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Challenges in conducting clinical trials in children: approaches for improving performance

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Abstract

Recent legislative changes in both Europe and the USA have increased the responsibility of drug developers to purposefully study the agents they market in children so that specific dosing recommendations can be made to assist clinicians in their use. Typically, clinicians use empiricalor experiential-based rationales for selecting the dose to use in children, generally in a manner that attempts to achieve the same dose-exposure or pharmacokinetic profile in children as in adults. However, whether this approach achieves the necessary dose exposure or exposure effect needed may not be systematically explored during off-label use. This creates the opportunity for under- or over-exposure in children, particularly in very young children (i.e., less than 2 years old) where a combination of factors during development can effect both pharmacokinetics and pharmacodynamics. The ethical, physiological and statistical differences of studying new therapeutic agents in children present economic challenges that may create unintended incentives – both positive and negative – for any individual developer who tries to meet the requirements of new legislation to study pharmaceutical agents in children. There should be a continued emphasis in academic clinical pharmacology programs towards creative methods and approaches to better understand these differences in children compared with adults. The ability to use information from knowledge obtained from adult studies, from preclinical studies, from studies of compounds with similar chemistry or pharmacology, or from known physiological differences between children and adults is essential to choosing a suitable dose for children and achieving these regulatory aims.

Keywords

economics; efficacy; ethics; modeling and simulation; pediatric; pharmacodynamics; pharmacokinetic

Brief history

Although the implementation of a significant regulatory agency authority in the USA emerged from a successive series of drug development disasters that affected children (e.g.,

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sulfanilamide in 1937 and thalidomide in 1962), it was not until the 1990s that a concerted effort to proactively study pharmaceutical agents in children began to develop [1]. This effort resulted in the inclusion in the 1997 US FDA Modernization Act (FDAMA) of provisions to incentivize drug developers to study their compounds in children by providing an extension of market exclusivity for completion of agreed upon studies in children, which were reflected in a written request from the FDA to the manufacturer at the time of market authorization for use in adults. This incentivized effort was extended in 2002 with the Best Pharmaceuticals for Children Act (BPCA), which continued the original incentives in FDAMA and established a group at the FDA responsible for monitoring the safety and outcomes from label changes that were authorized in children.

In 2003, these efforts continued with the implementation of the Pediatric Research Equity Act (PREA), which changed the statute from voluntary to mandatory, extended the range of products that must be studied in children, but added other restrictions to focus the effort on matching indications for new agents with those approved in adults. Both the BPCA and PREA were reauthorized in 2007 and continue to impact the state of pediatric clinical pharmacology in both the USA and worldwide (Table 1) [101].

During this time period, the EMEA in Europe was noting the perceived successes and failures of the US legislation to advance drug labeling and safe dosage determination in children. They developed similar, but in many ways more challenging, legislation for promoting the purposeful study of new pharmaceutical agents in children. First, drug developers were obligated to provide to the EMEA all the available information and data from existing products that they marketed that had been formally studied in children. The result was a list of products with data from studies in children [2]. Currently the EMEA is analyzing and organizing this data and plans to make it available in some form as a public resource. Second, beginning in 2007, all new pharmaceutical products under development and marketed products for which new indications are sought had to submit a formal pediatric investigation plan (PIP) which documents how the developer anticipates studying their agent in children.

Unlike the written request from the FDA, which initially was decided at market authorization for adult indications, the PIP must be submitted early in the drug-development cycle after the completion of initial pharmacokinetic studies in adults. This is typically referred to as Phase I of three main phases a new drug proceeds through before it is approved for use [3]. At this stage in development the developer may have very limited information on which to formulate a cohesive PIP. Therefore, the implementation of this plan is meant to be an iterative process whereby the developer and health authority exchange information as it becomes available and the plan is modified based on the new information learned. In the ideal world for drug development, this exchange will be critical to overcoming many of the challenges currently imposed by the interactions between drug developers and regulatory agencies [4].

Challenges

There are many challenges to conducting clinical pharmacology studies in children, particularly in comparison to the traditional paradigm for studying pharmaceutical agents in adults. These occur on ethical, physiological, pharmacometric and economic grounds – among many others – that contribute to making these studies more challenging. However, it is important to recognize that while challenging, these efforts are not impossible and, in fact, may be better suited to creative solutions that center on documenting outcomes in the context of the existing practice of medicine within these patient populations. These issues will be explored individually.

