Abuse of Minors in Clinical Studies

A Worldwide Ethical Challenge for the 21st Century

By

Klaus Rose

Abuse of Minors in Clinical Studies: A Worldwide Ethical Challenge for the 21st Century

By Klaus Rose

This book first published 2023

Ethics International Press Ltd, UK

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

Print Book ISBN: 978-1-80441-135-3

eBook ISBN: 978-1-80441-136-0

Table of Contents

Foreword

In this book I address very controversial issues and make statements critical of many traditional teachings. These thoughts could not have been formed without the internet, its search engines, the existence of clinicaltrials.gov (the largest and most user-friendly registry of clinical trials), many other tools that allow research of the literature, of regulatory decisions, and other information from a single laptop. Internet sources are very practical to get concise information for everyday issues. We cannot understand the world with Wikipedia alone, but we need to use all the information that is available.

The internet and its tools reflect a world that is developing at a rapid pace and does not allow an easy overview. I can read the international English language literature. I am a physician with a solid medical background and have worked in drug development for decades in a position that gave me access to decision makers in very different institutions and companies.

When we were preparing a conference on "pediatric drug development" in London almost twenty years ago, we tried to organize a pro and contra debate. We were unable to find a respectable opinion leader willing to play the devil's advocate. Everybody believed that it was a wonderful thing to let children participate in pharmaceutical progress. At the time I could not have imagined that many years later I would be the person to fundamentally criticize what is touted as pediatric drug development. Such is life.

The modern world offers new tools and it has become more complex, with institutions, illusions and doctrines that can only be understood with a broad look on the one hand, digging deeply on the other hand, and never stop asking critical questions. Much is said

about “Big Data” in modern research. Fear of artificial intelligence is raised. My thoughts needed less “Big Data” and more my background in languages and the history of culture.

“Pediatric drug development” is a matter at the interface of medicine and law. With this, forces flow in such as politics, traditions, science, pseudoscience, junk science, self-interests of institutions and professional organizations, a negative image of the pharmaceutical industry in the public, and much more. I relied in my analyses on common sense and appeal to the readers’ common sense as well.

Chapter 1

Introduction

Without modern medicine we would not live as long; many children with congenital defects would not survive; we would not have effective surgical care after accidents. Many formerly lethal diseases are now chronic challenges that you would rather not have but you can live with quite well. One key component of the ongoing development of medical care is the development of new drugs. Today, both the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) demand separate pediatric development plans before they approve new drugs. These plans consist mostly of clinical studies with minors, justified by the claim that without them child healthcare could not progress. Altogether, this is called "Pediatric Drug Development",[1,2] in the European Union (EU) also "Better Medicines for Children."[3] Only a scoundrel would speak out against better medicine for children - true? And what if most of these studies are pointless or even harm? If they are not being done for any real medical or scientific purpose, but to allow pseudo-scientific careers? If empty promises are made and someone addresses them? Who is then the scoundrel? This book explains how a broad systematic abuse of humans has slipped worldwide into medical research, much larger than the ones reported by Beecher in 1966 and the Tuskegee Study terminated in 1972.[4,5]

A hundred years ago, infant mortality was still high. This improved with better hygiene, housing, clothing, vaccinations, and effective medicines. The cause of death of most children had been infectious diseases. Today we prevent most and can treat many. Today's most frequent cause of death in young people is accidents, followed by suicide. Pediatric oncologists emphasize that cancer in children is

the most frequent cause of death in children "by disease".[6] Not true, but good marketing to mobilize sympathy and funds for pediatric cancer research. The underlying cause of many suicides is depression, which is definitely a disease.[7,8]

Historically, the discipline of pediatric medicine emerged late. Today it is a respected medical specialty. Extraordinary gains were achieved in the health of children under 5 years. In developed countries, the burden of disease in children and adolescents is increasingly characterised by complex non-infectious diseases including chronic physical disorders, neurodevelopmental disabilities, and behavioural & mental challenges.[9] Most children with cancer survive. Antisepsis, anesthetics, and antibiotics allowed pediatric surgery to correct malformations such as congenital heart defects and disfiguring challenges such as cleft lips. Better nutrition, hygiene, healthcare, mental stimulation and improved general living conditions also accelerated the process of puberty that transforms the child's body into a mature body, allowing the unfolding of sexual activities.[10-12]

Drug development is complex and expensive. To develop a new drug costs today two to three billion $ US.[13,14] Two different institutions control their use. They must be approved by the regulatory authorities, they are prescribed by officially trained, recognized and registered medical doctors, and they are dispended by pharmacists. All these institutions are governed by special laws. Drugs are approved for specific indications, such as gastric ulcer. The clinical studies account for the lion's share of the costs of drug development. Once a drug is approved, the production costs are comparatively low. This has led to the pharmaceutical industry being criticized for excessive prices, comparing the low production costs of drugs with the high market prices. People who do not know (or do not want to know) the complexity of drug development conclude that the pharmaceutical industry primarily

only enriches itself from the patients. An army of authors has established an entire industry that condemns the pharmaceutical industry.[15-17]

