Original Research Article

Questionable International Pediatric Studies in the United States and Russia Triggered by Regulatory Authorities

Abstract

Background: The concept of children as "therapeutic orphans" claims that children were/are denied the use of many modern drugs. Both the United States (US) and the European Union (EU) enacted laws based on this concept. Their regulatory authorities promote industry-sponsored pediatric studies. These studies recruit worldwide. We challenge their medical rationale.

Methods: We analyzed exemplarily international industry-sponsored pediatric studies in cancer and rheumatology listed in www.clinicaltrials.gov with at least one center in the US and Russia, respectively, for their medical value.

Findings: Most studies were/are pharmacokinetic (PK) and efficacy studies in young patients with limited or no medical value. Adolescents are physiologically (vis-à-vis drug metabolism) comparable to adults; for children only PK- and dose finding studies are necessary. Only newborns'/babies' organs are physiologically so different that separate proof of efficacy is needed for drugs with a therapeutic potential in this population. The identified studies were/are justified formally, regulatorily, but are medically unnecessary and therefore unethical. Parts of pediatric academia are misled by industry funds channeled by regulatory decisions into medically questionable studies. There are resulting substantial conflicts of interest; a blind spot in today's societal perception of drug development prevents us from recognizing them.

Interpretation: Pediatric studies triggered by regulatory demands constitute a worldwide systematic abuse of young patients. They are medically redundant at best, deter patients with lethal diseases participating in these studies from getting access to known effective innovative therapy, and have the potential to jeopardize public trust in science, research and authorities. Institutional Review Boards (IRBs)/ ethics committees (ECs) should become alerted. IRBs/ECs worldwide should suspend questionable pediatric studies and reject newly submitted ones. US and EU pediatric laws need revision.

Key Words: Pediatric drug development; pediatric legislation; pediatric laws; FDA pediatric written request (WR); pediatric investigation plan (PIP); absorption, distribution, metabolism, excretion (ADME) in children;

Abbreviations in alphabetic order: AAP American Academy of Pediatrics • **ADME** absorption, distribution, metabolism, excretion • **ALL** acute lymphatic leukemia • **AML** acute myelogenic leukemia • **CNS** central nervous system • **EMA** European Medicines Agency • **EU** European Union • **FDA** US Food and Drug Administration • **JIA** juvenile idiopathic arthritis • **NCT** number National Clinical Trial Number • **NRSTS** non-RMS soft

tissue sarcomas • **PK** pharmacokinetics• **PIP** pediatric investigation plan • **RMS** rhabdomyosarkoma • **R/R** relapsed/refractory • **US** United States of America • **WR** FDA pediatric Written Request •

Introduction

The United States (US) and the European Union (EU) promote pediatric clinical research [1], but the medical value of some of these studies has been challenged [2-4]. We analyzed exemplarily international pediatric studies with at least one center in both the US and the Russian Federation in pediatric oncology and rheumatology for their medical value. We challenge the concept of children as "therapeutic orphans" in the context of pharmaceutical treatment and drug development [5], and delineate the consequences of pediatric clinical research and pharmaceutical laws.

Background

The claim that children are discriminated against in drug development and treatment evolved after US law established in 1962 that clinical trials are the basis for regulatory approval, a principle now recognized worldwide. The same law also transferred jurisdiction over prescription drug advertising to the FDA [6]. In the 1950‘s, drug toxicities in newborns had been reported [7]. Drug developers thereafter included pediatric warnings into labels to avoid litigation. Due to the new FDA judicial authority, such drugs could not be advertised for children. Shirkey asserted that this denied children the use of drugs and characterized children as "therapeutic orphans" [5]. The American Academy of Pediatrics (AAP) maintained that drug prescription for children without explicit FDA certification was experimental [8] and that children required separate pharmacological evaluation of new drugs for all age groups [7]. FDA and AAP lobbying resulted in the 1997 US law that rewarded pediatric studies with voluntary "pediatric exclusivity": additional six months protection against generic competition [1,9]. The company submits a proposal; if the FDA agrees, it issues a "Written Request" (WR); upon report submission and FDA acceptance, pediatric exclusivity is granted [1,9] A second law authorized the FDA to mandate pediatric studies without reward [1].

