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# Paediatric Therapeutics in the USA and Internationally: An Unparalleled Opportunity

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**Abstract**

*Major initiatives have taken place in the USA and internationally to improve the study of drugs in children. In the USA the FDA Modernization Act has provided a financial incentive to the pharmaceutical industry to study medicines in children. The FDA Paediatric Rule gives the FDA the opportunity of mandating drug studies in children. It is to be hoped that the ICH Guidance on the Investigation of Medicinal Products in Children will standardise the design of clinical trials involving children and medicines on a worldwide basis, and that these initiatives will improve the safety and efficacy of medicines in children.*

*Key words:* Children – Legislation – Medicine

## Introduction

This is truly a remarkable time in the history of paediatric therapeutics. For too long, the majority of drugs available to adult patients have not been systematically evaluated for safety and effectiveness in paediatric patients[1]. Most drug labels carry 'disclaimers' about lack of paediatric data. Also for too long, most drugs available for adults have not been formulated for safe, accurate and compliant use in children[2]. Paediatric pharmacists have had to provide various extemporaneous formulations, many of which were not properly evaluated for stability and bioavailability[3]. This situation is rapidly changing in both the USA and internationally. The 'therapeutic orphan' of the past is at last being adopted.

Initiatives from the American Academy of Pediatrics, the National Institutes of Child Health and Human Development, the US Food and Drug Administration, the US Congress and the pharmaceutical industry have all come together in the interest of improved pharmacotherapy for children in the USA[4]. Indeed, it has been through extensive collaboration, partnering and focusing efforts on children that things have changed so dramatically. International efforts through the International Conference on Harmonization (ICH) have made great progress on providing harmonised paediatric drug development paradigms to be used by companies and regulatory agencies in the EU, the USA and Japan.

Rather than reviewing all the past efforts to encourage the study of medicines in children, this discussion will focus on three critical initiatives:

1. The paediatric provisions of the 1997 Food and Drug Administration (FDA) Modernization Act (FDAMA).
2. The 1998 FDA Pediatric Rule.
3. ICH E-11 (Investigation of Medicinal Products in the Pediatric Population).

## FDA Modernization Act (FDAMA)

The FDAMA provides an incentive to encourage the pharmaceutical industry to develop specific information about paediatric uses and doses of prescription medicines. It is fair to state that the legislation has revolutionised paediatric drug development, and that in the two years since its implementation, tremendous progress has been made towards reversing many years of inadequate

investigation of medicines for use in paediatric patients. The legislation provides six months of additional marketing exclusivity for all indications of a drug when a company performs and submits paediatric studies of a drug.

The process begins when a company approaches the FDA that it wishes to do paediatric studies. The FDA therapeutic review division then decides what paediatric data are needed to assure proper use of the medication; the review division discusses the proposal with the FDA PediComm (Pediatric Committee). A 'written request' is issued to the company detailing the precise studies which must be completed to fulfil requirements under FDAMA. When the studies are completed, the company then submits the data, and, if meeting the requirements, extended exclusivity is granted. While not required under the legislation, the clear intent is to provide the information required for drug labelling.

Stimulated by FDAMA, companies have proposed studies on 177 medicines to the FDA as of May 2000 (two years into implementation of the legislation). This represents a remarkable increase in interest in pursuing paediatric studies. The FDA has issued 145 written requests. 21 medicines have received extended exclusivity under the Act, and labelling has been changed with paediatric data for 7 medicines. The time lags between each phase of the process are discussed below.

The 145 written requests included 298 studies. 113 requested studies were classified as 'efficacy and safety', 86 as pharmacokinetic (PK) and safety, 26 as 'PK/PD', and 65 as safety. The nature of the requests in general have been based on evaluation of data required for the safe and effective use of the medication in paediatric patients of various ages (see below). Many of the studies required new formulations developing to cover younger age ranges of patients, as well as the development of novel clinical trial designs to evaluate safety and/or efficacy.