Initially companies developed and sold medicines without major supervision. This changed with two major catastrophes. The first, still "local" in the US only, occurred by a liquid form of the early antibiotic sulphanilamide. The used solvent diethylene glycol was toxic; about 150 people died.[18] The second disaster was already global. A German company developed thalidomide and sold and marketed it as a tranquilizer, also for pregnant women. Worldwide, it caused massive malformations in thousands of babies.[19] These disasters led to a new role for the regulatory authorities. In 1962, the US gave the Food and Drug Administration (FDA) the authority to only approve drugs whose safety and efficacy had already been proven, resulting in today's drug approval processes based on laboratory, animal, and human studies. Over the ensuing decades, the rest of the world followed the US. Drug development has progressed phenomenally.[20]

Prescription of drugs according to their approval/ label is called "on-label". The regulatory authorities have no right to tell doctors what to prescribe and what not. Once drugs are approved, doctors can prescribe them beyond their label. This is called "off-label" prescription. On one hand, it is correct to avoid that companies develop a drug in a tiny indication, market it after approval in different, larger areas, compromise safety, save development costs, and make higher profits. On the other hand, off-label prescribing is an integral part of medical work and contributes continuously to fine-tuning medical care and the use of existing drugs. The debate about on-label/off-label use is complex, goes on since decades, and keeps US lawyers and courts busy since many years.[21] There is no miracle recipe in this question. We will not resolve it here with a few lines. Anyway, a reasonable balance is crucial.

The on-label/off-label debate has taken on a special dimension with children. From 1962 on, companies inserted pediatric warnings into drug labels that the respective drug had not been tested in children. This was triggered by toxicities of antibiotics in preterm newborns reported in the 1950s.[22-24] These warnings had a *legal* purpose, reflecting the frequent lawsuits in the US for alleged damage. But Dr. Shirkey, first chairman of the American Academy of Pediatrics (AAP) Committee on Drugs, interpreted these warnings *medically*. He claimed they discriminated children and deprived them of the access to new, effective medicines. He coined the term of children as "therapeutic orphans",[25] which became extraordinarily successful. The AAP, the FDA, and pediatric researchers soon called for separate pediatric studies to end this alleged discrimination.[24,26] Eventually, this concept led to US pediatric laws from 1997 on, followed by an even more ambitious law of the European Union (EU), in force since 2007. Both demand separate proof of safety & efficacy in the "pediatric population", defined as younger than 18 years.[7,27] Industry must pay for these studies. In compensation, the US law initially rewarded such studies with a six months patent extension ("pediatric exclusivity"), allowing longer high-price sales. In the EU, there is also a reward at the end of patent life, but compared to the US it is negligible. In the EU, companies must commit to pediatric studies in a "pediatric investigation plan" (PIP) much earlier than in the US, years before marketing authorisation application. PIPs must be negotiated with the EU pediatric committee, coordinated by the European Medicines Agency (EMA).[7,27]

There is a catch in the concept of children as "therapeutic orphans", the consequences of which we see today. Of course, children were always treated with new effective drugs. Should doctors let have children die of infections because the new antibiotics were not approved in children? Apart from being murderous, such a logic did not even exist at the time. Children, adolescents and adults were

taken for granted as human beings. The administrative distinction between adults and minors is old on the one hand, as we see from the documentation of medieval court discussions about heritage and/or caregiving of orphaned minors from wealthy families. One the other hand, much less was known about the physiology of the developing body. Furthermore, today's complex administrative structures that affect more and more details of our daily life did not yet exist. The term "off-label" appeared decades after the 1962 introduction of US pharmaceutical law, in 1988.[28] Without new drugs, pediatric surgery, neonatology and all other pediatric sub-disciplines could not have developed. But a new dimension had entered the debate. From the beginning, the AAP defined children *legally* by their *legal* incapacity to consent to clinical studies before they reached adulthood. Developmental physiology and developmental pharmacology had emerged, showing fundamental differences between babies and adults. Not only in the size of organs (you do not need to be a scientist to know that the baby and its organs are smaller), but in the function of the organs that run absorption, distribution, metabolism and excretion (ADME) of food and drugs, including liver and kidneys. A premature baby's kidneys are much less efficient than those of a six-month-old, and the enzyme composition of the liver is still different. Pediatricians had used formulas and dosing tables, which on the whole served their purpose. But in very young premature babies and newborns formulas and tables were often too mechanical and led to incorrect – and hence dangerous - dosage recommendations. The fact that special caution is indeed needed in premature babies turned into the warning that all drugs posed a great risk for all children if they were not tested separately. Massively exaggerated, but it hit successfully a nerve of the time.