Consequently the EU established its own pediatric law, in force since 2007 [1,3,4]. Without a PIP, new drugs cannot get adult EU-approval, unless the targeted disease is PIP-exempted. [1,3,4]. PIPs must address juvenile animal studies, formulations (liquids vs. tablets), clinical studies, & more. The EMA has so far issued >1000 PIPs.

The toxicities the AAP referred to were reported in premature *newborns* [7]. The AAP warnings "extrapolated" potential toxicities from *physiologically immature newborns* to all children. However, this "extrapolation" used the *legal*, not the *physiological* term of children

[7]. Pediatric laws responded to the AAP's *"moral imperative to formally study drugs in children"* [7], which was based less on science and more on emotional appeal to protective instincts the word "child" triggers. US & EU pediatric laws define children not physiologically, but administratively: <16 (FDA)/ <18 years (EU) [1,10].

Methods

We identified in www.clinicaltrial.gov international industry-sponsored pediatric studies with at least one center in both the US and the Russian Federation using the terms 'malignancy' and 'juvenile idiopathic arthritis' (JIA) in patients from birth to 17 years of age. We disregarded studies involving adolescents & adults and those involving children, adolescents & adults in an effort to focus on truly pediatric studies; however, we included studies recruiting children and young adults up to 18/19/20/21/24/30 years of age because both FDA and EMA often request participation of underage and young adult patients into "pediatric" studies. We retrieved related Food and Drug (FDA)/ European Medicines Agency (EMA) documents from the internet. Studies' medical value was analyzed in context of physiology, developmental pharmacology, and utilitarianism. EMA pediatric investigation plan (PIP) decisions and studies in www.clinicaltrials.gov are given by PIP/National Clinical Trial (NCT)-number, allowing internet-retrieval.

Results

1. Oncology

Table 1 lists the oncology studies with centers in both the USA and Russia.

Table 1: International Industry-sponsored Pediatric Studies in Malignancies With Centers in USA & Russia

#	NCT#	Study Description	Sponsor	Patients/ Centers	Age	Status
1	NCT00106353	Two-part temsirolimus study in advanced pediatric solid tumors	Pfizer	71/30	1-21y	Completed 2005-2012
2	NCT03130959	Non-randomized nivolumab vs. nivolumab + ipilimumab study in high grade primary CNS malignancies	BMS	170/59	6mo-21y	Recruiting
3	NCT02190721	PK,PD,S&E of tbo-filgrastim in solid tumors without bone marrow involvement.	Teva	50/28	1mo-16y	Completed 2015-2017
4	NCT00952380	Dalteparin in treatment of VTE in cancer patients	Pfizer	50/67	≤18y	Recruiting
5	NCT03204279	MC R DB PK/PD DF study of netupitant + palonosetron for prevention of CINV	Helsinn	92/16	≤17y	Recruiting
6	NCT02197416	S of dabigatran in VTE prevention	BI	100/83	≤18y	Recruiting
7	NCT01088984	DF, S&E of bendamustine in R/R acute leukemia	Teva	43/50	1-20y	Completed 2010-2011
8	NCT02341417	Long-term cinacalcet safety extension in SHPT due to CKD	Amgen	28/33	1-17y	Completed 2015-2017
9	NCT02138838	OL R S&E cinacalcet + SoC vs. SoC alone in SHPT due to CKD	Amgen	55/60	6-17y	Terminated 2014-2016
10	NCT01277510	R DB PC S&E cinacalcet + SoC vs. SoC alone in SHPT due to CKD	Amgen	43/51	6-17y	Terminated*2011-2014

11	NCT01439867	OL S & T of cinacalcet + SoC in SHPT due to CKD	Amgen	18/42	≤6y	Terminated 2012-2016
12	NCT00643565	OL S&E bevacizumab + SChT vs. SChT alone in RMS or non-RMS sarcoma	Roche	154/60	6mo-18y	Active, not recruiting
13	NCT01077544	Nilotinib PK in Ph+CML or ALL	Novartis	15/18	1-18y	Completed 2011-2015
14	NCT01844765	S&E of nilotinib in Ph+CML	Novartis	59/36	1-17y	Active, not recruiting
15	NCT01056341	R PC S&E of propranolol in infantile hemangioma	PFD	512/59	35-150 d	Completed, 2010-2014
16	NCT02703272	Ibrutinib PK (phase 1) and E of ibrutinib + RICE or ibrutinib + RVICI vs. RICE or RVICI alone (phase 2)	Jannsen	96/99	≤30y	Recruiting
17	NCT00777036	Dasatinib in newly diagnosed chronic phase CML or Ph+ Leukemias resistant or intolerant to imatinib	BMS	145/82	≤18y	Active, not recruiting

