5) is a cream containing soaps and moisturizers, available "over the counter" (OTC). This study appears to be a marketing study, as do the two fluticasone studies (#9-10), for which we could not identify FDA/EMA pediatric requests/demands.

Table 2 lists in alphabetic order description and indication of the compounds in Table 1.

Discussion

Individual Studies

Numerous publications confirm the efficacy of innovative anti-inflammatory biologics in "underage" patients [35, 36]. Why should these drugs not work in patients that are younger than 16 or 18 years old? The immune system, receptors and organs of adolescents are the same before and after the 16th/18th birthday. Representatives of the pediatric rheumatology international trials organization (PRINTO) report that "children" up to 17 years were successfully treated with anti-inflammatory biologics by PIP-triggered studies [35, 36]. However, 17 years old patients are physiologically no longer children, but rather young adults. Multiple clinical trials with anti-inflammatory biologics have recruited worldwide over a thousand "pediatric" patients, but the justification for these trials was/is formal and regulatory, not medical [35, 36]. For prepubertal children dose finding is necessary. Once the body is mature, adult doses are adequate. The planned study to evaluate efficacy and safety (E&S) of tocilizumab in Chinese patients (table 1, study 19) will not answer medically relevant questions. The efficacy of tocilizumab in humans is already well known. It is not relevant if this study is directly triggered by the tocilizumab PIP or is being repeated in China for marketing reasons. This trial is medically unnecessary, questionable, unethical, and should be suspended before it starts recruiting.

Why investigate peg interferon alpha-2a separately in children and adolescents if the drug has been proven efficacious in adults? (Study 15 table 1). Peg interferon alpha-2a is a well-established treatment for chronic hepatitis B [37]. Study 15 table 1 is precisely the same clinical study no. 4 demanded in the EMA peg interferon alpha-2a PIP. Roche was forced to accept this PIP and to execute it. If they had not, the EMA would have blocked adult EU-approval. This clinical study is not driven by clinical beneficence as all clinical trials should be [26]. But by the EMA's obsession to enforce more pediatric studies. Since physiologically adolescent patients are no longer children, this study is unnecessary, questionable, unethical, and should be suspended in our opinion.

Why should a chemotherapy agent like clofarabine work differently in patients older or younger than 21 years? Based on an FDA WR [30]. This study afforded the sponsoring company a "pediatric exclusivity", i.e. protecting the drug against generic competition for 6 more months, which can for a company be quite rewarding n [18]. But this study was not in the participating patients' interest. When the study started in 2009, the role of clofarabine in the treatment of relapsing or remitting acute lymphatic leukemia was already well known.

Similarly, why should an antifungal compound like voriconazole work differently in patients older or younger than 17 years? (Study 21, table 1).

Bosentan is a compound for pulmonary arterial hypertension. Study 2, table 1 investigated PK, tolerability, and S&E in patients 3 months to 12 years of age; study 3 was an extension study. PK and dose finding studies in neonates and babies $\leq$1 year old are medically justified, but not in patients up to 12 years. The bosentan studies were medically justified only in a small proportion of the participating patients. Performed worldwide in 64 patients in 48 centers, these studies were to a large degree a waste of time and resources and were ethically questionable.

Table 1: International Industry Sponsored PIP-Triggered Pediatric Studies In China

