LETTER TO THE EDITOR

Regarding Combined Pediatric and Adult Trials Submitted to the US Food and Drug Administration 2012–2018

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To the Editor,

We wish to congratulate Tanaudommongkon *et al.* on demonstrating the success of a pathway to expedite labeling for pediatric patients.[1] We also advocate including children in trials supporting the initial submission. Yet, there is further opportunity. Data in Table 1 of the original publication indicate that one-third of all programs do not provide information for children under 12 years of age. This increases to nearly 50% when orphan drugs are excluded. Further, these cases are a fraction of overall prescriptions as up to 80% of drugs are used off-label in children. Thus, even with the success of the Pediatric Research Equity Act (PREA), a huge gap in pediatric dosing recommendations persists.

PREA requires all New Drug Applications to contain pediatric assessments unless a waiver or deferral is granted. Assessments must include a pediatric investigational plan to support dosing in each pediatric subpopulation for which the product has been assessed to be safe and effective.[2] It is considered unethical to study children without the chance for therapeutic benefit; thus, plans typically include initial pediatric doses predicted from adult data. Further, investigations of plans and final labels indicate that pediatric doses do not differ significantly from model-based predicted values.[3]

We believe it is unethical to delay access to meaningful use instructions for 9 years.[1] We have described a process elsewhere[4] to eliminate this time lag: The FDA and sponsors create a plan to obtain pediatric recommendations at initial New Drug Application approval. Even in instances where pediatric and adult trials cannot be run together, the initial approval can include a label with model-based dosing instructions for children along with an industry-funded mechanism to confirm dosing accuracy, efficacy and safety.

Science has progressed since the introduction of PREA. Drug development has been successful in showing that appropriate pediatric doses can be obtained by matching exposures in children to those found to be safe and efficacious in adults[3] and providing better dosing strategies and dosage forms. This same experience has shown that the pharmacokinetics in children are often well predicted from adult data and knowledge of ontogeny of metabolic systems. Yet, while PREA and other legislation has been successful in creating dosing recommendations for some drugs, most still suffer from the average 9-year lag after initial market approval. This lag can be either eliminated or minimized by reconsidering how we develop drugs for all patients not well represented by phase III trials and by applying what we have already learned.

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CONFLICT OF INTEREST

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1. 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).
2. Food and Drug Administration (FDA). Guidance for industry: how to comply with the pediatric research equity act <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf >. Accessed July 14, 2020.
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4. Powell, J.R., Cook, J., Wang, Y., Peck, R. & Weiner, D. Drug dosing recommendations for all patients: a roadmap for change. *Clin. Pharmacol. Ther.* **109**, 65–72 (2021).

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