The Initiative for Pediatric Drug and Device Development (iPD3)
A Promising New Model to Address the Unmet Needs in Pediatric Research in the United States

Maher Abdel-Sattar¹, Kimberly Gittings¹, Victor Nguyen¹, Nisreen Shamseddine¹, Lou Donne¹, Tommy Bramley², Janel Long-Boyle³,⁴, Emin Maltepe³,⁴*

¹Xcenda, Palm Harbor, FL; ²Lash Group, Fort Mill, SC; ³Initiative for Pediatric Drug and Device Development, San Francisco, CA; ⁴University of California San Francisco, San Francisco, CA

*Address correspondence to: Emin.Maltepe@ucsf.edu
www.ipd3.org

January 2018
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1.0 | EXECUTIVE SUMMARY

Clinical research surrounding pediatrics has been a large subject of debate in the past few decades. Controversy surrounding regulatory, legal, and ethical aspects of pediatric drug research has impeded advancements within the field, as have the significant investment risks. As a result, these vulnerable patients are often exposed to therapies that have yet to be proven safe and effective in children and neonates.¹

Academic research institutions have a unique opportunity and responsibility to contribute to better pediatric health. Clinical researchers recognize and acknowledge the need for drug development for this population, but conversely understand the need for a solid foundation to support pediatric research and the challenges this endeavor presents.

The University of California, San Francisco (UCSF) and the University of Maryland, Baltimore (UMB), two of the premier educational and research institutions in the nation that also house some of the world’s experts in pediatric clinical research and drug development, have launched the Initiative for Pediatric Drug and Device Development (iPD3).

iPD3’s mission is to become a world leader in facilitating efficient pediatric drug and device development by commercial or government organizations. They also aim to be the primary center of excellence for pediatric research that supports translational applications in this population, while enriching pediatric research as an academic enterprise.

2.0 | BACKGROUND AND OBJECTIVES

2.1 | Unmet Needs in Pediatric Research

Clinical research surrounding pediatrics has been a large subject of debate in the past few decades. Controversy surrounding regulatory, legal, and ethical aspects of pediatric drug research has impeded advancements within the field.

With up to 50% of pediatric trials failing due to poor design and/or difficulties in patient recruitment, the situation has been further aggravated by the high financial risk associated with conducting these trials.²

As a society, we have been transitioning from believing that children should be protected from research, to understanding how they can be protected by research.³ Clinical researchers recognize and acknowledge the need for drug development for this population, but conversely understand the need for a solid foundation to support pediatric research and the challenges this endeavor presents.
Legislative efforts have been led to address the lack of safety and efficacy data in many drugs used in pediatrics; however, ethical, and financial challenges continue to erode this foundation and the consequences often impact the pediatric population directly. These vulnerable patients are often exposed to therapies that have yet to be proven safe and effective in children and neonates.\textsuperscript{1} Physicians prescribe medications outside the approved provisions for the drug—also known as “off-label” use—in order to accommodate dosing and administration route for a child. This is common because neonates and small children have an immature and rapidly developing physiology, demanding unique medical needs that general adult medications do not cater to. This off-label use, however, is virtually an uncontrolled experiment, as there often is no clinical safety and efficacy data backing the medication’s use. As a result, pediatric patients are exposed to unnecessary risks and harms.\textsuperscript{1}

In 2002, one study demonstrated that 1 out of every 10 pediatric prescriptions had an error.\textsuperscript{4} Another study found that there was a 15% chance of a dosing error among the 22 most commonly prescribed pediatric medications.\textsuperscript{5} Potential adverse event rates were 3 times higher in the pediatric population compared with those in the adult population. These issues have been further exacerbated by the opaque ethical, regulatory, and noncompetitive landscape of pediatric clinical research. There is a critical need for pediatric research, as children, especially neonates, are suffering the consequences.\textsuperscript{1} In order to rectify the problem, the obstacles must be acknowledged and new solutions to facilitate and accelerate pediatric research should be explored.

### 2.2 Objectives

Despite some improvements in regulation over the past few decades, pediatric research is still not on par with adult research standards and continues to face many challenges, even with the rapid improvement in healthcare and medical technology.

This paper summarizes the unmet needs in pediatric research and describes iPD3, an innovative model proposed by UCSF and UMB, as a potential solution to address these remaining challenges by partnering with commercial and non-profit organizations to facilitate efficient pediatric drug and device development, while strengthening the academic commitment to this field.