Abbreviations in alphabetic order: **ALL** acute lymphatic leukemia • **BI** Boehringer Ingelheim • **BMS** Bristol Myers Squibb • **CKD** chronic kidney disease • **CNS** central nervous system • **CINV** chemotherapy-induced nausea and vomiting • **d** day(s) • **DB** double-blind • **DF** dose finding • **E** efficacy • **MC** multicenter • **OL** open label • **PD** pharmacodynamics • **PK** pharmacokinetics • **PFD** Pierre Fabre Dermatology • **Ph+** Philadelphia-positive • **Ph+CML** Philadelphia-positive chronic myelogenous leukemia • **RICE** rituximab, ifosfamide, carboplatin, etoposide • **R/R** relapsed or refractory • RVICI rituximab, vincristine, ifosfamide, carboplatin, idarubicin• **Roche** Hoffmann-La Roche • **S** safety • **SHPT** secondary hyperparathyroidism • **S&E** safety & efficacy • **T** tolerability • **SoC** standard of care • **VTE** venous thromboembolism •

Explanations: Study #10: Terminated: study was suspended in agreement between sponsor and FDA due to concerns about the study design after a fatality had occurred in the presence of hypocalcemia •

Table 2 indicates which oncology studies correspond to PIPs/ FDA WRs (WRs: temsirolimus [11], palonosetron [12], bendamustine [13]. We didn't find FDA/EMA documents for dalteparin (study#4 table 1); the dalteparin study design corresponds to regulatory-demanded pediatric studies in other drugs.

Table 2: Oncology PIPs/WRs

Compound	**PIP#/WR**
Temsirolimus	FDA WR 2011 + 5 amendments • Final study description in Amendment 5 [11]
Nivolumab	EMEA-001407-PIP02-15
Tbo-filgrastim	EMEA-001042-PIP02-11
Dalteparin	**?**
Netupitant/ palonosetron	FDA WR + 3 amendments on palonosetron [12] • waiver EMEA-001198-PIP01-11
Dabigatran	EMEA-000081-PIP01-07-M09
Bendamustine	FDA WR (*16*)
Cinalcalcet	EMEA-000078-PIP01-07-M08
Bevacizumab	EMEA-000056-PIP01-07-M02
Nilotinib	EMEA-000290-PIP01-08-M04
Propranolol	EMEA-000511-PIP01-08-M04
Ibrutinib	EMEA-001397-PIP03-14-M02
Dasatinib	EMEA-000567-PIP01-09-M04
Nilotinib	EMEA-000290-PIP01-08-M04

2. Rheumatology

Table 3: International Industry-sponsored JIA Studies With Centers in USA & Russia

