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CORRESPONDENCE

I-ACT for Children: helping close the gap in drug approval for adults and children

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The Institute for Advanced Clinical Trials (I-ACT) for Children was founded in 2017, emerging from the vision of leaders assembled by the American Academy of Pediatrics and initially funded through a grant from the US Food and Drug Administration (FDA), memberships by biopharmaceutical companies, and philanthropy. The explicit goal of the Institute is the facilitation of timely availability of innovative drugs for children. The disparity between the availability of novel drugs for adults and children has existed for so long, that pediatricians have learned to live with it as an unsurmountable given. Consequently, many drugs are prescribed and used *off-label* in pediatrics.[1] Progress has been made but many medicines are still not adequately studied in children, and for those that are, the time between an adult and pediatric label is nearly a decade.[1,2] The need is especially pronounced in neonates.[3]

As we enter the third decade of a new century, however, it is a time for guarded optimism. Foundational legislation (the Best Pharmaceutical for Children Act, and Pediatric Research Equity Act) have been made permanent in the USA. The RACE Act (Research to Accelerate Cures and Equity for Children)[4] now requires evaluation of new drugs and biologics directed at a target substantially relevant to growth or progression of pediatric cancer. And the Rare Pediatric Disease Priority Voucher Program was established, enabling companies to be awarded priority review for drugs targeting a list of rare diseases.[5] Meanwhile, the European Medicines Agency created the European Paediatric Regulation in 2007[6] specifically to address the low level of research and development into drugs for children by biopharmaceutical companies. Similarly, Canada created the Paediatric Expert Advisory Committee in 2009[7] in an attempt to increase the availability and safety of drugs for children. There is no question that, in the past two decades, government agencies have challenged the status quo and want to see better access to drugs in children.

At the same time, trial methodology and regulatory science have also significantly advanced. Bayesian statistics, adaptive trial designs, master protocols, modeling and simulation, fit-for-purpose tools, decentralized trials, use of real-world data, and better definition of how and when adult data may be extrapolated are all making their way into mainstream drug development. Applications in pediatrics can increase efficiency and improve timeliness, making many of the excuses for not doing studies in children moot.

This all led Dr. Gilbert Burckart of the FDA and his colleague Dr. Clara Kim from the University of Southern California School of Pharmacy to publish a paper in 2020 entitled, "The revolution in pediatric drug development and drug use: therapeutic orphans no more,"[8] in which they delineate strategies to overcome the various hurdles innate to pediatric medicine development. Clearly the trajectory of progress has picked up.

So why are we still living with the fact that many of the drugs used in children have not been approved for pediatric use and even when they are, it still takes way too long[9] between adult and pediatric labeling? While drug development for children is for sure more complicated, it does not need to be slow. Just look at the case of remdesivir for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) where the initial Emergency Use Authorization from the FDA included dose recommendations for even the very youngest children based on modeling.[10] We understand that obtaining data in adults is critical and often pediatric studies typically cannot start until some data from adults are available. We understand that adult development may take precedent, if adults are the primary population in need, or for reasons of financial return. There is the concern that simultaneous trials in pediatric age groups at the time drugs are being studied in adults would put adult licensing at risk. Studies looking at this issue have found no new contradictions, warnings or adverse events identified during the pediatric trials that would negatively impact adult licensure.[11] A study done by the FDA also supported the simultaneous development of adult and pediatric medicines and allowed concurrent approval in both age categories.[12] We suggest that once enough data are available to justify ethically and medically studying a drug in children, these studies must be done with a sense of urgency.

It is evident that solutions to this ongoing challenge in pediatrics must include many stakeholders. Regulatory agencies have advanced work in regulatory science and innovation in trial design, biopharmaceutical sponsors have a substantial pipeline of relevant products in development, pediatric investigators are eager and ready to study drugs in kids of all ages, and patients and parents are in desperate need of new therapeutics.

The Best Pharmaceuticals for Children Act provides a mechanism through the FDA and National Institute of Child Health and Human Development to catch-up with the information gap in pediatrics. The Pediatric Trials Network (PTN), led by Dr. Danny Benjamin at Duke, has made good progress over the past few decades in adding or modifying pediatric information in labels for these drugs.[13] For innovative (on-patent) new drugs, there continues to be room for improvement in the US. Connect for Children (C4C) based in the EU, works in both spaces.

