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INVITED REVIEW

Advancing Pediatric Antibacterial Drug Development: A Critical Need to Reinvent our Approach

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The Clinical Trials Transformation Initiative convened with several groups in the pediatric antibacterial drug development community with the goal of identifying challenges and recommending ways to improve current practice. Attention to 5 major areas hold the promise of making new antibiotics available for use in children as soon as possible after they are approved for use in adults.

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The emergence of antimicrobial resistance to many important bacterial pathogens has renewed interest in developing new antibacterial drugs. The process for advancing these critically needed therapies to the clinic is expected to start with studies that involve adults and will occur well before studies are conducted in children. Although requirements for assessment of the safety and efficacy of new drugs in children as defined in US law [1] are being met, recent experience indicated that the completion of pediatric trials necessary for US Food and Drug Administration (FDA) approval and updated labeling for a pediatric indication for a new antibacterial drug often takes 5 to 10 years after approval for use in adults [2]. Because children are at risk of infection from the same drug-resistant bacteria as adults, it is likely that once a new antibacterial drug is approved for adults, using that drug in children will be considered by many clinicians even before the safety and efficacy of it in children have been established [3–5]. This use can result in suboptimal treatment of infants and children and underscores an urgent need for the process for developing and evaluating antibacterial drugs for children to be improved and accelerated.

To address this challenge, the Clinical Trials Transformation Initiative, a public–private partnership with funding from the FDA, convened experts to identify factors that contribute to delays in the completion of pediatric antibacterial drug trials and to offer recommendations for improvements. Through extensive discussions and investigations by stakeholders representing the FDA, drug developers, academia, clinical research networks, parents, and care providers, barriers to pediatric antibacterial drug trials were identified, and suggestions for addressing these barriers were developed [6]. The key consensus elements that resulted from this effort belong to 5 major areas: early planning, protocol development and trial design, informed consent, healthcare provider engagement, and reporting and labeling.

DRUG-DEVELOPMENT PLANNING

Planning for pediatric trials should begin as early as possible in the drug development process. To ensure optimal alignment with global regulatory expectations and the medical needs of children, company sponsors and other funders should consider early collaboration with regulators. They also should seek input from the pediatric infectious diseases community, the neonatal community, and parents with the goal of planning a development program that addresses all stakeholder needs.

In nearly all instances, early data regarding the pharmacokinetics, safety, and efficacy of a new antibacterial drug in adults will provide sufficient information to enable clinicians to outline a rational plan for its development in children. Unnecessary delays in beginning a pediatric program can be avoided by starting pharmacokinetic studies that involve children once data from early-phase adult trials provide preliminary evidence of efficacy with no concerning safety signals.

PROTOCOL DESIGN AND DEVELOPMENT

Successful completion of a pediatric trial depends on the active engagement of parents, children, nurses, physicians, study coordinators, sponsors, and regulators. The goal of broader stakeholder engagement in the development of a trial protocol should be to design that trial to generate sufficient information to establish safety and efficacy for a new antibacterial drug while

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considering the unique needs and risks inherent in managing sick neonates, infants, and children.

In constructing a pediatric drug development program, consideration should be given to how data generated in adult trials can be extrapolated to inform conclusions about antibacterial drug efficacy in children. For many bacterial diseases, especially in older children and adolescents, the pathophysiology of the disease in children will be sufficiently comparable to that in adults to allow for extrapolation of a drug's efficacy from adults to children. In these circumstances, trials focused on defining the dose to match the drug exposure in adults and safety in children might suffice to support pediatric labeling [7].

INFORMED CONSENT

The chaotic disruption of family life that accompanies the diagnosis of a serious acute bacterial infection in a child needs to be recognized and addressed when helping a family navigate the process of informed consent for a trial. Whenever possible, this process should be led and managed by personnel who have established a relationship with and are trusted by the child and family, including hospital and nursing staff or the child's primary care provider. Discussion with families who might have participated in clinical trials already or been involved in protocol design will help investigators to better anticipate the needs and concerns of families and children who are new to clinical trials. Throughout the child's participation in the trial, families should be encouraged to continue discussion related to their child's safety and well-being.

HEALTHCARE PROVIDER ENGAGEMENT

Involving the child's usual healthcare providers in planning programs, designing protocols, and serving as trial investigators is critical for ensuring that children's medical needs are met and trials are conducted efficiently. Although it might not be possible for a child's primary care provider to serve as a trial site investigator, the involvement of a trial site's healthcare providers in trial planning can be very effective in connecting trial sponsors to those physicians and nurses who best understand the medical needs of children in their community. By making this connection, it might be possible for healthcare providers to prepare children and their families for the possibility of participating in a clinical trial and to serve as a resource of information to those who choose to be involved in such a trial. The time and energy needed to establish relationships based on trust and respect between the sponsors and healthcare providers/investigators are often not accounted for sufficiently in the development process. Providers must have a transparent view of the goals and objectives of new antibacterial drug-development programs. They also must be committed to generating the most accurate and useful data from children who are receiving experimental drugs so that study findings can inform both regulatory agencies and the healthcare providers who will eventually prescribe those drugs.

Likewise, a sponsor's knowledge of an investigator's experience and available clinical infrastructure is critical for ensuring that investigators have access to appropriate resources to conduct a trial in accordance with good clinical practice. Experience in ensuring the safe conduct of trials that involve children indicates that pediatric trials will likely require substantially greater resources than are typically needed for adult trials. This must be considered when planning for the resources needed to complete this work and will require a detailed and realistic discussion of these resources among sponsors, clinical research organizations, and research sites. A sponsor's or clinical research organization's budget for a pediatric trial must reflect the likelihood that more resources per subject enrolled will be needed to complete it than is needed to complete a trial that involves adults, and consideration that substantial variation across sites might exist on the basis of available infrastructure and local healthcare costs should be given. Providing inadequate funding is not in the best interests of any stakeholders and can lead to substantial delay and costs that exceed that which would have been needed if the funding was adequate initially.

REPORTING AND LABELING

Rapid widespread dissemination of findings from pediatric trials is needed to ensure that practitioners caring for children understand the benefits and risks of using new antibacterial drugs. Publication and presentation of information at national and international forums should occur as soon as a study has been completed. Public discussion of this information can be helpful in identifying important issues that should be addressed as the development program progresses. In addition, labeling related to children can be updated and expanded as important pharmacokinetic, safety, and efficacy data for different pediatric age groups are generated.

Recommendations in each of these areas reflect a single theme: the imperative for collaboration across all groups and individuals who have a stake in the development of new antibacterial drugs for use in children. Although collaboration undoubtedly is important in other therapeutic areas, the urgent need to understand optimal dosing, safety, and efficacy of new antibacterial agents in infants and children makes it an especially important issue for those engaged in antibacterial drug development. It is clear that new antibacterial therapies must be developed to address the medical needs of our youngest patients. Being well prepared to collaborate in bringing these advances to children is the responsibility of and challenge to everyone concerned about the health of children.

Notes

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