#	NCT#	Study Description	Sponsor	Pts/ Centers	Age	Status	PIP#/WR
1	NCT01844518	**Abatacept** PK, S&E in pJIA	BMS	187/55	2-17y	A, non recr	WR + EMEA-000118-PIP02-10-M02
2	NCT01357668	Observational **abatacept** registry in JIA	BMS	900/82	≤17y	recruiting	WR + EMEA-000118-PIP02-10-M02
3	NCT02296424	**Canakinumab** S&E in JIA	Novartis	180/68	2-20y	recruiting	EMEA-000060-PIP02-08-M06
4	NCT00891046	OL **canakinumab** extension study in JIA	Novartis	270/73	2-19y	Completed 2009-2014	EMEA-000060-PIP02-08-M06
5	NCT00652925	S&E of **celecoxib** vs. naproxen in JIA	Celecoxib	225/58	2-18y	Completed 2002-2005	WR 14
6	NCT01550003	**Certulizumab** in pediatric arthritis	UCB	163/36	2-17y	A, not recr	EMEA-001071-PIP03-14
7	NCT00807846	**Etanercept** in 3 subtypes of pediatric arthritis	Pfizer	201/39	2.17y	Completed 2009-2012	EMEA-000299-PIP01-08-M03
8	NCT02277444	PK, S&E of **golimumab** in pJIA	Jannsen	130/38	2-17y	A, not recr	EMEA-000265-PIP01-08-M03
9	NCT01230827	S&E of **golimumab** in JIA	Jannsen	173/35	2-18y	Terminated* 2010-2014	EMEA-000265-PIP01-08-M03
10	NCT02991469	Repeated **sarilumab** DF in sJIA	Sanofi	36/34	1-17y	Suspended**	EMEA-001045-PIP01-10
11	NCT02776735	OL ascending repeated **sarilumab** DF in pJIA	Sanofi	36/41	2-17y	recruiting	EMEA-001045-PIP01-10
12	NCT03031782	**Secukinumab** S&E in JPsA & ERA	Novartis	80/28	2-17y	Recruiting	EMEA-000380-PIP01-08-M03
13	NCT00988221	**Tocilizumab** in pJIA	Roche	188/69	2-17y	Completed 2009-2013	EMEA-000309-PIP01-08-M07
14	NCT01904292	**Tocilizumab** in sJIA	Roche	52/42	1-17y	Completed 2013-2017	EMEA-000309-PIP01-08-M07
15	NCT01904279	**Tocilizumab** in pJIA	Roche	52/35	1-17y	Completed2013-2016	EMEA-000309-PIP01-08-M07
16	NCT02165345	S&E **tocilizumab** extension study in sJIA+ pJIA	Roche	96/31	2-18y	A, not recr	EMEA-000309-PIP01-08-M07
17	NCT01734382	Decreased dose frequency **tocilizumab** in sJIA	Roche	65/30	2-17y	Recruiting	EMEA-000309-PIP01-08-M07
18	NCT02592434	E of **tofacitinib** in pediatric JIA	Pfizer	210/101	2-17y	Recruiting	EMEA-000576-PIP01-09-M06
19	NCT01500551	Long-term safety of **tofacitinib** in JIA	Pfizer	340/104	2-18y	Recruiting	EMEA-000576-PIP01-09-M06

Abbreviations: **JIA** juvenile idiopathic arthritis • **BMS** Bristol Myers Squibb • **Roche** Hoffmann-La Roche • **DF** dose finding • **sJIA** systemic JIA• **pJIA** poliarticular JIA • **OL** open label • **S&E** safety & efficacy • **E** efficacy • **PK** pharmacokinetics • JPsA juvenile psoriatic arthritis • **ERA** enthesitis-related arthritis

*Terminated: trial failed to meet primary & major secondary endpoints • **Suspended: In order to optimize the study design and procedures, sponsors have decided to amend the current protocol before initiating the patient recruitment

The celecoxib study was WR-related [14]; all other rheumatology studies correspond(ed) to PIPs (table 3)

Discussion

<u>Oncology</u>

Table 4 lists description/indication(s) of oncology drugs. The order of studies discussed below corresponds to the order in tables 1,2,4.

Table 4: Description/Indications of discussed drugs in malignancy

Compound	Description/Indications
Temsirolimus	Renal cell carcinoma.
Nivolumab	Malignant melanoma in combination with ipilimumab
Tbo-filgrastim	Neutropenia due to chemotherapy
Dalteparin	Prophylaxis/ treatment of deep vein thrombosis
Netupitant + palonosetron	Prevention of chemotherapy-induced nausea & vomiting
Dabigatran	Oral anticoagulant
Bendamustine	Cytotoxic for chemotherapy
Cinalcalcet	Seconday hyperparathyroidism in chronic kidney disease
Bevacizumab	Colon cancer, lung cancer, glioblastoma, renal-cell carcinoma
Nilotinib	tyrosine kinase inhibitor approved for imatinib-resistant CML
Propranolol	Beta blocker against high blood pressure
Ibrutinib	Mantle cell lymphoma, CLL, Waldenström's macroglobulinemia
Dasatinib	Cytotoxic for CML and ALL
Abbreviations: CML chronic myelogenous leukemia • **CLL** chronic lymphatic leukemia • **CML** chronic myelogenous leukemia • **ALL** acute lymphoblastic leukemia •	

It is unclear why a drug, as temsirolimus, that works in adults with various solid tumors should not work in adolescents or children if appropriately dose adjusted. The report from the temsirolimus study (that included some children but also adolescents and adults) suggested further studies [15].