When the US & EU regulatory authorities request or demand pediatric studies and the companies commit to these studies, patients are recruited worldwide. When the lawmakers enacted

pediatric laws, they were told by the scientific community that these studies would be essential to further improve the medical care of children. In its 2001 report to Congress, the FDA stated: "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 from childhood illnesses, with fewer attendant hospital stays, physician visits and parental work days lost".[29] These expected improvement were reasonable and would have been measurable. No such results have ever been published, neither by the FDA, the EMA, or academic publishers. Instead, later reports by FDA and EMA describe other types of "successes": number of pediatric patients recruited, number of pediatric studies performed, number of pediatric label changes, etc. Not real clinical successes, but administrative reports about bureaucratic activism.[30-32] The one truly important question is never asked and never answered: did all these activities improve hands-on child healthcare? To put it even more bluntly: did and do they make any scientific and/or medical sense?

Medical research has enormously advanced our therapeutic ability. During the years of preparation and enactment of pediatric legislation, there was much debate about the ethical justification of clinical research involving children. In all these discussions it was taken for granted that the studies to obtain separate drug approvals for minors were in their interest. But this assumption is flawed. The term "child" has different legal/administrative and physiological meanings. Blurring these different meanings attributes nonexistent bodily changes to a chronological age limit. By using the chronological age limit of initially 17, later 18 years, the demand for "pediatric" studies included adolescents that bodily are already mature. Drugs treat the body, not the administrative status. In itself, this blur is just semantic. But it has resulted and continues to result in thousands of pointless or massively exaggerated clinical studies

that in many cases are even harmful. Individual clinical areas are discussed in later chapters of this book.

Society and humanity are changing rapidly. A century ago, there were only a few effective drugs, including strong painkillers (opiates), alcoholic beverages, laxatives, quinine, and topical wound remedies. Acetylsalicylic acid (aspirin) had just reached the market. The prerequisites for the societal changes had been profound intellectual changes in the Renaissance, the printing press, industrialization, the worldwide expansion of European states with large, cannon-equipped ships, and many other factors. The two world wars accelerated these changes, both on a technical and on a human level - for those who survived. Word War I brought tanks, chemical warfare, air warfare, hand grenades, flame throwers, submarines, and more useful inventions. World War II brought the radar, antibiotics, and the atomic bomb. Both wars broke down traditional mental structures and led to the collapse of many monarchies. The role of the state in directing societal efforts has two sides. The state can help to advance new inventions that otherwise would take longer to be developed, such as the industrial development of penicillin during World War II that was supported by US governmental institutions. But such advances come at a price, paid by those who are killed or maimed in a war, and all the human suffering that is inseparable from war.

Modern technology, academic research and the world wars developed in competition. States wanted to dominate. Individuals wanted to get to the top. This basic mechanism will never change, just that in different societies the rules for advancement are different and open competition is not always accepted. One strategy for getting to the top as a scientist consisted a century ago of unleashing the resources of the human body and mind. The world wars were marked on all sides by research in human capacities. American psychiatrists helped to select recruits for the armed forces. Nazis like

Mengele hoped to be rewarded after the war with academic honors for their horrifying "research". But the Nazis and Japan lost. After the war, criminal experiments of German and Japanese researchers were rightly condemned worldwide. For a long time, crimes against humanity were thought a peculiarity of the Nazis and the Japanese unit 731.[33-36] But in 1966 Beecher described how US researchers had carried out questionable experiments in humans and published them in recognized scientific journals.[4] By today's standards these experiments were criminal and inhuman. Then the Tuskegee study was brought to light in 1972. It was terminated within days after it had been published in a national US newspaper. In this study, African American men with syphilis had been observed since decades and had not been given antibiotics when these became broadly available from World War II on. Syphilis can be treated by antibiotics.[5,37]

"Pediatric" studies in adolescents that are bodily already mature are pointless, as the investigated subjects are physiologically no longer children. They are based on an artificial classification of these people as belonging to the "pediatric population". The researchers in developmental physiology and pharmacology know well that the major changes in the child's body occur during the first days and weeks after their birth.[38] Furthermore, the changes are more relevant in premature newborns. Pediatric researchers also know that the bodily maturation has accelerated during the last century.[10-12] But they refuse to apply these learnings to reality. Also in younger children, separate proof of efficacy is pointless. An antibiotic will work before and after the 12th birthday. Of course, toxicities must be avoided. But not by multicenter international studies, as the EU PIPs demand them for many or even most new drugs.[7] One group profits mainly from these studies: the researchers themselves and their institutions. But the entire issue is more complex. One essential condition for this spook to continue is that scientific journals publish reports about "pediatric" studies that violate the most elementary

condition of the Declaration of Helsinki: that research on humans must be medically meaningful.[39] Nowhere does the Declaration of Helsinki justify conducting pointless studies to meet dogmatic regulatory requirements. These studies would not be performed if scientific journals would refuse to publish banal studies that for example confirm that insulin works also in "children",[7,40,41] or if peer reviewers, Institutional Review Boards (IRBs) and Ethics Committees (ECs) would be more careful in assessing study rationales. The FDA rewarded a "pediatric" study in nasopharyngeal carcinoma (cancer of the throat and larynx). The study was performed and published,[42] and the sponsoring company got its patent extension. But nasopharyngeal carcinoma is not a pediatric disease. It occurs in patients of all ages. Today, in hindsight, we can see the chain of sloppiness that triggered this study: the flawed assessment of a disease as "pediatric"; the offered reward for this "pediatric" study; the pseudo-scientific justification for the study; the acceptance of the justification and the study rationale by all clinicians that were happy to participate in an international study; the approval of the study by the responsible IRBs/ECs; the acceptance of the publication by the editor-in-chief of the journal that accepted the study; and the lack of criticism from the scientific world.