Requests have covered drugs in a wide range of therapeutic areas, from common problems such as the treatment of fever and simple skin infections, to cardiac disease, endocrine problems, gastrointestinal drugs, serious infections including HIV, seizures and other neurological disorders, and the management of pain. Studies have included paediatric patients across all ages, although only a minority of studies have included neonates and premature infants. The selection of age ranges has been based on therapeutic need, although there remain situations where there are insufficient validated approaches to evaluate certain medications in younger patients. The range of conditions addressed, the variety of drugs being studied, and the nature of the scientific data requested suggest that FDAMA is successfully addressing unmet therapeutic needs in children. No other approach, legislative or regulatory, has had such a profound impact on the evaluation of medicines in children.

The legislation has been such a success because it addresses the fundamental impediments that have hampered paediatric studies of medicines in the past. Fortunately, most children are healthy. In the adult population, however, there are large numbers of patients with diseases such as heart disease and cancer, and, therefore, large numbers of patients to study in clinical trials, and a large market for medicines to treat these disease.

In contrast, among paediatric patients, serious and chronic illness is caused by a wide range of diseases, and relatively few children are affected by any specific disease. For example, fewer than 0.5% of patients with arthritis are children, and juvenile rheumatoid arthritis is a different disease than adult rheumatoid arthritis or osteoarthritis. This has several consequences.

Performing clinical trials in children is inherently more difficult[5]. There are relatively few children with a given condition, and thus few patients to enter into clinical trials. The children are distributed over varying ages. They may need different, age-appropriate formulations of medicines for accurate and compliant administration; for example, an oral liquid may be needed for young children, different concentrations for neonates, or chewable tablets for children unable to swallow pills or capsules.

The pharmacokinetics of drugs varies widely across the age spectrum. Age-specific study designs to assess effectiveness and safety may need to be developed. Studies are particularly complex in tiny premature infants who may weigh less than one kilogram, and yet who represent one of the sickest populations of children. When formulations are produced and validated, studies performed, regulatory hurdles met and labelling ultimately changed, the market for most medications in children is very small.

Research resources are finite. Paediatric studies are always in competition with studies of important new medicines for large numbers of adult patients. By providing a financial incentive, FDAMA raises the priority of paediatric studies. By focusing on the needs of children, and recognising fundamental impediments to paediatric drug development, the legislation is accomplishing the goals set forth by Congress. It is the right legislative solution to a major health problem.

It is important to comment on some of the 'metrics' of success at this point. There is a time lag from a company proposing studies, to the FDA issuing a written request. The agency must review the proposal and decide on the content of the written request to assure that the data generated will meet the therapeutic needs of children. The actual studies performed by companies take a substantial amount of time; patient numbers and research centres are limited (see below), and some of the safety studies required, by definition, require substantial observation time. Once data are submitted to the FDA, the review for exclusivity occurs within 90 days, but subsequent review of data for labelling changes may require 10–12 months. Thus, while only seven labels have been changed as of May, 2000 (actually, a remarkable accomplishment to date), the process to change a large number of labels and make information available to paediatricians has been initiated. It is expected that the vast majority of requests will result in label changes (except in certain circumstances where studies do not result in data warranting specific changes).

## The FDA 1998 Paediatric Rule

As FDAMA was being implemented, the FDA set forth the 1998 Rule to further define paediatric drug development. The Rule mandates paediatric studies of medications, both older drugs, at the time of a supplemental new drug application [sNDA] for a new indication or use, and of new drugs. The mandate applies when the drug is to be used for the same indication in children and adults, and there is likely to be a 'meaningful therapeutic benefit to children and absence of labelling poses a risk, or there is substantial use (> 50 000 paediatric prescriptions) and absence of labelling poses a risk'. Companies will be specifically asked to present a paediatric plan for the drug. This may be a 'waiver' if the drug has no use in paediatrics, a 'deferral' if additional safety or efficacy data are required in adults before initiating a paediatric program, or a specific plan for paediatric studies. The Rule does not apply when paediatric indications are different from those in adults (often the case for neonatal disease).