Similarly, nivolumab has been studied, so far failed to show efficacy beyond melanoma and was not approved for various malignancies including those involving the central nervous system (CNS). There is no solid scientific rationale that nivolumab should work in young patients with brain cancer just because they are $\leq$21 years old.

The tbo-filgrastim study report confirmed that tbo-filgrastim was as efficacious in children as in adults [16].

Bendamustine monotherapy clinical trials failed to be helpful in children with relapsed/refractory (R/R) acute lymphatic leukemia (ALL) or acute myelogenous leukemia; the authors suggested further studies [17], but in our opinion the availability of innovative therapy like tisagenlecleucel for R/R ALL makes this suggestion questionable.

Separate clinical trials were not needed to show that cinacalcet works in young patients. The EMA reports the PIP as completed and approved cinacalcet in children.

Rhabdomyosarcoma (RMS) affects predominantly patients <14 while non-RMS soft tissue sarcomas (NRSTS) impacts adolescents and young adults [18]. Bevacizumab, added to chemotherapy, appeared tolerable in metastatic RMS/NRSTS, but showed no efficacy. The EMA justifications for this study were regulatory, not science-based. The study authors suggested further studies in NRSTS subtypes, but fail to address that the NRSTS age limit for this drug was regulatory and administrative, but *medically* arbitrary [19].

Evaluating nilotinib pharacokinetics (PK) in school age patients is medically appropriate, but not in adolescents with mature absorption, distribution, metabolism and excretion (ADME) [20].

In 2008, propranolol efficacy in infantile hemangioma was reported [21]. The propranolol PIP required PK measurement (justified), and randomized double-blind placebo-controlled proof of efficacy of four propranolol regimens in babies [22]. The serendipitously found efficacy of propranolol in infantile hemangioma led to regulatory excesses. In our opinion, PK and confirmation of clinical efficacy in a small study would have sufficed.

Measuring ibrutinib PK in children is justified; separate efficacy studies are not.

Rheumatology

Table 5 contains the decription/indications of the drugs discussed in rheumatology/ juvenile idiopathic arthritis.

Table 5: Description/Indications of drugs discussed in JIA

Compound	Description/Indications
Abatacept	Fusion protein IgG1 Fc region + CTLA-4 extracellular domain; antiinflammatory
Canakinumab	Human MAB against IL-1 beta, antiinflammatory
Celecoxib	COX-2 selective nonsteroidal anti-inflammatory drug
Etanercept	TNF inhibitor, antiinflammatory
Golimumab	Human MAB against TNF-alpha; antiinflammatory
Salimumab	Human MAG against IL-6 receptor; antiinflammatory
Secukinumab	Human IgG1κ MAB against IL-17A; antiinflammatory
Tocilicumab	Humanized MAB against IL-6 receptor; antiinflammatory
Tofacitinib	Janus kinase inhibitor, antiinflammatory

Abbreviations: **CTLA-4** cytotoxic T-lymphocyte-associated protein 4 (protein receptor that works as immune checkpoint • **Ig** immunoglobulin • **IL** interleukin • **MAB** monoclonal antibody • **TNF** tumor necrosis factor •

Numerous publications confirm unsurprisingly the efficacy of antiinflammatory drugs in minors. These studies were *regulatorily* justified, but *medically* a waste of time and money. Why should antiinflammatory compounds work differently above/below a specifc age (tables 3,5)? Although PK measurement in pre-adolescents is justified, safety registries would suffice. Separate efficacy trials in children ≥1-2 years lack medical utility.

Pediatric oncology developed by systematic testing cytotoxics in children [23] with survival rates of ~90% in ALL. Although the FDA & EMA claim to promote pediatric cancer studies, they define children as <16 (FDA)/ <18 (EU) [1,10]. Adolescents are no longer children. Even school-age children have a mature ADME [20]. In table 1, only RMS is a truly pediatric cancer; even NRSTS is not. Many of these pediatric studies even recruit(ed) young adults.

Although newborns and infants have different ADME [20]; the body matures over months and years and not at a specific age. WRs/PIPs *appear* to be in line with the AAP's definition of pediatric age [24], but the AAP discusses *clinical care*. The "therapeutic orphans" theory has led to a regulatory concept of two distinctive populations above/below 16/18 years, for which FDA/EMA demand separate efficacy studies. This has resulted in an "industry" in pediatric academia for medically unnecessary studies that are expensive and delay accessibility of medications to children.