Before World War II, there had been no internationally accepted code of conduct of research in humans. After the defeat of Nazi Germany, the Nuremberg code was created in the verdict of one of the Nuremberg trials that dealt with various war crimes committed by Nazi Germany. It was a set of ethical research principles for human experimentation, articulated as part of the court's verdict.[43] It later became significant together with the Declaration of Helsinki, enacted by the World Medical Association in 1964, which is now widely regarded as the cornerstone document on human research ethics. It has been updated and fine-tuned several times since 1964.[39] The Declaration of Helsinki defines as the primary purpose of

medical research in humans to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions. It emphasizes that even the best proven interventions must be evaluated continually through research for safety, efficacy, and quality. Furthermore, it emphasizes that medical research is subject to high ethical standards.[39,43] Both the Nuremberg Code and the Declaration of Helsinki emphasize as one of the key requirement for human research the voluntary consent of the trial participant.

Consent requires that the individual is legally capable, which is not the case with minors, where parents or caretakers are responsible for giving permission to participate.

Coordinated by regulatory authorities, scientifically supported by academic researchers, and codified by "pediatric" laws, "pediatric drug development" is numerically the largest abuse of patients in medical research in history. It is not openly cruel "research" like the Mengele twin studies,[32,45] or the atrocities of the Japanese unit 731.[35,46,47] The concept began in the US probably with the best intentions. But it contained from the start the semantic blur that equated administrative/legal definitions of children with an alleged physical difference between adults and "children". The caution that is undoubtedly warranted in the case of premature infants is misplaced in the case of adolescents. A publication by FDA employees shows that for practically all drugs the doses determined in "pediatric" studies for adolescents from the age of 12 on were identical to the adult doses.[48] Not a surprise. Adolescents are already physically mature, even if legally/administratively they are still children. That they are mentally not yet mature is another story. Also the separate testing of the efficacy of drugs in school children is massively exaggerated. Medicines have to be dosed correctly. But large international multicenter studies are not necessary for dose finding.

The AAP and developmental pharmacologists have been central to the call for "pediatric" studies. Several myths have been built up over time. One such myth is that approved drugs are safer for children. But the entire discipline of pediatrics evolved without regulatory influence, "off-label," decades before the term "off-label" was first used in 1988.[7,28]

Research in developmental pharmacology and specialized branches of pediatrics needs funding. While industry had poured a lot of money into developing drugs to tackle serious problems in adults, such as high blood pressure, strokes, or gastric ulcers, representatives of pediatric research complained that hardly any money came from industry. That changed abruptly with the first US pediatric law in 1997.

A second factor was the aforementioned negative characterization of the pharmaceutical industry. It now came handy to justify the enforcing of "good" studies from the "bad" industry.[7]

While the FDA is in close contact with academic research and in many areas has waived the requirement for separate "pediatric" studies, at least in adolescents, the EMA is much more isolated from the general public. Its working language is English, which at its inception was widely spoken only in England and Ireland. The EMA demands are dogmatic and stick to the demand for "pediatric" studies, even where they are now rejected by relevant sections of academic research.[7] On the other hand, the EMA and the FDA together adhere to the fundamental justification of "pediatric drug development", see the recent jointly published position paper on "pediatric" studies in the development of vaccines against COVID-19.[49]

We live in an era of good sanitation, nutrition, and housing. That plus effective vaccines and medicines have significantly changed the composition of humanity in developed countries. Few children still

die from infectious diseases. Many diseases that were once overlooked in the deluge of infectious diseases have become the subject of own pediatric disciplines. For a while it was thought that malignancies only existed in old people. In the mid-20th century, with improved communication, transportation, and the scientific literature, it became clear that, in rare cases, young people could also contract malignancies. The first children's cancer wards were established in the middle of the 20th century. At the same time, rare forms and sub-types of rheumatic diseases became known which can also affect minors. For a while, it had been thought that adolescents and children could not get depressed;[50] we know today that this is the case. Chronic diseases that primarily affect adults can also appear in minors, such as multiple sclerosis, an autoimmune disease of the central nervous system that leads to muscle weakness, abnormal sensations, poor eyesight, blindness and more. And so on. The myth that adults only get adult diseases and children only childhood diseases is flawed, as is the belief that any disease detected in somebody before his 18th birthday is therefore a "pediatric" disease. But with precisely this logic the EMA has meanwhile defined diseases such as amytrophic lateral sclerosis (ALS/ Lou Gehrig disease), hepatic cancer, malignant melanoma, Parkinson disease, and others as "pediatric" diseases and demands for drugs that target these diseases "pediatric" studies in those unfortunate few patients in which such a disease is diagnosed before the 18th birthday.[51]