Ethical challenges

Fundamental differences in the approach to studying new pharmaceutical compounds in children compared with adults. While adults can legally consent to participate in clinical research studies, children in general can at best provide assent to participate while legal consent for participation must be provided by an appropriate adult parent or guardian. Depending on the age of the child to be enrolled, the relative risk of the study under consideration and the practices of the institutional review board locally, the need for consent from both parents when present may also be necessary. These aspects generally slow the rate of recruitment and limit participation in clinical trials with children when compared with adult trials.

Differences in the allowable level of risk to which children may be exposed in the context of clinical trials also present a challenge. The need to maintain equipoise within study arms by balancing risks across groups adds complexity to study design, recruitment and also adequate patient consent [5]. When achieved, this allows the parent's decision to involve a child in a clinical study to be on a similar risk and benefit basis as the nonresearch alternative for care. In fact, in the USA, regulatory guidelines restrict the allowable risk exposure for children when there is no perceived direct benefit to them for their participation in the study. Furthermore, restrictions are also placed on the justification for risk exposure in terms of potential direct benefits when they are possible for a given study. These differences mean that studies deemed ethical for consenting adult participation may not meet the same standard if the study population is children [5]. Thus, study sponsors cannot simply replace adult dosing with pediatric appropriate dosing in creating a clinical study protocol. Purposeful study reassessment must be made to insure that the study design balances risk appropriately for the population of children under study. This balance can differ for adolescents, children, infants and neonates.

In the EU, there are additional challenges of assessing differences in the laws across the member states, particularly with respect to obtaining appropriate consent for participation in studies by children [6]. The guidelines from the EMEA regarding the ethical consideration for clinical trials in children provides a cohesive reference for considering these issues [7]. It is critical to understand the issues of balanced risk and appropriate consent in order to conduct appropriate clinical trials in children. In a study of parents who had been approached for consideration of their children in a clinical trial, Chappuy *et al*. showed that following an adequate consent process does not assure parents made their choice with objective knowledge regarding the study risks and benefits [8]. While recent literature suggests that adequate procedures are still evolving for achieving appropriate expression of risk and benefit for consent, there is considerable agreement that off-label use of drugs, even when viewed as beneficial by physicians, is itself a suboptimal, and at times potentially unethical, situation that must be addressed [1,5,9–12].

Physiological challenges

As has been often stated in review articles, children are not 'small adults' from a physiological and pharmacological perspective [13,14]. Differences in all fundamental aspects of drug pharmacokinetics (absorption, distribution, metabolism and elimination) can occur in children compared with adults that will alter the dose-to-drug exposure relationship. In addition, pharmacodynamic differences can also exist that alter the required exposure– response relationship. Perhaps the greatest challenge in this area is not working with what is known, but working with what is not known. Knowledge of differences in drug metabolizing enzyme activity continues to grow, and with it new opportunities arise to predict differences in drug metabolism that will likely occur between children and adults [13,15–17].

However, very little is known about the differences in transporters that exist between children and adults and if these differences impact drug transfer across a biomembrane. This could have significant pharmacokinetic and pharmacodynamic consequences that need to be better understood. Furthermore, there is a lack of appropriate animal models to represent the differences in physiological responses to pharmacological agents that correlate well with the changes observed in humans. Many preclinical animal species have lifespans that demonstrate maturation in time frames of days to months rather than months to years. Thus, modeling appropriate dose–exposure–response relationships in these systems to produce meaningful clinical insight is challenging [18–20].

As noted in many reviews of physiological differences between children and adults, the relative proportion that a particular organ system has in terms of body mass or percent of total blood volume in a developing child versus an adult can be another source of physiological variability that is important to consider for achieving a comparable dose–effect relationship [13,21]. The consequence of this difference could be that even though pharmacokinetic exposures in the plasma are matched between children and adults, the relative percent of a dose that reaches a target organ could differ. This is important for most therapeutic agents where the site of drug effect is not the systemic circulation. While this might appear to be a pharmacodynamic difference between children and adults, it may actually be a difference in the resulting concentration profile at the site of effect (e.g., the brain, liver, kidney or a distant tissue region) [22].