### 3.0 CHALLENGES FOR PEDIATRIC RESEARCH

#### 3.1 History of Regulation in Pediatric Drug Development in the US

Prior to 1999, regulations for pediatric research in drug development were scant. According to reports by the Food and Drug Administration (FDA) 80% of listed medication labels disclaimed usage or lacked dosing information for children.\textsuperscript{6} Only 20% to 30% of drugs approved were labeled for pediatric use (1984–1989 survey, 1991–2001 repeat survey) and only 38% of new drugs potentially useful in pediatrics were labeled for children when initially approved.\textsuperscript{6}

Over the last couple of decades, the focus transitioned from protecting children from research to protecting them through research,\textsuperscript{3} allowing for a movement to improve regulation for pediatric drug development (Table 1). While it was evident that there were many obstacles and dilemmas in conducting pediatric research, there was also as much benefit to be gained.
### Table 1. Key FDA Regulations for Pediatric Drug Development

<table>
<thead>
<tr>
<th>Date</th>
<th>Regulation</th>
<th>Brief Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>Pediatric Rule (Labeling)</td>
<td>Permit pediatric indications to be extrapolated from adult efficacy data in approved drugs</td>
</tr>
<tr>
<td>1998</td>
<td>Food and Drug Administration Modernization Act (FDAMA) Pediatric Exclusivity Incentive</td>
<td>Grant 6 months’ exclusivity in return for conducting pediatric studies (Sunset January 1, 2002)</td>
</tr>
<tr>
<td>1999</td>
<td>Pediatric Rule</td>
<td>Require pediatric studies of a new drug or biological product if product is likely to be: used in a “substantial number of pediatric patients” or provide a “meaningful therapeutic benefit” to pediatric patients over existing treatments (Federal court invalidates; ruling FDA has no authority to enforce)</td>
</tr>
</tbody>
</table>
| January 2002 | Best Pharmaceuticals for Children Act (BPCA)                              | • Reauthorized exclusivity incentive  
• Public dissemination of exclusivity; incentivized studies  
• Public review of safety of drugs granted exclusivity  
• Testing of off-patent drug (Sunset October 1, 2007) |
| December 2003 | Pediatric Research Equity Act (PREA)                                       | • Required pharmaceutical companies to conduct pediatric tests for new drugs likely to be used in children  
• Mandatory pediatric assessment and plan for specific drug  
• Criteria to waive or defer pediatric study (Sunset October 1, 2007) |
| September 2003 | Food and Drug Administration Amendments Act (FDAAA)                      | • Reauthorized BPCA and PREA  
• Established Pediatric Review Committee  
• Labeling mandates inclusion of results, regardless of outcome (Sunset October 1, 2012 for BPCA/PREA) |
| July 2012 | FDA Safety and Innovation Act (FDASIA)                                     | • Permanent reauthorization of PREA and BPCA  
• Require timely submission of pediatric study plan from sponsor after Phase 2  
• FDA must hold report accelerations of products for rare pediatric diseases |

Abbreviations: BPCA – Best Pharmaceuticals for Children Act; FDA – Food and Drug Administration; FDAAA – Food and Drug Administration Amendments Act; FDAMA – Food and Drug Administration Modernization Act; FDASIA – FDA Safety and Innovation Act; PREA – Pediatric Research Equity Act.

The FDA may issue a Written Request to a manufacturer or sponsor for voluntary pediatric studies that may lead to health benefits in that population. Currently, the FDA does not allow use of off-label data retrospectively to support marketing approval, despite most treatments in pediatrics being off-label. Therefore, sponsors must design and implement pre-clinical or clinical studies for submission. Sponsors who receive Written Requests and submit studies that fulfill these requests are eligible to receive pediatric exclusivity for an additional 6 months. Between 1998 and 2014, the FDA issued 464 Written Requests to manufacturers to obtain necessary pediatric information on drug products. Of the sponsors who submitted information for review, 92% were granted pediatric exclusivity.