There are serious and massive conflicts of interest behind "pediatric drug development" beyond the mere semantic blur described above. But these conflicts of interest have so far been overlooked by the system of precautions society has built against abuse in human research. This abuse has the official blessing by mainstream science, the regulatory authorities, and representatives of major life science companies.[52-56] In publications that are on a regular base published in high-ranking peer reviewed journals the principles of "pediatric

drug development" are outlined and justified, however, without addressing the difference between the legal and the physiological meaning of the term "child".[52] Several myths outlined above are taught as mantras to generations of scientists, including that only drugs that are officially approved are allegedly safe and effective. Children-are-no-small-adults is a mantra which is correct for premature newborns, but not for all legally/administratively defined "children" until they come of age.

The administrative side of medicine has increased in importance. Several decades ago, a conference discussed the efficacy of antiepileptic drugs in minors.[57] The participants reported no problems with the payment by reimbursement institutions for antiepileptic drugs not approved in minors. Today, this has changed. Modern drugs can be very expensive, and the treatment of one single patient can put financial strain on any reimbursement institution. With increased complexity, procedures have also become more bureaucratic. If the computer reports a specific drug as not approved in minors, the administrator might demand justification from the treating doctor or, worse, might simply refuse to reimburse the costs.

There is the feeling of academic researchers and clinicians that they are morally superior to people working in for-profit companies. Such thoughts have been and are expressed in numerous medical publications,[14-16,58,59] but often such thoughts are elusive. The EU pediatric regulation explains in the preamble that the forces of the market are not sufficient to ensure enough pediatric research to meet the medical needs of the "pediatric population".[60] To correct this, the EU created the pediatric committee with the authority to enforce pediatric studies from pharmaceutical companies. Few academic researchers are aware of the "pediatric" debate between industry and EMA with its pediatric committee. So far, more than two thousand pediatric investigation plan (PIP) procedures have been

performed, including many discussions about PIP modifications.[61] We should remember at this point that mankind has seen other experiments where a central bureaucracy, instead of the market, dictates what is to be produced. Ultimately, the Soviet Union perished because of its inability to meet the needs of its citizens.[62-64] The same inability to adapt to reality has happened and continues to happen to the EMA and its pediatric committee. There are not enough underage patients worldwide for the many "pediatric" studies.[7,65] Anybody who visits the sales exhibitions of a conference on neonatal care can see how the range of products in neonatology has expanded over the last few decades. This market is represented by the feedback of neonatologists that tell others, including sales representatives, what they need. Furthermore, they publish. The scientists that develop and produce drugs for neonatal care read these publications and recommend new developments. But in drugs, the EMA has established a position where it proudly knows better what the neonatal community needs. It acts accordingly and tells pharmaceutical companies which clinical studies are needed. They have allies in the neonatal clinical world and can, to some extent, influence the allocation of funding. They control the EnprEMA network where bona fide clinicians discuss access to funds for research projects and share experiences.[66] The EMA officials do not control neonatal research as a whole. But it is sufficient to show the support of individual clinicians in case of doubt.

Distrust in the market is another underlying factor resonating in "pediatric drug development". The demonization of the pharmaceutical industry is not only a favorite topic of industry haters.[14-16,58,59] The belief that business is too independent and should be controlled more by the state is quite strong among academics. We can call this the academic flirting with socialist ideas. Behind this flirtation are fundamental philosophical ideas about the desirable structure of our society. Again, we come back to the chilling

historical examples of command economies that ultimately culminated in the collapse of the Soviet Union, the Holodomor in Ukraine,[67] and Stalinist mass murder.[68] All, of course, with reference to noble higher purposes.

There are multiple ethical challenges of "pediatric drug development". Patients are exposed to pointless and even harmful studies. The public has been and is being systematically deceived. Publications appear in reputable journals that report banal results such as that certain medications also work in minors. Why should they not work? All "pediatric" studies required by the FDA and EMA go through approval procedures by Institutional Review Boards (IRBs) and ethics committees (ECs). The International Committee of Medical Journal Editors (ICMJE) has not yet spoken out against the pseudo-scientifically justified "pediatric" studies.[69] It would be desirable if the Declaration of Helsinki would address "pediatric drug development" in its next update.

A challenge that appeared as highly ethical and noble half a century ago has developed an ugly face behind the shiny surface. Medieval stonemasons depicted the devil above the portals of cathedrals as a sympathetic young man. You had to step to the side of this portal figure to see toads and snakes crawling on his back.[70,71] It is not new in history that perspectives change. The discovery of the Americas is no longer celebrated as just a great discovery. But only blaming their negative consequences is just as wrong. We cannot turn back the wheel of history. Everything and every institution that dogmatically attempts to maintain mechanical formulas beyond their time is doomed to perish in the long run. It is time for a critical revision of the ethical challenges of "pediatric drug development".