Finally, it is necessary to remember that heterogeneity within a pediatric population is likely to be significantly larger than that observed in an adult population. From the stand point of differences in weight with age, organ maturation and body composition differences, children can be subclassified into at least four different population categories [23,24]: adolescents (12–16 or 18 years old), children (age 2–11), infants (28 days–23 months) and neonates (birth to 28 days). The age ranges for these designations change for different research groups and different countries. While the precise cut-off is not important, what is important is the degree of similarity of children within a group. There may be differences in the largest age group (children aged 2 years to puberty) that justifies dividing this group even further, particularly with regard to the child's ability to participate more purposefully in a clinical study or have an active role in their own health condition that could impact the dose–effect result for a particular trial.

Pharmacometric challenges

The challenges to quantitative modeling in the pediatric population essentially center on the ability to do more with less. That is, the number of subjects, number of measurements and size of the measurement in terms of blood volume will all generally be reduced for pediatric studies compared with studies in adults for a similar compound. Thus, any approach to quantitatively assess the results of a trial need to consider the limitations of the data and adjust to optimize the information that can be obtained from the available samples. In this manner, nonlinear mixed effects modeling has excelled compared with traditional pharmacokinetic modeling because of its ability to characterize both patient-specific and interindividual differences in pharmacokinetics that can be used to define the dose–exposure response with good precision [25–30]. Furthermore, the ability to identify covariates within the diverse population of pediatrics that can be used to explain differences in pharmacokinetic parameters that significantly alter dosing strategy is important to avoid the 'one size fits all' approach to scaling doses from adults to children.

A common pharmacometric challenge in pediatric studies is that the studies are often conducted in the context of ongoing clinical care for a patient. Unlike adults studies where typically healthy volunteer trials allow the clinical pharmacologist to understand the initial dose–

exposure relationship, in children this must be considered while concomitant therapy is being continued, or tapered down and replaced by the new therapeutic if it can be ethically justified [31]. This also adds to challenges of study design in terms of sequencing pharmacokinetic sampling relative to drug administration. If the study is conducted within a clinical facility then these intervals can be potentially proscribed. However, if the study is conducted on an outpatient basis, flexibility in pharmacokinetic sample times relative to when the dose was administered must be tolerated in the study design and quantitative analysis.

In addition, the pharmacometrician must be able to anticipate differences in drug pharmacokinetics between adult values, which are usually known in advance, and the resulting group of children under study. For instance, children have differences in intestinal transit time that can alter the absorption of drugs from the gastrointestinal system. If a significant delay compared with adults is present, the sampling times must be adjusted relative to dosing interval. Otherwise, early samples may produce concentration measurements that are negligible or below the level of assay quantification. This would not only waste precious resources, since plasma samples are generally limited in the population, but can also cause needless harm. For pharmacokinetic studies, children usually have an indwelling intravenous access line in place from which drug samples can be drawn. Otherwise, each sample taken comes from a venapuncture episode that is painful. This alone may be a reason for many parents to withhold consent for their children to participate in a study because of the potential trauma from multiple venapunctures. Thus, any sample taken from the child must be selected because it will provide maximum information content to the study question at hand. In this regard, the pharmacometrician has the responsibility to only draw samples from the child that are absolutely needed. In addition, the ability to use scavenged blood samples, that is, samples left over from another clinically indicated reason to draw blood, can be an effective way to obtain maximal information from a clinical trial with children. The caveat is that the sample has to be of significant quantitative integrity to be useful for the trial. However, recent advances in drug assay technology has significantly improved the ability to make accurate quantitative measurements from very small sample volumes, making this less concerning [32].

Economic challenges

In the early 1990s, after a consensus meeting with clinicians, and members of the pharmaceutical industry, the NIH and the FDA had identified the need for pediatric labeling in medical products, only 11 agents had pediatric-specific changes to their labeling information before the passage of the FDAMA in 1997 [1,33]. Beginning in 1997, when the inducement of an additional 6 months of marketing exclusivity was added to US and subsequently EU legislation along with requirements of manufacturers to study their products in children, the rate of label changes increased significantly.

As reported by investigators from the Duke Clinical Research Institute and the FDA, the economic return for conducting pediatric clinical trials can produce significant gains. These researchers estimated a range of economic returns as high as US$508 million and as low as a loss of US$9 million [34]. Within the subgroup of antihypertensive drugs, all showed a positive return on investment, with a median gain of 17-fold on the estimated cost of US$4.3 million to complete the necessary trials to support the label change [33]. There can clearly be adequate incentives for manufacturers to obtain pediatric labeling with exclusivity, but this does not occur without risk. In fact, studies of antidepressant medication in children resulted in addition of a black box warning to the overall drug label [34].