### 3.2 Current Regulatory Requirements for Industry in the US and Europe (EU)

In the past, pediatric research was viewed as harmful to children rather than a necessity to properly, safely, and effectively treat the many children who suffer from disease. Over the last couple of decades, newer legislation sought to encourage pediatric research and highlight its benefits. In 1994, the FDA published a rule requiring manufacturers to survey existing data to determine whether those data were sufficient to support adding pediatric use information to the drug's labeling. The ruling did not impose any implication on future research, and therefore did not move the needle on pediatric research.\(^7\)
The Best Pharmaceuticals for Children Act (BPCA) – Pediatric Exclusivity Program was enacted in 2002, and amended in 2007. This Act provides a 6-month extension of patent exclusivity to drug developers and manufacturers that voluntarily complete specific pediatric trials. The 6-month extension of patent exclusivity is applied to both the pediatric and adult dosage forms of the drug. The BPCA also states that a positive trial outcome is not a necessity in order to gain the extension in patent exclusivity. This helps to emphasize the importance of research in pediatric patients.

Though incentives exist for manufacturers that choose to conduct pediatric trials, there are also regulations in place meant to ensure the safety of children in clinical trials. The Pediatric Research Equity Act (PREA), enacted in 2003 and amended in 2007, requires companies that file any new drug applications to have an initial Pediatric Study Plan (iPSP) (known in EU as a “Pediatric Investigation Plan” [PIP]). In the US, the FDA Safety and Innovation Act (FDASIA) of 2012 requires the iPSP to be completed early in the development process. Unless the investigational drug has orphan designation, the PSP must be in place within 60 days of the end of Phase 2 product testing. In the EU, the PIP must be in place by the end of Phase 1 testing for all products planning to seek regulatory approval in the EU.

The FDASIA made both BPCA and PREA permanent Acts to help promote pediatric research. Through these efforts, progress has been made in terms of the number, timeliness, and successful completion of pediatric studies; however, much work remains to be done.7

Table 2. Pediatric Regulations in the US and EU8

<table>
<thead>
<tr>
<th>Requirement</th>
<th>US BPCA</th>
<th>US PREA</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Optional Written Request</td>
<td>Mandatory Pediatric Plan or Assessment</td>
<td>Mandatory Pediatric Investigation Plan</td>
</tr>
<tr>
<td>Waiver</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Deferral</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Plan Discussions</td>
<td>End of Phase 2 Post-approval</td>
<td>End of Phase 2 New Drug Application/Biologic License Application approval</td>
<td>Phase 1 Completion of adult pharmacokinetic studies</td>
</tr>
<tr>
<td>Reward</td>
<td>Pediatric exclusivity</td>
<td>-</td>
<td>Supplementary protection certificate extension</td>
</tr>
<tr>
<td>Drugs</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Biologics</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Biosimilars</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Orphan Drug</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Decision’s Authority</td>
<td>Review Division</td>
<td>Review Division</td>
<td>Pediatric Committee</td>
</tr>
</tbody>
</table>

Abbreviations: BPCA – Best Pharmaceuticals for Children Act; EU – Europe; PREA – Pediatric Research Equity Act; US – United States.
3.3 | Ethics of Patient Recruitment in Pediatric Trials

Pediatric research studies are associated with multiple complex ethical issues, which result in more restrictive regulatory oversight compared with adult research studies. Pediatric studies are grounded on the ethical principle of respect for the individual. Following this principle, child assent and parenteral permission are required for research studies and function synergistically to protect the child and foster the development of the child’s self-determination.\(^9\) Parents are generally hesitant to willingly enroll their children in research studies. If the studies do not appear to offer perceivable immediate benefit, parents are even more reluctant to enroll their children.\(^10\) Parents often fear that research studies could harm or hurt their children. Many misconceptions exist regarding the use of placebos in research studies, adding more hesitation to parents’ willingness to enroll their children. Additionally, the complexities of information sheets tend to overwhelm parents and contribute to their reluctance.\(^10\)

In addition to the ethical issues that surround pediatrics research, many problems regarding recruitment and implementation of pediatric studies exist. The pediatric population is much smaller and healthier than the adult population.\(^10\) Recruiting a sample size large enough to meet specific statistical power can be difficult in this smaller population. Additionally, there are many issues regarding assessment scales used in pediatrics. Clinical outcome assessments that are used in adult studies cannot be used in pediatric studies. Children are at different cognitive, linguistic, physical, and behavioral stages, depending on their age and development. For this reason, they are unable to complete patient-reported outcome measures in the same manner as adults or engage in interviews. This raises the question of to whom reporting outcomes should be entrusted: the child or parent/caregiver? The FDA offers limited guidance for manufacturers on how to approach patient-reported outcomes in pediatric trials, discouraging proxy-reported outcome measures and advising that instrument development within relatively narrow age groupings is important to account for developmental differences between children.\(^11\)

3.4 | Lack of Investment in Pediatric Research

High risk, high development costs, and low return on investment for manufacturers discourage spending on pediatric research.