The treatment of malignancies in minors is a very special case. When child mortality by infectious diseases had substantially declined, childhood diseases that had been overlooked so far began to come

to the attention of scientific and medical research. One such area was malignancies in children, another one rheumatic diseases that begin early in childhood. There are many more, but we will address them later. Previously it had been assumed that cancer and other malignancies existed in adults only. In the 1940/50s, attention began to be given to malignancies in children. Malignancies are much less common in children, but when a child develops it, the whole family is devastated. This family will not be interested in hearing that this is just exceptionally bad luck. They want help for their child, period. The peculiarity of the fight against childhood cancer was that the progress up to around the year 2000 was not due to new drugs,[6,72,73] but by drugs used and approved since decades for adult cancer: chemotherapeutic agents. There were encouraging early results in the treatment of leukemia, particularly the most common childhood malignancy, acute lymphoblastic leukemia (ALL). Up until around the year 2000, chemotherapy for childhood cancer was continuously refined to e.g., 90% survival rate for ALL. Only with the surmounting of the plateau that had been reached in 2000, pediatric oncology returned, so to speak, into the mainstream development course of medical development: real new drugs and treatment methods were now required for further advances. The first successful new approach occurred with CAR-T cell therapy, which saved the life of Emily Whitehead who was with 6 years the youngest patient to participate in the pivotal trial of tisagenlecleucel.[74-77] It is crucial to emphasize here that the entire discipline of pediatric oncology emerged "off-label", decades before this term even began to exist. During the first decades of pediatric oncology, the regulatory authorities had no active role in its emergence. Today, as the mentioned peculiarity is over, there are attempts by regulatory dogmatists to criticize the merits of pediatric oncology to the effect that its emergence and development did not lead to the approval of the developed treatment schemes.[72,73] The purpose of medicine is to treat people, not to approve drugs. A dogmatic over-regulatory approach wants to impose retrospectively

a process that exists today on the past, distorting what really happened at the time.

A central element of "pediatric drug development" is the desire to accelerate the fight against childhood cancer. In the early decades of pediatric oncology, the use of chemotherapy agents was switched from adult to childhood cancer. The regulatory authorities had no part in the original development of pediatric oncology. But they dream of achieving a successful repetition of the mentioned switch with new targeted anticancer drugs. Aside from criticizing the fact that pediatric oncology has not led to the regulatory approval of treatment regimes,[72] they now coerce the industry to clinically test new targeted adult anticancer drugs in different types of pediatric cancer. In this they are supported by a group of pediatric oncologists who profit from the studies industry is coerced to commit to. Fifteen years of such pediatric childhood cancer studies enforced by the EMA has not yielded clinical success.[7] It is psychologically understandable that under pressure of affected parents in the US, too, the FDA can now force the industry to carry out such pediatric cancer studies with the RACE for children act.[78-81] In addition to parents' associations, institutions that are active in child cancer research were particularly involved in the demand for this law.[82,83] Emily Whitehead was healed by advances in real, innovative research, not by coerced regulatory studies. Two schools have emerged in pediatric oncology and many other pediatric research areas: those that benefit from studies enforced by the regulatory authorities, and those that conduct real, meaningful, and innovative research.

Another layer of conflict of interest is the self-interest of the EMA, a powerful institution established in 1995.[84] The concept of "pediatric drug development" originated in the US, but has been dogmatically augmented and sharpened by the EMA. Supported by academic scientists who benefit materially from "pediatric" research studies, the EMA has even set up an own "pediatric" research structure, the

"European Network of Paediatric Research at the European Medicines Agency"(Enpr-EMA).[66] Many pediatricians participate in Enpr-EMA in the hope to find funds for their research activities. EMA employees are invited to prestigious academic conferences where they praise the purported contributions of their institution for the further development of pediatric medicine.

We see here a new type of conflict of interest that could only emerge in today's complex society. It could not exist without the framework that justifies "pediatric" research as if children were another species, demanding mostly pointless "pediatric" studies from pharmaceutical industry that banally repeat what we know already: that compounds such as insulin, antibiotics or chemotherapeutic agents work the same before and after the 12th or 18th birthday. Currently, the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" published by International Committee of Medical Journal Editors (ICMJE) represent the internationally accepted gold standard in the documentation of potential conflicts of interest by authors in scientific medical publications.[69] The structural conflict of interest in "pediatric drug development" is not well captured by these recommendations. With thousands of "pediatric" studies enforced by PIPs,[7] the relevance of studies in chronologically defined "children", which often also include physically adult young people, such pointless and often harmful studies deserve a strong mention in the ICMJE recommendations.