Furthermore, the need to create pediatric-appropriate formulations for adult medicines can be very challenging as compounds that are generally regarded as safe for adults may not have similar designation in children. Thus, the need to assure that a child-suitable formulation can be manufactured in a manner that is safe and provides appropriate dose exposure presents

another level of complexity to testing drugs in children [23]. This aspect, along with the aforementioned challenges, all pose risks for pediatric drug development that contributed to the rationale for adding the inducement of extended exclusivity for conducting these additional investigations in children.

While this obligation and reward approach – a 'carrot and stick' as it has been often referred – has produced demonstrable changes in the number of pediatric labels, the labels changed are driven by the compounds being made by the pharmaceutical industry that may or may not be the most important therapeutic agents for children. In terms of the need for many commonly used agents for which there are no specific labeling instructions, both the USA and EU have mechanisms for encouraging research to achieve labeling for these compounds. In the USA, the BPCA legislation provides funding for studying drugs for which no market exclusivity is available. These studies are typically carried out by consortia of academic clinical research sites. In the EU, the Pediatric Use Marketing Authorization (PUMA) is the pathway for interested groups to apply for studying drugs that are off patent but commonly used. Completion of the appropriate studies for a PUMA gives the sponsor 10 years of protected labeling for the generic compound in a pediatric indication. To date, significantly fewer compounds (nine in 2 years since the legislation) have followed the route for generic agents than those that are eligible for extended market authorization [35]. Nonetheless, economic incentives from the EU for studying off-patent agents will help promote this effort.

It should be no surprise that the agents that have received pediatric labeling are the ones of most interest to the manufacturers to meet their pediatric obligations and obtain their exclusivity extension reward. A review by Boots *et al*. in 2007 showed that while the BPCA and PREA legislations in the USA have increased the number of drugs with pediatric labels, it has not done so proportionately in the agents used in children. Instead, the distribution follows the drug utilization pattern found in adults [36]. This outcome has challenged the assertion that the incentivized programs provide the proper inducement to make therapeutic agents safer for children. However, with the increasing attention paid to pediatric clinical pharmacology, the knowledge base of how children are similar or different from adults with respect to clinical pharmacology is increasing. It is incumbent now on all who are working in this area to use this information to improve drug dosing knowledge for children, particularly where it matters most.

Methods for improvement

Given these consequential challenges and the direction of success so far for improving medicines for children, what are the steps that can be advanced to make this effort more efficient, more focused in areas of clinical need and can truly harmonize the international efforts to improve medication knowledge for children? Since there is a limited amount of resource available for conducting trials in children – including willing parents and children, motivated physicians, drug developer time, effort, money and time to complete studies, which are often longer in duration than adult studies – efforts should be prioritized on developing labeling for agents that are used in children with high prevalence for which there are no current dosing guidelines. While efforts to assure that new agents are studied in children has had positive attributes, this effort has limited utility if the agents are not likely to be often used in children or if there are suitable alternative therapies already available for the indication [36,37].

Instead, investment in fundamental research to understand how children differ compared with adults in terms of drug metabolizing enzymes, transporters and changes in fundamental pharmacokinetic properties with age including absorption, distribution and clearance parameters, would be a greater benefit to physicians in terms of understanding how to better dose existing medications and for drug developers to understand how to better study new agents with pediatric efficacy potential. This approach is part of the efforts by both the USA and the

EU health authorities through partnerships with their respective governmental funding agencies [3,35]. To date, these efforts have had positive but limited contribution and could be dramatically increased if all the pediatric labeling effort was concentrated towards addressing the highest priority questions. This may require a consortium between industry, health authorities and clinical researchers to achieve and it will require a diversion of effort away from studying every new drug just because it is new. If, instead, every new drug was studied primarily for the new generalized information it could provide information to better understand how children differ from adults in clinical pharmacology, and subsequently the scientific basis for determining appropriate doses of drugs – new and old – in children would be improved, and ultimately could make the process of studying new drugs in children more effective and efficient.

Use of all available knowledge

While there are many agents used in children that do not have approved dosing labels and guidance, there is a large body of knowledge that has been generated on the clinical pharmacology of a wide range of therapeutic agents that have been used in children. This can serve as a knowledge base for understanding the differences and similarities between children and adults if the disparate sources of information can be assembled in a synthesized manner. These sources include published research articles, unpublished data from drug developers and filed data from health authorities. In the EU regulations that were established by the EMEA, manufacturers were required to submit data from all studies conducted in children as part of the first component of the legislation. This produced data from many existing products [2]. There is tremendous potential for this information to provide better insight into unique aspects of pediatric pharmacology that will improve dosing for children. Efforts to explore and use this data should be paramount in all efforts for improving medicines for children [38].