In 2008, only an estimated 50% to 60% of prescription drugs that were being used to treat children had actually been studied in the pediatric population. The likelihood that a medicine had actually been studied in neonates—children less than a month old—was close to zero.\(^12,13\)

One study that presented a detailed comparison of the cost of pediatric trials in relation to the economic return of exclusivity reported a median cost per Written Request of $12.34 million and a median economic benefit of $134 million.\(^10,14\) The net economic return for 6 months of exclusivity after completion of FDA-requested pediatric trials, however, varies substantially among products. Net economic return ranges from –$8.9 million to $507.9 million, while net return-to-cost ratio ranges from 0.68 to 73.63. Therefore, the economic return for pediatric exclusivity is extremely variable.\(^14\)
Although most pediatric trials have typically tested approved drugs that were already shown to be safe and efficacious in adults, up to 50% of pediatric trials have failed. This high failure rate is often due to poor study design and failure to account for how growth and development in children influence the ways in which medicines are adsorbed, distributed, metabolized, and excreted by the body (pharmacokinetics) and what medicines do to the body (pharmacodynamics). Of 189 products studied under pediatric exclusivity from 1998 through 2012, 173 (92%) received new labeling information. Importantly, however, pediatric efficacy was not established for 78 (42%), including 81% of oncology drugs. Subsequent to approval, the therapeutic success of these drugs was only 50%. That is, the drugs approved for pediatric indications only work in half of the children who take them.

4.0 | iPD3

4.1 | Introduction to iPD3
Academic research institutions have a unique opportunity and responsibility to contribute to better pediatric health. UCSF and UMB are 2 of the premier educational and research institutions in the nation that also house some of the world’s experts in pediatric clinical research and drug development. Through a joint effort, UCSF and UMB have launched iPD3, which will work with pharmaceutical companies and other entities as a one-stop shop to address all phases of product development, from inception to regulatory filing, including pediatric clinical trials.

4.2 | Why iPD3?
iPD3 can be a partner and aid in strategic planning by providing guidance and resources throughout product development. With dedicated support, iPD3 can assist from preclinical research support and strategy through the regulatory submissions and approval process. Since pediatric studies are resource-intensive and sensitive to timing, such efforts require copious planning and proper execution. iPD3 has the necessary tools and expertise to guide and support companies through that journey (Figure 1).

This institution plans to be the largest organization with the widest range of pediatric specialists in the nation. As part of iPD3, the UCSF Benioff Children’s Hospital will serve as the clinical facility for pediatric studies and clinical trials. The UCSF Benioff Children’s Hospital is a world-renowned, state-of-the-art, free-standing facility with 183 beds, including 50 for its neonatal intensive care unit. The facility also includes a National Institute of Health-funded Clinical and Translational Science Initiative and Pediatric Research Center, and the Benioff Children’s Hospital Oakland houses an American College of Surgeons-verified Level 1 Pediatric Trauma Center dedicated exclusively to children. Each year the facility admits approximately 5,000 patients, making it an excellent database resource.
4.3 | Center of Excellence

iPD3 is dedicated to excellence in research, education, and care of infants, children, and young adults.

iPD3’s mission is to become a world leader in facilitating efficient pediatric drug and device development by commercial or government organizations.

iPD3’s vision is to double pediatric drug-device development and therapeutic success by becoming the primary center of excellence for pediatric research that supports translational applications in this population, while enriching pediatric research as an academic enterprise.

5.0 | CONCLUSION

Pediatric research has been historically impeded by many ethical, regulatory, and financial challenges in the US. As a result, children are often treated with medications being used off-label, with a higher error rate and limited evidence supporting efficacy and safety in pediatric patients. iPD3 is a promising new model designed and well equipped to help address the unmet needs in pediatric research by partnering with commercial and government organizations to facilitate efficient pediatric drug and device development, while strengthening the academic commitment to this field. To accomplish their mission and vision, iPD3 will rely on the generosity of philanthropic organizations and investments from various stakeholders who are equally dedicated to advancing pediatric research in the US.
REFERENCES