Readers may have wondered why there are no comparable initiatives to develop safer medicines for young animals. Pets living with humans often develop comparable diseases, including obesity, high blood pressure, rheumatic diseases and more. Animal rights activists are very resourceful when it comes to demanding more government protection for animals. But demands for the development of safer medicines for young animals have not

emerged. The reason is simple: in the extended animal kingdom, humans are the only species that uses a legal definition of minority for young members.

This introduction gives a high-level overview. The blind enforcement of "pediatric" studies for all newly developed drugs not only results in pointless studies. In many medical fields, such studies have also directly harmed young people. These will be discussed in later chapters. Not all involved scientists will welcome a critical debate. Numerous critical assessments of harmful "pediatric" studies have been published in international peer-reviewed journals,[85-90] and in two medical textbooks.[7,91] Here we focus on the ethical evaluation of the entire initiative of alleged "pediatric drug development".

If we put "pediatric drug development" in historical perspective, it has certainly served a useful function. The recognition of rapid development processes in the body of the newborn and especially the premature baby were elementary scientific advances. But they encountered a new societal framework, represented by new institutions with massive self-interests, including the regulatory authorities, the professional representations of developmental pharmacology, academic research institutions that needed funding, the prosperous life science industry and its critics that appeal to protective instincts against injustice, and more. In a few hundred years, "pediatric drug development" will be just a spot on the historical map that will be smiled at in hindsight. When this debate started, there was no internet. Doctors had to refer to the printed labels for dosing recommendations for minors. The date of birth played a lesser role than today. Anybody who was physically mature was given medications at the usual adult dosage. All other methods to retrieve information, including asking advice from colleagues, correspondence, or search through the libraries would have taken days, weeks, or even months. Life-threatening situations

do not allow a generous delay in decision making. Today the internet allows worldwide access to information with a few mouse clicks, provided you know where to look. In the advancing 21st century, the regulatory authorities argue with a century-old logic. Administration of drugs to special patients requires continuous adjustment. For premature babies who weigh just half a kilogram, fixed dosage recommendations for medicines are hardly possible. It may be the case that in the evening the dose that was correct early in the morning is already too high or too low.

In this introduction I give an overview and first idea how the drug treatment of children, a perfectly reasonable issue, has fallen into a framework that has turned it into an administrative nightmare, resulting in thousands of pointless and often even harmful studies with young people. Many of these studies are ongoing. It is time to separate meaningful studies with young people from pointless or exaggerated studies, or even worse. Young people need scientifically founded dosing recommendation, not dogmatically enforced, medically pointless regulatory studies. It is a challenge at the interface of medicine and law, involving ethical questions that have so far only been marginally addressed in the literature. Hopefully, this book will contribute to tackle and master this fundamental ethical challenge of the 21st century. In history, science and ethics had to overcome many obstacles on their zigzag path to intellectual, technical, and social progress. This entire issue is highly controversial.

It is unusual in our time that mainstream science supports a flawed concept. But it is not entirely new in history. For many centuries science was firmly convinced that the sun revolves around the earth and that we see stars in the sky. Today we know that the earth revolves around the sun and that most stars we see with the naked eye are actually distant galaxies. The Catholic Church, which for centuries represented the highest moral and scientific authority in Europe, has done everything in its power to halt the advance of

science. At the end, she failed. That controversial positions can be expressed at all is a privilege of our time and of our free world.

I have worked in the pharmaceutical industry for decades. That does not mean that I liked everything I saw. The pharmaceutical industry, today also called the life science industry, is closely linked to the academic world. Advances in drug development mirror newest academic learnings, such as first the understanding of monoclonal antibodies, then their industrial production, the growing understanding of the body's mechanisms of inflammation, defense against pathogens, today's armamentarium of anti-inflammatory treatments, and last not least the development of an effective vaccine against the corona virus based on messenger RNA (mRNA) technology by a company that planned to use this technology to develop therapeutic vaccines against cancer.[92] Working in large pharmaceutical companies brings the convenience of being able to seek out, meet and interact with the world's leading specialists. I have always appreciated the relaxed and free nature of debate in the academic world, but I have also seen how determined project management allows successful product development, which then has a lasting impact on medical treatment worldwide, far beyond what a single clinician could achieve. It would be pointless to start a discussion about what is more important: clinical work or drug development. Both have become part of healthcare. What we have yet to achieve is to ensure that the clinical medical profession's high level of self-awareness gives way to a real team spirit. Drug development is complex and full of contradictions. Science, market research, marketing, competitive intelligence, and much more are included. No one can understand all of this alone. But that is not even necessary. It is teamwork.

