

Introduction

This is the first book of its kind that specifically addresses pediatric formulations in the context of drug development. Before you read it, we hope that you have asked yourself why such a book was not published 50 or 100 years earlier. When we were asked to edit this book, having asked that question ourselves, we reflected on the existing formulations and found most of them wanting. Now we think that we know where we want to go, and we identified several obstacles. We didn't produce a "how to formulate" textbook for pharmaceutical scientists. The subtitle "a roadmap" indicates that all we can do is to contribute to overcome obstacles we are aware of, help find obstacles we are not aware of, and establish a platform that we hope will help people and institutions to build up the required knowledge.

After you have read the entire book, you will know that you just scratched the surface, but we also hope that you will have found a path to further walk through the jungle of information in print, the internet, related industries, and other sources.

Medicines have a complex background. The good news is that today there are many more effective medicines compared to 100 years ago. There are many players: physicians prescribe medicines, hospital pharmacists procure them at the hospital, and community pharmacists provide them outside the hospital. Companies develop and market new drugs, and after a while, new drugs lose their patent protection and can be produced and sold by other companies as generics. Academic scientists work on the theoretical understanding of diseases, pharmacology, chemistry, and many more aspects. Pediatric pharmacologists have elucidated a lot of what the child's body does to a given drug, and what the drug does to the child's body. All drugs are regulated by authorities to block quack medicines or wrongful claims, to detect side effects, to uncover counterfeits, and many more tasks. Drugs are paid by reimbursement organizations, which may be private, state-owned, or a combination. And of course the patients play a major role as well. And those are just the core players. There are many more, as our society has become more complex, to name a few: law enforcement and the judicial system, the press and other communication channels, the transport systems, and finally, the patients, the parents, the caregivers, patient organizations, and institutions, each with their particular perception of medicines and interests.

All healthcare players will emphasize that the patient's health is the one and only focus of their attention. Depending on your *weltanschauung*, your professional and personal experience, your cynicism, and many more factors, you will accept the statements at face value, or you will put their statements and self-perception into context.

The position of children in our society has changed dramatically during the last century. Entire industries have evolved around them, earning their money by providing toys, clothing, literature, electronic gizmos, education, entertainment, and many more. Among medicinal specialties, pediatrics is a very young discipline. There were many assumptions that took decades to erode. One such assumption was that children need to be protected, so they were protected against clinical trials, but it was clinical trials that have changed the prognosis of most malignancies in children.

The development of age-adjusted drug formulations is not only a technical challenge. Otherwise, you would now be reading the 20th edition of this book. The dynamics behind the development of new medicines and of age-adapted formulations are complex. Background information is given in this volume.

There are two types of drugs on the market: generics (i.e., drugs whose patent protection has expired), and patent protected new ones, developed predominantly by the research-based pharmaceutical industry and, to some degree, by academia. For new drugs, today there are laws, both in the USA and in the EU, that compel the research-based pharmaceutical industry to consider children during drug development. One of the major demands of the authorities is the development of age-appropriate formulations. The other type of drugs, generics, is exempt from mandatory pediatric development, but there are incentives to stimulate it. Ultimately, industry will produce pediatric formulations if there is enough demand.

Let's have a look at which effective medicines existed 100 years ago. There were, for example, powerful cough suppressants containing opioids that were labeled as "suitable for children and adults." They were effective—so effective that you could kill your child with it. We will never know the number of children who didn't survive this treatment.



Source: www.wellcomecollection.org

If you go to a pharmacy museum, you will see that pharmacies sold many, many items 100 years ago. Apart from opioids, there were alcohol, creams and ointments, spices, dried fruits, powder of pulverized mummies, bones and other body parts of convicted criminals, dried fish, and many more. Most of this merchandize is not regarded as medicine today.