The Rule and FDAMA can be viewed as complementary approaches to assuring paediatric study of medications. FDAMA is voluntary, driven by an incentive. The Rule is mandatory. The Rule is limited to the same indications in children and adults, while FDAMA can be applied to encourage studies in different indications, thus extending therapeutic benefit to smaller populations of children with diseases which differ from those in adults. When a company fulfils studies under the Rule, including these studies in an FDAMA 'written request' also makes the company eligible for FDAMA incentives. The ultimate goal is to make paediatric drug development an integral part of general drug development. For medications for serious/life-threatening diseases, the FDA will expect discussion of paediatric plans at the end of Phase 1 meeting, and for other compounds, at the end of Phase 2.

Several lessons have been learned as paediatric pharmacology studies have expanded. The NICHD-sponsored Pediatric Pharmacology Research Units, now 13 in number, have been critical to performing many of the needed studies[3]. However, it is clear that even these units and their patient populations are being 'saturated' by the number of studies underway. There is therefore a need for expanding paediatric clinical investigative capacity, and for PK, PK/PD, efficacy and safety trials. Efforts are now underway to increase training funds for the next generation of paediatric clinical investigators.

There is a need, too, to develop novel clinical trial designs. Much success has been made in PK studies. Analytical tools have advanced, leading to the requirement for smaller blood samples to measure drugs and drug metabolites. Sparse sampling and population PK approaches have been developed. Much work needs to be done to develop and validate clinical end-points for efficacy and safety for many disease processes. Often, different end-points are required for patients of different ages. Academic paediatric departments will face the challenge of integrating advances in basic science with clinical investigative tools so that future paediatric clinical trials will more successfully assess therapeutic benefit and risks of older and new medications.

The increased investigative activity has also raised awareness of the need for assuring the very highest ethical standards in paediatric clinical investigation. There have been extensive meetings and discussion about current ethical guidelines, and a review of these as part of the ICH process. Ongoing vigilance to assure protection of vulnerable subjects in research is vital to this entire initiative.

## ICH E-11: Investigation of Medicinal Products in the Paediatric Population

The International Conference on Harmonization is an effort to harmonise drug development regulations among the US, the EU and Japan. Recently, the effort has extended into paediatric drug development. An expert working group was

assembled from industry and regulatory agencies in each of the regions. Current regulatory documents for paediatric clinical trials were reviewed, areas of consensus and disagreement evaluated, and a draft document produced. Once agreed upon by the expert working group, the document was circulated for comment. Comments were integrated and the document adopted as a 'Step 4' document by the ICH secretariat in July, 2000. The document will become an official ICH document in November, 2000. It is available on the ICH website (ICH.org).

The hope of this effort is to provide optimal pharmacotherapy for all the world's children. The aim is to encourage international collaboration among paediatric investigators, studying drugs under the same protocols, with data generated from the studies being acceptable for drug labelling internationally. This will have the immediate practical benefit of expanding patient populations and investigative sites to assure that needed studies are completed, of familiarising paediatric centres with therapeutic advances as they are being developed, and to make information on the safe/effective use of medications available to paediatricians. It will also provide the basis of assuring that regulatory agencies, pharmaceutical companies and paediatric centres in the US, the EU and Japan are aware of the therapeutic needs of children, and that studies of children internationally maintain the highest scientific and ethical standards.

## The Future

This is indeed the most exciting time in the history of paediatric therapeutics. As new and important medicines are discovered and developed, the groundwork has been laid to ensure that sick children will participate in therapeutic advances in a timely manner. The challenges remain of maintaining a collaborative and co-operative focus on the needs of sick children among government agencies, academic and practice-based paediatricians, parent/patient groups, paediatric societies and the pharmaceutical industry. This partnership has been crucial in the legislative gains made in the USA and in expanded efforts, such as the PPRU network. It will be important, as investigative activity continues, to foster the basic and translational science necessary to understand paediatric disease pathogenesis and related pharmacological interventions. This includes support for the training of paediatric clinical scientists. Remarkably, one of the 'side effects' of the investigative activity currently underway is that there is now a clear career path for trainees in paediatric clinical pharmacology. The need for well trained investigators will expand in academic settings, government agencies and the pharmaceutical industry. The best news of all is that sick children will benefit from our efforts today and in the future.

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