By Christopher J. Leintz, MPH, DBe

To increase the safe use of pharmaceuticals in pediatric populations by ensuring pediatric pharmaceutical prescriptions are based on scientific evidence, the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) are enforcing drug development pathways that attempt to address the need for pediatric data for new and established medications. Current legislation in both regions prompts research sponsors to complete a pediatric development program in parallel with development of medications for the adult population. In the US, the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) describe research parameters, while in Europe, the Paediatric Regulation ensures the pediatric goal is met.1,2 While the efficacy of these regulations can be debated, ancillary ethical issues have arisen that need to be addressed.

Ethical Uncertainty

Achieving equity in clinical research by serving traditionally underserved populations is a key goal for regulatory agencies around the globe, and pediatric drug development is one of their top priorities. However, a dichotomy exists in pediatric clinical research. The call for an evidence-based approach in pediatric pharmaceutical development is being pitted against the cautionary flags raised by children’s advocates.3 While the latter express strong concerns over the mandate to include children in drug trials as a precondition for regulatory approval, the voices that support evidence-based pediatric medicine are just as adamant, stating that continued off-label drug use in pediatric medical practice is ethically unacceptable, scientifically unsound and medically dangerous.4

The societal response to this debate has been swift and overwhelming. The practice of giving unsubstantiated doses of approved adult medications to children is giving way to a call by regulators for evidence-based dosing in pediatric medicine.5 Assumptions in dosing now are being replaced with certainty, thanks to the increasing amount of drug research...
in pediatric populations resulting from government mandates. Sponsors now commonly implement pediatric research as a standard part of their drug development programs.

While it is indisputable that increasing the safety and scope of therapies for children is a good thing, caution and reflection are essential when using inherently vulnerable populations in clinical research. On the surface, collecting controlled pediatric data on medicines earlier in development sounds like an effective way to address issues of pediatric safety and social justice, allowing an equal distribution of research across all age groups. However, an in-depth probe finds broader, often unwanted outcomes including ethical lapses arising from the existing pediatric research mandates.

**Regulatory Mandates: Risk and Redundancy**

Defining the ethical problems that exist in pediatric medicine is crucial to judging the appropriateness of conducting research in children. First and foremost is the realization that children are exposed to therapeutic agents on a continual basis, regardless of the availability of scientific evidence in the pediatric population. Off-label drug use accounts for a significant portion of pediatric drug dosing. The phrase “off-label” is simply a way of stating that a drug is given to a person or group for a use that has not undergone the full scientific and regulatory rigor available for a so-called “on-label” use. While this may seem innocuous, the potential physiological and psychological differences between adults and children could lead to grave, even life-threatening, consequences when drugs are used in an untested population. Anecdotal evidence of the safety and efficacy of a drug used in children is not the same as robust, controlled scientific data to inform the prescribing physician. It is on the basis of this premise that regulators have inserted themselves in the arena of pediatric drug development.

Until recently, research sponsors have treated pediatric research largely as an afterthought, leaving most decisions about dosing children appropriately with approved adult drugs on the shoulders of pediatricians and their staffs. Among the primary issues inhibiting pediatric research is the limited pool of pediatric subjects available. This limitation is due to a combination of factors, including the large number of pediatric studies being conducted at any given time, the small number of pediatric patients with the requisite disease state, ethical issues associated with consenting/assenting children and, on a global scale, disparate local regulations regarding guardianship and child protection. Negative public opinion also plays a role, with research sponsors acutely sensitive to being perceived as exploitive.

Pragmatically, FDA, via BPCA and PREA, gives research sponsors a fair amount of latitude to meet the US pediatric research mandate. Research sponsors have plenty of leeway on when to begin pediatric research and when the data generated should be submitted to the agency for inclusion in updated drug labeling. Because of this flexibility, research sponsors may delay the implementation of pediatric research programs and have the option to wait until the adult drug is approved before completing their pediatric drug assessments.

EMA is more rigid than FDA on the subject of pediatric research. Once first-in-human pharmacokinetic studies are completed for a novel therapeutic agent, research sponsors are expected to submit a detailed Paediatric Investigation Plan (PIP) to EMA consisting of the details and timing for formulation and nonclinical (non-human) and clinical (human) measures that will be undertaken for the pediatric population, covering all subsets. This is very early in the drug development timeline. The Paediatric Regulation does allow for class- and product-specific waivers and deferrals when justified. These options offer valuable constructs to mitigate certain concerns; however, both are steeped in bureaucratic processes that consume valuable resources and do not promise a positive outcome.