#	NCT# / PIP#	Abbreviated Study Description	Sponsor	Age	Pts/Centers	Status	PIP#/WR
1	NCT00486083	Atomoxetine in ADHD**	Eli Lilly	6-16y	330/?	C 2003-2004	FDA WR [29]
2	NCT00471354	Atomoxetine in ADHD***	Eli Lilly	8-11y	228/?	C 2007-2008	FDA WR [29]
3	NCT01223352	Bosentan in PAH	Actelion	3mo-12y	64/ 48	C 2011-2013	EMEA-000425-PIP02-10-M04
4	NCT01338415	Bosentan in PAH	Actelion	3mo-12y	58/ 47	C 2011-2014	EMEA-000425-PIP02-10-M04
5	NCT02589392	Cetaphil Restoraderm in AD****	Galderma	2-12y	120/ 8	C 2015-2016	NRI - OTC
6	NCT02544789	Clofarabine in R/R ALL	Betta	1-21y	44/ 6	C 2009-2012	FDA WR [30]
7	NCT00396877	E&S of clopidogrel in STPASP	Sanofi	<92 days	906/ 31	C 2006-2010	FDA WR [31]
8	NCT00565448	Docetaxel + cisplatin in NPC	Sanofi	1mo-21y	75/ 26	C 2007-2012	FDA WR [32]
9	NCT01915914	OL R Fluticasone cream in AD*	GSK	1-18y	107/ 4	C 2013-2015	NRI - phase IV study
10	NCT02424539	Two fluticasone doses in AR*	GSK	2-12y	360/ 16	Recruiting	NRI - phase IV study
11	NCT01687296	Fluticasone vs prednisone in A*	GSK	4-16y	261/ 11	C 2012-2013	EMEA-000431-PIP01-08-M10
12	NCT01223131	Insulin glargine vs. NPH insulin	Sanofi	6-17y	162/ 10	C 2011-2014	Chinese reg. requirements
13	NCT02427958	E&S of leuprorelin in CPP*	Takeda	1-9y	300/ 9	Active NR	NRI - phase IV study
14	NCT02932410	Macitentan	Actelion	2-17y	300/ 86	Recruiting	EMEA-001032-PIP01-10-M02
15	NCT01519960	Peginterferon α-2a in HEP B	Roche	3-17y	165/ 44	Active NR	EMEA-000298-PIP01-08-M05
16	NCT02072824	Pregabalin in POS	Pfizer	1mo - 3y	113/ 118	Recruiting	FDA PREA [33,34]
17	NCT02234843	Rivaroxaban in venous Thromb	Bayer	6mo-17y	270/ 162	Recruiting	EMEA-000430-PIP01-08-M10
18	NCT02201108	Teriflunomide in MS	Genzyme	10-17y	166/ 69	Active NR	EMEA-001094-PIP01-10-M04
19	NCT03301883	Tocilizumab Ph4 study in sJIA*	Roche	2-17y	65/?	not yet recr	EMEA-000309-PIP01-08-M07
20	NCT01493778	Turoctocog in hemophilia A	Novo N	<6y	60/69	Active NR	EMEA-001174-PIP02-12-M02
21	NCT01092832	Voriconazole in TCI	Pfizer	2-17y	23/ 14	Terminated	EMEA-000191-PIP01-08-M05

Centers: *China (中夏) only **中夏, Korea, Mexico ***中夏, Korea, Taiwan ****中夏, Philippines All others: 中夏 + ROW

Abbreviations in alphabetic order: • 中夏 China • **A** asthma • **AD** atopic dermatitis • **ALL** acute lymphoblastic leukemia • **ADHD** attention deficit hyperactivity syndrome • **AR** allergic rhinitis • **CPP** central precocious puberty • **C** completed • **DM** diabetes mellitus • **E&S** efficacy & safety •**GHD** growth hormone deficiency • **GS** GeneScience • **GSK** GlaxoSmithKline • **HEP** hepatitis •**MS** multiple sclerosis • **Novo N** Novo Nordisk • **NPC** nasopharyngeal carcinoma • **PMR** post-marketing requirement • **NPH** neutral protamine hagedorn • **NR** non recruiting • **NRI** No regulatory involvement • **OTC** over-the-counter •**OL** open label • **PAH** pulmonary arterial hypertension • **PEG** pegylated • **POS** partial onset seizures • **PREA** Pediatric Research Equity Act • **R** randomized • **recr** recruiting • **reg** regulatory • **ROW** rest of the world • **R/R** refractory or relapsed • **S** Syndrome • **sJIA** systemic juvenile idiopathic arthritis • **STPASP** Systemic To Pulmonary Artery Shunt Palliation • **TCI** throat candida infection • **TS** Turner Syndrome • **venous Thromb** venous Thrombosis •