A second source of knowledge exists in the clinical literature of investigator-initiated studies of therapeutic agents in children. Particularly in the case of neonates and infants, most of the available information regarding how these youngest children differ in terms of dosing compared with older children and adults most likely comes from this source given the large percentage of pharmaceutical agents given off-label to this group [1,12,23]. This is an often overlooked resource that should be fully explored before any new study in children is undertaken to make sure that the investigator is working with the most up to date information and to assure that clinical efforts are not being duplicated. Many examples of publications in the clinical literature with neonates and infants have begun from the initial basis of published literature [17,39].

A third source includes data from therapeutic agents that have already received pediatric labeling approval from health authorities and are being followed for safety and efficacy assessment. This is a critical step for following the development of rare, serious and pediatric-specific adverse events that are not uncovered in initial evaluation [40]. This information will most likely only be present to developers and health authorities, but it is important that it be available for insight to all involved in pediatric studies. As research by Benjamin *et al*. revealed, for therapeutic agents that received exclusivity as a result of completing pediatric trials, less than half of the trials were reported in the clinical literature [41]. Interestingly, this rate is similar to that found for adult trials and probably reflects the priorities of drug developers that are not as focused on peer reviewed publication as academicians [42]. By combining data and knowledge from these different sources of information, a better overall landscape of how pediatric clinical pharmacology differs with age compared with adults can emerge.

Role of modeling & simulation

There is an increased focus on using quantitative information in an organized manner to assist and improve the process of drug development. Beginning with the FDA's Critical Path Initiative, where the regulatory agency has made an argument for improving the science in clinical drug development stages, a greater emphasis on the use of modeling and simulation to support and inform drug development efforts has been evolving [43,44]. In the area of understanding how children differ from adults, modeling and simulation has been extensively applied in a number of different platforms. This includes traditional pharmacokinetic and pharmacodynamic modeling, physiologic-based pharmacokinetic modeling, and also modeling to bridge preclinical results with anticipated clinical first in human studies [15,24–26,30,45–50].

These efforts have been positively received in the USA by the FDA and represent an advance to drug development because the approach builds on cumulative knowledge from the complete development of the compound under investigation as well as similar compounds from which rational comparisons can be made [51–53]. Given the limited amount of clinical data that is available from pediatric dosing trials compared with adult trials, modeling and simulation is anticipated to play a primary role in supporting pediatric dosing determination. While computer simulation cannot completely replace clinical trials, informed, well-designed trials supported by well-qualified modeling and simulation results can together provide information that is supportive for pediatric labeling. At the very least, it provides an integrated manner to combine existing clinical knowledge and data to alter dosing in patients being treated with an agent [54–56].

These approaches have been useful for modeling and simulating results from clinical trials to provide additional insight into the findings [57–59]. In particular, combined pharmacokinetic and pharmacodynamic modeling provided an understanding of the impact of maturation on the pharmacokinetics of morphine and the formation of its glucuronide metabolites provided insight into the development of Phase II enzyme capability in infants. In addition, it revealed an apparent lack of clinical efficacy of morphine to block response to intubation in the preterm infant. Using a physiologic based pharmacokinetic modeling approach, Edginton *et al*. were able to predict the clearance of a series of pharmacologic agents that had different mechanisms of metabolism and different physicochemical properties. This approach, which assembles a series of models for each organ system of interest, can provide insight into predicting drug response based on first principles when actual clinical data is not available [46]. In addition, extensive work from an industry/academic consortium that works to bridge from preclinical to clinical estimation of drug clearance based on the drug physicochemical properties and the capacity of the drug metabolizing organs to biotransform the compound has provided fundamental insight into estimating first in child doses [15,17,24,60–63]. This effort from the SimCyp consortium group will continue to provide insights that can help particularly in early stage drug development, where the available clinical literature is limited.