Bleeding from gastric ulcers was a frequent cause of death half a century ago. Over time, it became preventable and treatable with a sequence of discoveries and increasingly powerful medications. It

started with antacids; followed by the discovery of histamine H_2-receptors and the development of histamine H_2-receptor antagonists; then the identification of H^+K^+-ATPase as the parietal cell proton pump and the development of proton pump inhibitors; and finally the identification of Helicobacter pylori as the major cause of gastric & duodenal ulcer and esophagitis, and the development of effective eradication regimens.[93] Communication and leadership in industry is different from that in science. People do not remain in positions they will hold for decades. That alone makes the competition tougher. Decades of work in the industry does not mean that one fully identifies with the respective company. That definitely did not happen to me. I have had the privilege of being involved in the emergence and development of "pediatric drug development" in a leading position that allowed me to observe things for decades. Furthermore, I had access to the generation of key representatives in developmental pharmacology that had contributed to the emergence of the entire concept. Then the years of being self-employed and consulting a multitude of small, medium, and large companies opened my eyes to the conflicts of interest described in this book. Beyond realizing the blur of the various meanings of the term "child" were the discussions about European Union (EU) "pediatric investigation plans" (PIPs) and FDA pediatric requirements that finally resulted in my conclusions. Many examples I give about pointless, exaggerated, and/or harmful clinical studies in minors might be dismissed as isolated cases. What I then realized over the last few years was that there is a pattern that logically explains all of the seemingly isolated flaws in these studies.

The pharmaceutical industry is not a monolithic bloc. The research-based companies are represented by organisations that represent their interests to regulatory authorities, to the public, and to other institutions.[94-97] Many people who work in industry and manage after many years to advance to a senior rank where they can represent their company in a large and/or international organization

are often content with this career move. They earn well, fly business class, and exchange high level ideas with authorities and scientists. So far, the principles of "pediatric drug development" are undisputed at this level. An additional thought that came to me in a discussion of this was the concern that too much criticism might lead the authorities to call for even more nonsensical studies and other "pediatric" measures.

To sum up my potential personal conflicts of interest, the positions in this book are not sanctioned, paid, or supported by any pharmaceutical company, nor by any regulatory agency, nor by any academic group. I managed to get my thoughts published in many peer-reviewed journals and was able to get enough academic support to be accepted as a medical textbook author. I managed to develop and maintain my own opinion in a demanding professional environment. I never had to deal with a university bureaucracy. In the industry, once things are approved, they are done without much frills. I understand medical terminology by having studied medicine and through my knowledge of classical Latin and Greek. And I have been outside of the direct medical clinical sphere of power long enough to be critical of its side effects as well. Not being operationally blind has its advantages.

In addition, our first daughter had Sturge-Weber-Syndrome, a very rare condition in which causal treatment will probably never be possible.[98-104] However, symptomatic treatment is available, including drug treatment of epilepsy, surgical treatment of congenital glaucoma, laser treatment of portwine stains, and much more. Our first daughter passed away when she was 27 years old. These years have shaped me at least as much as my studies and my professional experience.

There are many more challenges of our time. One of them is that the times when basic and applied science were sharply separated are

over. The universities have preserved and advanced the scientific knowledge of mankind for centuries. But that role is not set in stone. A lot of knowledge only comes from putting principles into practice. With the scientific penetration of more and more areas of industry and business, there is a growing challenge to the academic world to encourage feedback in the composition of the academic teaching staff. This cannot work where academic positions are guaranteed lifetime jobs. In this regard, this introduction touches on further questions about what professional conflicts of interest are. I made some further reflections on this in the final chapter of this book. For now, I hope you will enjoy reading it.

References

1. Mulberg AE, Silber SA, van den Anker, JN (Eds). Pediatric Drug Development – Concepts and Applications. Wiley-Blackwell, Hoboken, NJ, USA, 2009

2. Mulberg AE, Murphy MD, Dunne J, Mathis LL (Eds). Pediatric Drug Development: Concepts and Applications. 2nd ed., John Wiley & Sons, Chichester, UK, 2013.

3. European Medicines Agency (EMA) 2015. Better Medicines for Children
https://www.ema.europa.eu/en/documents/leaflet/better-medicines-children_en.pdf

4. Beecher HK. Ethics and clinical research. N Engl J Med. 1966 Jun 16;274(24):1354-60.
https://www.observatoriobioetica.org/wp-content/uploads/2016/09/Beecher_Ethics_and_Clinical_Research_1966.pdf

5. Brandt, Allan M. 1978. Racism and research: The case of the Tuskegee Syphilis study. The Hastings Center Report 8(6): 21-29.
https://dash.harvard.edu/handle/1/3372911

6. Adamson PC. Improving the outcome for children with cancer: Development of targeted new agents. CA Cancer J Clin. 2015 May-Jun;65(3):212-20.
https://acsjournals.onlinelibrary.wiley.com/doi/epdf/10.3322/caac.21273

7. Rose K. Considering the Patient in Pediatric Drug Development. How good intentions turned into harm. Elsevier, London, UK, 2020

8. American Academy of Child & Adolescent Psychiatry (AACAP).Suicide in Children and Teens. AACAP 2021.
https://www.aacap.org/AACAP/Families_and_Youth/Facts_for_Families/FFF-Guide/Teen-Suicide-010.aspx

9. Sawyer SM, McNeil R, Francis, KL, et al. The age of paediatrics. The Lancet Child & Adolescent Health 2019 Nov;3(11):822-830