The PIP is a binding document that must be followed to the letter in order for the drug to be considered for any type of regulatory approval, including as an adult therapy. While there is a procedure for PIP modification, the European regulators also require a PIP compliance certification at the time of submission of the Marketing Authorisation Application (MAA) to demonstrate the pediatric plan was carried out in accordance with the agreed-upon PIP. Therefore, there is complexity associated with procedural overlap. Further, EMA has the legal authority to force research sponsors to include pediatric plans for indications not currently under consideration, regardless of feasibility or sponsor interest.
The divergent pediatric regulations in the US and EU may lead to troubling consequences in research ethics. First, the likelihood that a drug in Phase 1 of development will reach the market is very slim. Therefore, pediatric testing of early phase compounds with little chance of reaching the market poses an unnecessary risk to vulnerable children. Also, the EMA pediatric mandate may result in children's exposure to compounds with scarce safety data and likely limited, or no, efficacy data available.

FDA mandates, on the other hand, do not require a pediatric research plan until later in development, when much more safety and efficacy data are available and the chances of a drug's reaching the market are much higher. These regulatory differences leave open the possibility that FDA and EMA will not agree on a common pediatric development plan or timeline. Drug sponsors are left with the choice of either adding exponential costs to their overall development plans or simply skipping markets where return on investment is questionable. These differences in pediatric regulations also potentially lead to outcomes that violate the key facets of the Declaration of Helsinki. Unnecessarily exposing a vulnerable population to research that likely has no benefit is a fundamental prohibition laid out in the declaration. Exposing children to a research study that offers nothing new to the scientific or medical communities is also a violation. Carrying out research as a simple means to meet a bureaucratic check-box is not an ethically defensible position.

The argument that any research done in children is ethically justifiable because any scientific information gathered may help future generations of children is foundationally unsupportable. Completing rudimentary adult efficacy testing prior to initiating pediatric studies is a more targeted and ethical approach to testing drugs in children. Simply put, this would greatly reduce the potential of children's exposure to highly toxic drugs for no scientifically justifiable reason.

Social Justice: Unfair Research Burden

A reality in pediatric research is the limited pool of children available to participate. In order to enroll pediatric trials, sponsors and their agents must continually search for new sources of research subjects, often targeting developing countries where quality healthcare may be scarce and available only to the affluent. The prospect of being able to receive the free healthcare that is included in a research study can place a heavy burden on parents who must decide whether to allow their child to participate in a clinical study. Placing an unfair research burden on socioeconomically vulnerable groups of children, which include a disproportionately high concentration of racial and ethnic minorities, is a reality that must be faced when complying with government research mandates.

Infants and children are inherently vulnerable groups whose lack of cognitive maturity requires special protections. Choosing between allowing a child to suffer without medical treatment or entering into a risky research study should not be based on a family's socioeconomic status. This is not an argument against pediatric research in general. Rather, it is an indictment against a mandate that does not recognize or require a more equitable divvying of the research burden across socioeconomic and geographic strata. The lack of a social justice component in the pediatric mandates has the effect of turning these rules into bureaucratic activities that lack true scientific merit or community spirit.

Better Serving our Children

While the intent of pediatric research mandates is to bring safe and effective therapies to an often neglected group, there are ways to address this issue without violating ethical principles. Among these:

- Global regulatory agencies should strive to be more collaborative across borders to limit duplicative research.
- Plans and research should be timed such that more data on the therapeutic agent are collected before dosing of children is required, and so the pediatric mandate does not delay or hinder the development of drugs for other vulnerable populations.
- Pediatric regulations should strive to ensure pediatric research is distributed equitably across all representative socioeconomic, ethnic and racial groups.
Greater harmonization of pediatric regulations would not only alleviate the ethical problem of duplicative research, but also would promote faster development of therapeutic agents for the non-pediatric population. Saving research sponsors the time, effort and money involved in developing separate pediatric programs would allow them to devote more resources to adult drug development programs. However, more still would need to be done to ensure pediatric mandates do not unnecessarily delay or hinder adult drug development programs.

Completely fixing the ethical issues described above would require separating the approval of pediatric drugs from the approval of adult drugs. The main argument regulators might make against this suggestion is that when these approvals were separate activities, research sponsors all but ignored pediatric development. However, holding up adult drug approvals based on pediatric concerns is not the answer.

**Conclusion**

The advent of global pediatric drug development mandates put in place by the world’s most prominent regulatory bodies, FDA and EMA, should cause all involved in regulated clinical research to consider the unstated implications of these laws. Principlism, the bioethical approach founded on the respect for individual rights, shows us these mandates can lead to ethical missteps ranging from violations of autonomy and social justice to contravening medical ethics norms such as reducing harm and enhancing good. Collaborations of regulators, industry and the public, coupled with a more pragmatic approach of linking pediatric and adult drug development, have the potential to bring safer pediatric drugs to market more quickly and ethically.

**References**


**About the Author**

Christopher J. Leintz, MPH, DBE, has been a regulatory professional in the pharmaceutical industry since 2001, focusing on new drug development and human subject research. He served in the United States Peace Corps in Bulgaria, where he acquired a keen interest in clinical research and the potential for exploitation of people living in former Soviet Bloc countries. Leintz holds a doctorate in bioethics from Loyola University Chicago and an MPH from the University of Illinois at Chicago. He can be reached at komanderovka@hotmail.com.

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