Five-year view

The opportunity exists, in the next 10 years to change the status of children with respect to available therapeutic agents for improving their health. While in the past, children have been treated as 'pharmacologic orphans', recent legislative efforts have motivated an increased emphasis of purposefully studying therapeutic agents in children [1]. This effort needs to develop into a direction that primarily supports gathering information for children to improve their health. While it provides incentive for drug developers to actively participate by studying all new agents developed for adults, there is a need to understand fundamental aspects of how children differ compared with adults in terms of their absorption, distribution and clearance of pharmaceutical agents. If this opportunity is managed well, then the next decade will provide

a tremendously increased knowledge base for pediatric pharmacology that will allows drug developers to understand and predict how their compounds are likely to behave in children.

If this opportunity is not managed well, then there is the opportunity for drug developers to obtain increased marketing exclusivity for a number of individual agents without gaining the integrated knowledge that will be essential for adequately dosing therapeutic agents in children from neonates to adolescents. Which direction this will migrate is difficult to predict. The components are present for this effort to succeed, but only time will tell if this is indeed accomplished.

The role of modeling and simulation in this effort will be critical to extending information from sparse experiments into a context that allows broader understanding of how therapeutic agents behave in children. Owing to the limitations and constraints of pediatric clinical trials, developers have little choice than to use modeling and simulation efforts to their fullest in support of their pediatric drug development efforts. In doing so, it will be incumbent on the developers to engage in a dialogue with health authorities to understand and ratify modeling approaches taken in support of a regulatory submission for children [4]. There must also be continual assessment and validation of simulation results with clinical outcomes as they emerge to assure that the models and gathered data converge. It will also be incumbent on the health authorities and clinical pharmacologists to work together with drug developers to efficiently study therapeutic agents with the greatest need and highest priority. This priority must be motivated by the need of children rather than the opportunity for adult therapeutics.

The opportunity exists to transform drug development for children and for all categories of patients who receive these therapeutic agents. In their forecasting report on the future of pharmaceutical development, the consulting firm PriceWaterhouseCoopers predict the movement of greater amounts of pharmaceutical research and clinical development towards *in silico* approaches with the rapid approval in select populations for new chemical entities that ultimately can migrate into greater populations and clinical areas as need and indication develop [102]. Although this is presented as a model for the future, in fact what is proposed is precisely the opportunity that is present in pediatric drug development. Through a number of opportunities, there is momentum, data and need to improve the process of understanding existing therapeutic agents used in children and in studying new agents as they emerge. With the committed effort from academics, drug developers and regulatory authorities, the chance to greatly improve drug development for children exists if these groups work together to optimize resources, energy and finances to answer the most important questions for pediatric clinical pharmacology. This can provide a framework for improving drug development in general by combining existing clinical pharmacology knowledge with quantitative modeling of drug behavior *in vivo* and disease progression. Together, these factors can dramatically improve drug development, not only for pediatrics, but for all.

Key issues

- Many pharmaceutical agents are used off-label in children without guidance to clinicians for dosage initiation or adjustment.
- The lack of dosing guidance stems from ethical, pharmacological, statistical and economic challenges to studying pharmaceutical agents in children.
- Current legislative efforts are changing this to increase efforts to study pharmaceutical agents in children.

- Increasing effort is needed to focus these efforts on understanding the most important characteristics that distinguishes pediatric from adult clinical pharmacology.
- Children differ dramatically with age and maturity from neonates to adolescents and dosing adjustment is required to match these changes.
- Modeling and simulation can provide significant insight into understanding how children differ from adults in clinical pharmacology.
- There is increasing acceptance of modeling and simulation efforts by health authorities combined with clinical data to support new compound submission.
- The opportunity exists to improve pediatric drug development efforts – and drug development efforts in general – through a collaborative interaction between academicians, drug developers and health authorities.

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Table 1

US and European legislative initiatives to support assessment of medicinal products in children.

Legislation	Implementation year	Region	Feature
FDAMA	1997	USA	Voluntary written requests with incentives to increase study of medicine in children
BPCA	2002	USA	Renewal of written requests and incentives, establishment of pediatric therapeutics at US FDA, identification of list of medicines in need of study
PREA	2003	USA	Requires new drugs to be studied with written requests
EC 1901/2006	2007	Europe	Establishes EU requirements for studying medicinal products in children, establishes the rules for submitting PIP for new agents and PUMA for off-patent agents, establishes the PDCO as a authority for the process of reviewing PIPs and PUMAs

BPCA: Best Pharmaceuticals for Children Act; FDAMA: US FDA Modernization Act; PDCO: Pediatric committee; PIP: Pediatric investigation plan; PREA: Pediatric Research Equity Act; PUMA: Pediatric Use Marketing Authorization.