Table 2: Compound Description/ Indication In Alphabetic Order

Compound	Description/ Indication
Atomoxetine	Noradrenaline reuptake inhibitor for ADHD
Bosentan	Dual endothelin receptor antagonist for pulmonary arterial hypertension
Cetaphil Restoraderm	OTC product for eczema, containing soaps and moisturizers
Clofarabine	Chemotherapy drug for relapsed or refractory ALL
Clopidogrel	Platelet activation inhibitor for prevention of heart disease and stroke
Docetaxel	Chemotherapy drug for various cancer types
Fluticasone	Glucocorticoid: anti-inflammatory and vasoconstriction effects
Insulin glargine	Long-acting basal insulin analogue
Leuprorelin	GnRH receptor agonist, used for various cancer types and early puberty
Macitentan	Endothelin receptor antagonist for pulmonary arterial hypertension
Peginterferon α-2a	Pegylated interferon alpha-2a
Pregabalin	Drug against epilepsy, neuropathic pain, fibromyalgia, and GAD
Rivaroxaban	Oral anticoagulant
Teriflunomide	Immunomodulatory drug for multiple sclerosis
Tocilizumab	Humanized MAB against IL-6R
Turoctocog	Recombinant antihemophilic factor VIII, used in haemophelia A
Voriconazole	Antifungal drug
Abbreviations in alphabetic order: ADHD attention deficit hyperactivity disorder • ALL acute lymphoblastic leukemia • **GAD** generalized anxiety disorder • **GnRH** gonadotropin releasing hormone • **IL-6R** interleukin-6 receptor • **MAB** monoclonal antibody • **OTC** over-the-counter •	

The study of fluticasone in asthma (study 11, table 1) was triggered by a PIP. However, there is no question regarding the efficacy of inhaled fluticasone in patients younger than 16 years. This study was therefore superfluous.

Why should insulin glargine or neutral protamine Hagedorn (NPH) insulin work differently in persons above or below the 18th birthday? The FDA issued in 1998 a WR for insulin glargine [38], which triggered a clinical trial in 349 children and adolescents? [39], which led to FDA pediatric exclusivity and registration in children? [38]. Study 12 table 1, was initiated many years later. The insulin glargine study was initiated because the drug was not licensed in children in China [40]. The reason that Sanofi paid for this study, as documented in www.clinicaltrials.gov, was probably that Sanofi wanted pediatric approval also in China. While this made sense from an economic point of view, there was no medical value in this study. It simply repeated what was already well known.

Docetaxel is a chemotherapy agent used for various cancers. Cytotoxics are also cytotoxic in children and adolescents. The development of pediatric oncology involved the systematic investigation of chemotherapy in various pediatric cancers, which improved survival of child malignancies considerably [41]. Although there was no medical logic in a separate investigation of docetaxel efficacy in pediatric patients, the FDA nonetheless had issued a docetaxel WR. Study no. 8, table 1, which corresponds to study no. 3 of the FDA WR [32]. Performed worldwide including centers in China. The study was reported in 2015 [42]. And not surprisingly the outcome was negative. This is a good example of pediatric studies that are triggered by regulatory requests/demands, but have no medical value. For patients and parents, such studies create(d) unfounded hope. The drug manufacturer could balance the study costs with 6 months pediatric exclusivity, so economically this study made sense. Apart from the manufacturer, the other group that profits are pediatric oncologists. These international studies are complex, require demanding logistics, and result in international meetings, networking, and publishing.

Multiple sclerosis (MS) is an inflammatory autoimmune disease that predominantly affects adults, but rarely also underage patients. Although pediatric MS appears to be overall a more inflammatory disease than adult MS, with more frequent relapses and magnetic resonance imaging (MRI) lesion accrual [43]. There is no doubt that it is an inflammatory autoimmune disease

in younger patients as in adults [44, 45]. A well-known specialist in pediatric MS stated that whether "both children and adolescents should be included in the same ‚paediatric' category is also a matter of debate; however, most societies have, for social, judicial, ethical and educational purposes, made this distinction for those under the age of 16–18" [45]. And: "If we truly believed that this was the same disease, then there would be no need to study the effect of treatments in the paediatric population, because ‚equipoise' would not exist as to their efficacy" [45]. We fully agree with this statement, but challenge her fundamental assumption. Even though for social, judicial, ethical and educational purposes the age limit of adulthood is somewhere around 16-18 years, that does not imply that this must also be the case for pharmaceutical treatment. There is no equipoise in separate pediatric MS trials. Treatment regimens in younger MS patients might be required and could/should be the aim of meaningful clinical studies. But these studies should not be regulatory studies. Also in MS, the best approach is personalized medicine and combination therapy [46]. Study no. 18, table 1 compares teriflunomide vs. placebo in young MS patients. There is no doubt regarding the anti-inflammatory efficacy of teriflunomide. To expose young patients to placebo is regulatory excess and not in the patients' interest. This study was triggered by one of the numerous MS PIPs [47]. It prevents adequate treatment of the enrolled patients, is not driven by clinical beneficence [26]. Is unethical and should be suspended.

Similarly, why investigate rivaroxaban in treatment/ prevention of venous thrombosis separately in patients 2-17 years old? (Study 17 table 1).