Representatives of pediatric oncology and rheumatology publicly support pediatric legislation despite obvious conflicts of interest [25,26]. Regulatory decisions have channeled industry funds into medically unnecessary "pediatric" studies [2-4]. The number of patients and study centers in tables 1 and 3 reveal the dimension of the diverted funds. While the FDA/EMA have strengthened their position in the triangle of influence between clinical care, industry and regulators,2 minors and their families paid/pay the price.

General Discussion

Overall, children have profited from medical/pharmaceutical progress. Pediatric cancer was not even a footnote in medical textbooks a century ago, but is today the most frequent cause of nonviolent death in minors. Most diseases that in the past killed children can today be prevented or treated. Historically pediatric oncologists ignored drug labels and treated their patients. Shirkey noted that most pediatricians simply ignored pediatric warnings [5]. Chemotherapy combinations increased leukemia survival. Regulatory clinical trials for persons <18 became required despite the fact that confirmation by double-blind randomized placebo-controlled clinical trials was not truly needed. The demand to prove efficacy of parachutes via double-blind randomized trials mocks clinicians' and regulators' obsession for clinical studies [27]. Today's definition of "children" and "pediatric" confuses legal age and physiology [4]. Many malignancies in minors are the same or similar to adult malignancies despite the fact 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. Novartis' decision to develop tisagenlecleucel first in young patients was physiology-based, in contrast to FDA/EMA's obsession for "pediatric" trials.

The first FDA pediatric report to congress described expected clinical outcomes: "quicker recoveries from childhood illnesses, with fewer attendant hospital stays, physician visits and parental work days lost" [28]. The FDA in 2016 reported "significant progress in terms of the number, timeliness, and successful completion of studies of drugs in pediatric populations" [29]. This is an obvious shift towards a *regulatory* focus. Most FDA/EMA-triggered "pediatric" studies are justified based on regulations, but *medically* unnecessary with resultant wastage of money and delays in therapies becoming available to children.

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.

Parts of pediatric academia are corrupted by industry funds, channeled voluntarily (US)/ involuntarily (EU) into medically unnecessary studies in underage (and adult) patients. 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, reminding us of past historical abuses as the Tuskegee study or the Willowbrook experiment [30].

The "therapeutic orphans" concept emerged when regulatory clinical trials entered the world of clinical medicine, drug development and drug approval. Pediatric laws intend to improve child healthcare. Trial centers worldwide that participate in pediatric studies, that in our opinion are questionable, perform good medical care on a daily basis and also participate in other valid clinical studies. Most clinicians that participate in questionable studies are not aware of the regulatory background of drug development and welcome the opportunity for international networking. The "therapeutic orphans" concept was not born with dishonest intentions. It was born in a period when drug development was still beginning, when the horror of the thalidomide tragedy was still around and when thinking about childrens' rights and wellbeing became a major issue in societal thinking. But today it is time to challenge the "therapeutic orphans" concept that has become a regulatory dogma which exposes children, adolescents and young adults to unnecessary clinical studies worldwide, including the US and the Russian Federation.

US and EU pediatric legislation need revision. Institution Review Boards (IRBs)/ ethics committees (ECs) have failed to detect medically unwarranted studies. We recommend that IRBs/ECs suspend ongoing superfluous studies and reject new ones. Also, in our opinion, IRBs/ECs need urgent emergency training in developmental physiology to become aware of the flaws of most pediatric studies triggered by regulatory-authorities' demands.

While false prophets promise improvement of childhood diseases by medically unnecessary studies [25,26], ordered by bureaucracy, innovation against cancer and autoinflammatory diseases continues, but we could do better. Continued innovation needs the unleashed forces of science *and* the market.

References

1. Hirschfeld S, Saint-Raymond A. Pediatric Regulatory Initiatives. Handb Exp Pharmacol 2011;205,245-68
2. Rose K, Grant-Kels JM. Most adolescents' melanomas are conventional malignant adult-type melanomas. Eur J Cancer 2018, Eur J Cancer. 2018 Feb 20.