You would think that when Alexander Fleming approached British chemical companies in 1940 with the newly discovered penicillin, the companies would jump at the offer to initiate mass production. They all turned him down. The same happened when his successors at his institution flew to the USA in 1941 and approached US chemical companies. Eventually, the Office of Scientific Research and Development helped. It assigned capacities in parallel to its Manhattan project, better known for its key role in the construction of the atomic bombs. In hindsight, the companies that turned Fleming and his successors down were not overly smart, yet in contrast to real-life decisions, it is much easier to say in hindsight what was right and what was wrong. NSAIDS (non-steroidal anti-inflammatory drugs) can help close the arterial duct, but it took decades for clinicians to discover that. Is it reasonable to expect that just by allocating enough resources during drug development, all the potential pediatric uses will be uncovered? Whether it is possible as well as what allocation of resources toward this vision is rational are two additional questions.

Wherever there is a demand, somebody will try to sell something. A hundred years ago, there were many medicines sold against tuberculosis, cancer, infection, aging, and other health challenges. Most had two characteristics in common: First, they provided a good income to manufacturers and pharmacists. Second, they didn't work.

Modern pharmaceutical treatment evolved with the scientific revolution and with modern industry, which was the chemical industry first, the pharmaceutical industry later, and is today the life science or health industry. Powerful drugs were synthesized. It took two major catastrophes—the sulfanilamide elixir in 1936 and the thalidomide in 1961—to open the path to modern drug regulation, where the safety and efficacy of any drug must be proven by clinical and other trials. This signaled the advent of the modern label, a shift from claiming whatever the manufacturer wanted to claim towards a document that reflects what has been proven about the respective medicine for the given condition. This legislation led to new pharmaceutical terms such as “Off-Label,” which refers to the use of drugs outside of its label, meaning the use in a therapeutic area or age group for which the drug is not registered. Unlicensed use in pediatrics often involves crushing tablets or opening capsules and suspending the contents to produce a liquid formulation suitable for oral intake. From 1961 on, most drugs in children were prescribed off-label.

Medicine is perceived as something that needs to be taken, not enjoyed, and for most adults, this works: You have a headache, you ingest a tablet. Your senses tell you that shape, surface, hardness, smell, and taste are wrong, but you force the tablet down your throat because you know from experience or because you trust the prescriber that it will help. Children cannot make this informed decision because they do not understand the connection between medicine and disease or because they are unable to override the reactions triggered by their senses. That said, many adults

are unable to swallow adult dosage forms. Therefore, children need oral dosage forms that resemble food they are used to ingest.

Today, many more children diagnosed with cancer survive than in the past. Pediatric oncologists systematically tested adult anticancer drugs in new doses and combinations in children. Most of these treatment schemes were off-label and still are today. These treatments can be life-saving, so off-label use is not bad per se. It can be dangerous if the treating physician or the compounding pharmacist knows too little about the respective drug.

Pediatric legislation was introduced in the USA in 1997 and in the EU in 2006, as a growing gap was perceived by academic scientists and regulatory authorities between the wealth of information available for adult patients and the limited information about drugs in children. The EU legislation is newer and more ambitious and asks for a pediatric investigation plan (PIP) early in development. A standard part of this PIP is often the development of one or even several pediatric formulations. One consequence of the mandatory PIP is that EMA asks for pediatric formulations for all new drugs, resulting in a higher demand for pediatric formulations, in turn felt by companies that have specialized in contract formulation. This applies even for rare and ultra-rare conditions.

We come back to the question about why this book was not published 50 or 100 years earlier. The answer is simple: nobody would have understood the need for such a book, as most of the drugs that today we use routinely did not exist yet. The increased demand for pediatric formulations is triggered by changing regulatory requirements that are discussed in depth in some chapters.

The debate about better medicines for children has in the meantime also reached the global discussion about availability of medicines for all children of this planet. The WHO program “make medicines child size” has special focus on children in developing countries. However, the requirements of medicines in the developed world sometimes contradict those of the developing countries. Technologically advanced formulations should not only be good but also be affordable. We have refrained from addressing this additional dimension.

This book intends to cover the anatomy and physiology of this population group as well as the technical state of the art of formulations where possible, to provide hints about where to find inspiration—such as the food industry—and to give a suitable background on the regulatory framework. Have we covered everything we wanted to cover? Certainly not. However, we tried to provide as accurate an exploration into pediatric formulations as we could, and we hope you enjoy it.

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Pediatric Formulations

A Roadmap

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