Study no. 16, table 1, pregabalin in patients with partial onset seizures, was triggered by an FDA PREA demand, corresponding to study no. 1576-2 in the approval letter [33, 34]. Why perform a placebo-controlled study with a compound whose clinical efficacy has already been proven? Dose finding in younger children (aged 1 to 3 years old) is necessary, but not separate proof of efficacy.

Atomoxetin is FDA-approved in adults and children ≥6 years for attention deficit hyperactivity syndrome (ADHD). Ely Lilly received an FDA WR in 2001. The FDA requested two double-blind randomized placebo-controlled trials in children plus a pharmacokinetic (PK) study [29]. While a PK study is justified, separate proof of efficacy in 6-16 years old patients represents regulatory excess.

What is the need to investigate macitentan separately in patients 2-17 years of age, i.e. including children and adolescents? (Study 14 table 1).

In contrast, the study of clopidogrel in systemic to pulmonary artery shunt palliation, triggered by an FDA WR [31]. was performed in newborns and small babies and was medically justified.

A study of leuprorelin/leuprolide in 22 patients with central prococious puberty had launched the basis of FDA approval of a special pediatric injection of leuprorelin/ leuprolide [48]. Study 13, table 1 appears to be a marketing study run by Takeda without involvement from US or EU regulatory authorities.

Why should toroctocog work differently in children above or below 6 years of age? There is no doubt about the compound's efficacy (study 20, table 1).

Studies triggered by PIPs and PREA are not performed voluntarily by pharmaceutical companies, but they are coerced into doing so by FDA/EMA. WR-triggered studies reward companies financially. It is natural for companies to respond to offered rewards. It is not the companies who are at fault but the authorities who request/ demand them.

Pharmaceutical industry, academia, patient organisations and science have so far failed to conceptualize intellectually the flaw in the „therapeutic orphans" concept, which has become a dogma by and large accepted worldwide. In the classical triangle of influence between academia, industry and regulatory authorities it would and should be the job of academia to counterbalance regulatory overzealousness; however, essential parts of pediatric academia have become corrupted by industry funds channeled by FDA/EMA-decisions. This is not a conspiracy of dishonest indivdiuals, but a flawed concept that blurs the difference between the physiological assessment of the body's maturity and legal definitions of childhood vs. adulthood. This issue is amplified by the bad reputation of pharmaceutical industry in western countries and the "Robin-Hood"-sentiment of the regulatory authorities of protecting the vulnerable [49]. This creates a dilemma for international pharmaceutical companies. If they do not execute the requested pediatric studies, they are putting their business in jeopardy. However, by executing FDA/EMA-demanded studies, they make themselves vulnerable to a possible lawsuit by parents whose child was harmed. This danger is specifically relevant in life-threatening diseases. For example, the FDA approved avelumab for Merkel-cell carcinoma [50], while the EMA PIP EMEA-001849-PIP02-15-M01 demands clinical trials

in patients from birth to 17 years in all solid cancer types except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms. If a young US melanoma patient should be treated within a PIP-triggerd avelumab study, and later the parents learn that this study prevented effective combination treatment [4-6], the parents could demand punitive damages against the pharmaceutical company who sponsored the trials and thereby withheld potentially effective therapy.

General Discussion

Overall, children have profited from medical/pharmaceutical progress. Pediatric cancer is no longer an automatic death sentence. Most diseases that in the past killed children are today prevented, can be treated, or both. When pediatric oncology began, the treating physicians ignored drug labels and treated their patients with available drugs. Even Shirkey noted that most physicians simply ignored pediatric warnings [10]. The demand for separate regulatory studies for persons <18 years old reflects the turmoil created by traditional eminence-based medicine and the state's demand for double-blind studies and anonymous studies data. Replacement of hands-on experience by clinical studies data became a mantra [51]. The AAP guidelines for pediatric studies were historically innovative because systemic clinical trials in children had until then been taboo. However, the guidelines also created conflicts of interest as specific sub-groups wanted access to funds for pediatric research to enhance their careers. It is time to re-assess the "therapeutic orphans" dogma and the use of the words "children" and "pediatric" as far as this use confuses legal age and physiology [21]. Many malignancies in minors are the same or similar to adult malignancies despite that minors' bodies are different and dose adjustment is required. There are also differences we still don't understand completely, such as young patients' reserves, or the reasons why MS in younger patients has often a different clinical course [43-45]. The decision to develop tisagenlecleucel first in young patients was physiology-based [52]. In contrast to FDA/EMA's obsession for "pediatric" trials, absorption, distribution, metabolism, excretion (ADME) of the child reach levels comparable to the adult body after the first six months of life.[28] From then on, dose adjusting and PK measurement are still required, but not separate repetition of proof of E&S in underage patients.