3. Rose K, Walson PD. Do the European Medicines Agency (EMA) Decisions Hurt Pediatric Melanoma Patients? Clin Ther 2017 Feb; 39 (2):253-265

4. Rose K, Walson PD. Do Pediatric Investigation Plans (PIPs) Advance Pediatric Healthcare? Pediatr Drugs 2017 Dec;19 (6):515-522

5. Shirkey H. Therapeutic Orphans. J Pediatr 1968 Jan; 72 (1), 119-120

6. Donohue JA. History of Drug Advertising: The Evolving Roles of Consumers and Consumer Protection. Milbank Q. 2006;84(4):659–699

7. Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations. Committee on Drugs. American Academy of Pediatrics. Pediatrics 1995 Feb;95(2):286-94

8. American Academy of Pediatrics. Committee on Drugs. Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations. Pediatrics 1977 Jul;60(1):91-101

9. Li JS, Eisenstein EL, Grabowski HG, et al. Economic return of clinical trials performed under the pediatric exclusivity program. JAMA 2007 Feb 7;297:480-8

10. Karesh A. Pediatric Drug Development: Regulatory Expectations https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM466469.pdf

11. Temsirolimus FDA Written Request final version https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM295688.pdf

12. Palonosetron FDA Written Request https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM396089.pdf

13. Bendamustine FDA Written Request https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM307141.pdf

14. Celecoxib FDA Written Request https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM449287.pdf

15. Geoerger B, Kieran MW, Grupp S, et al. Phase II trial of temsirolimus in children with high-grade glioma, neuroblastoma and rhabdomyosarcoma. Eur J Cancer 2012 Jan;48(2):253-62

16. Federman N, Dragomir MD, Kizyma Z, et al. A Phase 2, International, Multicenter, Prospective Clinical Trial of Subcutaneous Tbo-Filgrastim in Pediatric Patients with Solid Tumors Undergoing Chemotherapy. https://ash.confex.com/ash/2017/webprogram/Paper106027.html

17. Fraser C, Brown P, Megason G, et al. Open-label Bendamustine Monotherapy for Pediatric Patients With Relapsed or Refractory Acute Leukemia: Efficacy and Tolerability. J Pediatr Hematol Oncol 2014 May;36(4):e212–8

18. Loeb DM, Thornton K, Shokek O. Pediatric soft tissue sarcomas. Surg Clin North Am 2008 Jun;88 (3):615-27

19. Chisholm JC, Merks JHM, Casanova M, et al. Open-label, multicentre, randomised, phase II study of the EpSSG and the ITCC evaluating the addition of bevacizumab to chemotherapy in childhood and adolescent patients with metastatic soft tissue sarcoma (the BERNIE study). Eur J Cancer 2017 Sep;83:177-184

20. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology - drug disposition, action, and therapy in infants and children. N Engl J Med 2003 Sep 18;349(12):1157-67

21. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, A. Taïeb A. Propranolol for severe hemangiomas of infancy. N Engl J Med 2008 Jun12;358(24):2649-51

22. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. N Engl J Med 2015 Feb19;372(8):735-46

23. Adamson PC. Improving the outcome for children with cancer: Development of targeted new agents. CA Cancer J Cli 2015 May-Jun; 65 (3), 212-20

24. Hardin AP, Hackell JM; Committee On Practice And Ambulatory Medicine. Age Limit of Pediatrics. Pediatrics 2017Sep;140(3)

25. Vassal G, Rousseau R, Blanc P, et al. Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer. Eur J Cancer 2015 Jan; 51 (2): 218-24

26. Ruperto N, Vesely R, Saint-Raymond A, Martini A, for the Paediatric Rheumatology International Trials Organisation (PRINTO). Impact of the European paediatric legislation in paediatric rheumatology: past, present and future. Ann Rheum Dis 2013 Dec; 72 (12), 1893-6

27. Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomized controlled trials. BMJ. 2003 Dec 20;237 (7427): 1459-61

28. The Pediatric Exclusivity Provision. January 2001. Status Report to Congress. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049915.pdf

29. Best Pharmaceuticals for Children Act and Pediatric Research Equity Act. July 2016. Status Report to Congress. Department of Health and Human Services. Food and Drug Administration. https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM509815.pdf

30. Rose CD. Ethical Conduct of Research in Children: Pediatricians and Their IRB (Part 1 of 2). Pediatrics 2017 May;139(5)