I-ACT for Children was established to foster and, where indicated, provide, consistent leadership, accountability, conviction, and a critical mass of like-minded individuals willing to effect change. Its focus is on innovative on patent-drugs that have an application in pediatrics. Since its inception, it has worked to test the organization's capacity and potential and establish evidence that its mission can be accomplished. Specifically, it has:

- Worked with biopharmaceutical sponsors and advocacy groups to advance the use of innovative trial designs and methods that improve the feasibility of studies;

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- Worked with partner organizations gathering essential real-world data in newborns and other populations;
- Formed a site network to provide qualified sites in the US and elsewhere capable of performing regulatory grade clinical trials, including difficult-to-recruit pediatric clinical trials;
- Launched a quality improvement program, creating a learning ecosystem to ensure the best data and processes in pediatric clinical trials;
- Led the implementation of a national leader's program to support a high priority international clinical trial through intensive site engagement activities;
- Worked with parents, advocates, children, clinicians, regulators, sponsors, academicians, and others to accelerate completion of clinical trials. For example, we have actively helped develop consensus for inclusion of adolescents in adult trials,[14] contributed to the methodology for adaptive platform trials, and addressed challenges in trials for children such as those with inflammatory bowel disease and other chronic and rare diseases.

As an independent organization that acts collaboratively across the pediatric community to accelerate pediatric drug development, the Institute serves as a strong advocate for pediatric drug development and has developed into a critically important participant in a momentous cause: closing the considerable gap between adult and children's drug approval and labeling.

Max J. Coppes [1,2,3]✉, Cindy Jackson[3] and Edward M. Connor[3,4]
[1]*Departments of Pediatrics and Internal Medicine, University of Nevada Reno School of Medicine, Reno, NV, USA.* [2]*Renown Children's Hospital, Reno, NV, USA.* [3]*I-ACT for Children, Rockville, MD, USA.* [4]*Departments of Pediatrics, Microbiology, Immunology, and Tropical Medicine, George Washington University School of Medicine and Health Sciences, Washington, DC, USA.*
✉*email: mcoppes@renown.org*

REFERENCES

1. Allen, H. C. et al. Off-label medication use in children, more common than we think: a systematic review of the literature. *J. Okla. State Med. Assoc.* **111**, 776–783 (2018).
2. Sachs, A. N., Avant, D., Lee, C. S., Rodriguez, W. & Murphy, M. D. Pediatric information in drug product labeling. *JAMA* **307**, 1914–1915 (2012).
3. de Lima Costa, H. T. M., Costa, T. X., Martins, R. R. & Oliveira, A. G. Use of off-label and unlicensed medicines in neonatal intensive care. *PLoS ONE* **13**, e0204427 (2018).
4. RACE Act poised to advance pediatric cancer research. *Cancer Discov*. **10**: 1434 (2020).
5. Hwang, T. J., Bourgeois, F. T., Franklin, J. M. & Kesselheim, A. S. Impact of the priority review voucher program on drug development for rare pediatric diseases. *Health Aff.* **38**, 313–319 (2019).
6. Union EPCotE. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on Medicinal Products for Paediatric Use and Amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. *Official J. Eur. Union* **L378**, 1–19 (2006).
7. A Paediatric Expert Advisory Committee. *Paediatr. Child Health*. **14**, 289 (2009).
8. Burckart, G. J. & Kim, C. The revolution in pediatric drug development and drug use: therapeutic orphans no more. *J. Pediatr. Pharmacol. Ther.* **25**, 565–573 (2020).
9. Carmack, M., Hwang, T. & Bourgeois, F. T. Pediatric drug policies supporting safe and effective use of therapeutics in children: a systematic analysis. *Health Aff.* **39**, 1799–1805 (2020).
10. Noel, G. J. & Connor, E. Commentary: "Emergency Use Authorization for remdesivir: a pediatric perspective". *Pediatr. Infect. Dis.* **39**, e234 (2020).
11. Beleck, A. & Nachman, S. Understanding pediatric drug lag time: review of selected drug package inserts. *J. Pediatr. Infect. Dis. Soc.* **10**, 509–513 (2021).
12. Tanaudommongkon, I. et al. Combined pediatric and adult trials submitted to the US Food and Drug Administration 2012–2018. *Clin. Pharmacol. Ther.* **108**, 1018–1025 (2020).
13. Randell, R. L., Benjamin, D. K. & Greenberg, R. G. An innovative approach to building an effective and efficient pediatric trial network. *Hosp. Pediatr.* **12**, e309–e311 (2022).
14. Noel, G. J. et al. Inclusion of adolescents in adult clinical trials: Report of the Institute for Advanced Clinical Trials for Children's Pediatric Innovation Research Forum. *Ther. Innov. Regulat. Sci.* **55**, 773–778 (2021).

AUTHOR CONTRIBUTIONS

All three authors have contributed to the commentary, its content, the relevant points that the commentary makes, the historical perspective, and the relevant references used.

COMPETING INTERESTS

One of the authors, C.J. is an employee of I-ACT for Children. Both other authors are non-compensated Board members of I-ACT for Children.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Max J. Coppes.

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