The discussion about pediatric clinical studies reached truly global dimensions when in 2007 the World Health Organization (WHO) launched its compaign "make medicines child size" [53, 54]. It accused the "usual suspects"[55] that too many children die in this world, claiming that pharmaceutical industry didn't develop medicines for children, and that many drugs are used in children in an unlicensed or off-label manner, provoking adverse events and death. The Pediatric medicines Regulators' Network (PmRN) was established, [56] international conferences were organized, funds were assigned, and numerous articles were published [57-60]. The EMA established the European Network of Pediatric Research at the EMA (Enpr-EMA) which annually organizes a conference and offers ample opportunities for pediatric researchers to network [61-63]. The EU funded the Global Research in Pediatrics (GRiP) network to stimulate and facilitate the development and safe use of medicines in children, justified by "lack of appropriate testing of pediatric drugs, with most drugs having inadequate information about dosing regimen, dose adjustment and administration"; it lists 21 partners on its website, including the WHO [64]. The regulatory global "pediatric cluster" is also mentioned in the FDA report to congress 2016 [65]. An investigation of the impact of this activism in Uganda showed that essentially nothing had happened on a country level [66]. Essentially, almost all alleged accomplishments are regulatory accomplishments [57-59]. They have not improved child healthcare.

It is essential to start differentiating between real needs for children, and empty demands and promises. Most children below the age of 7 years cannot swallow tablets, so they need child-friendly formulations. Children's' bodies are vulnerable during the first months of their life.

The link of China to international western regulatory authority-triggered pediatric studies is still rather weak. Challenges offer also opportunities. The tragedy of unprecedented abuse of children, adolescents and young adults in medically useless studies evolved not on the basis of malicious intentions of individuals, but on the basis of society's struggle to intellectually conceptualize the place of innovative drugs in medicine and society. Shirkey's concept of children as therapeutic orphans, born in the US in 1968 [10], has moved towards the EU, Japan and is now triggering worldwide medically questionable studies. But much has changed. Today, we know much more about development of ADME in young person's [28]. China's voice is heard worldwide. Which country will be the first to introduce innovative legislation that allows pharmaceutical treatment of young person's

based on physiology, not the date of birth? The treating physician should make such decisions, not bureaucrats with a legal, administrative or regulatory background. This challenge offers the opportunity to non-US and non-EU countries to set an innovative precedent. Innovative Chinese pediatric pharmaceutical legislation could help to correct the framework of pharmaceutical treatment of minors [4-6, 21, 22].

Conclusions

With the exception of newborns and babies, pre-pubertal children need PK and dose-finding, not separate efficacy studies. Adolescents with mature ADME deserve adult treatment. Rare adverse events are rarely caught in clinical trials; registries should be used more. The AAP's definition of pediatric vs. adult patients as patients up to 21 years of age (and even older for patients with special needs as regards clinical bedside care) [67] is not adequate as an age limit for pharmaceutical treatment.

Most WRs, PREA demands and PIPs are a waste of money and resources and a senseless abuse of children, adolescents and young adults. They harm young patients with serious and lethal diseases by deterring them from innovative, effective treatment. They have become a worldwide obstacle against innovative drug development. They have poisoned and corrupted parts of pediatric academia into performing medically senseless clinical trials, into competing for participation in such studies, and into demanding more such studies. The less scientific value the EMA's pediatric activism has, the more it emphasizes its "scientific" content. The PIP template on the EMA website is named "Template for scientific document (part B-F)" [68]. But there is nothing scientific in it. Minors and young adults with serious and lethal diseases are enrolled in needless studies that are potentially the largest systematic abuse of patients in history [69].

US and EU pediatric legislation need revision. Institution Review Boards (IRBs)/ ethics committees (ECs) have failed to detect medically unwarranted studies. IRBs/ECs should suspend ongoing superfluous studies and reject new ones. Also, IRBs/ECs need instructions on the role of developmental physiology in pharmaceutical treatment and drug testing. Innovative Chinese pharmaceutical legislation, allowing physiology-adapted drug treatment instead of a rigid focus on the date of birth would be welcome and would have the potential to vitalize a worldwide debate that is overdue.

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