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A review of paediatric development challenges, FDA collaboration and future trends

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SUSAN MCCUNE, M.D., is a paediatrician and neonatologist, with 18 years' academic clinical and research experience. This was followed by 18 years at the United States Food and Drug Administration (FDA) where, from 2017 to 2021, she was the director of the Office of Pediatric Therapeutics in the Office of the Commissioner. She was responsible for international paediatric cluster activities with the FDA, European Medicines Agency (EMA), China's National Medical Products Administration (NMPA), Health Canada and Australia's Therapeutic Goods Administration (TGA). Dr McCune currently serves as vice president for paediatrics and clinical pharmacology, PPD clinical research services, Thermo Fisher Scientific. She is dedicated to supporting pharmaceutical development across rare diseases and paediatrics with a focus on neonatology, clinical pharmacology and biomarker development.

CATRIONA ROSCOE-CUTTING and **CHARITY-ANNE M. SCHULLER**, both with Thermo Fisher, talked to their colleague about challenges in paediatric development, collaborations between the regulatory agencies and her thoughts on the future trends in paediatric development. Dr McCune's answers represent her opinion and don't represent any official responses from Thermo Fisher Scientific or the FDA.

Q: What do you see as the most significant challenges for sponsors in the development of products for paediatrics?

A: Great progress has been made in paediatric therapeutic development over the past 20 years, following the establishment of regulatory requirements. For example, in the US, the Best Pharmaceuticals for Children Act (BPCA) provides an incentive, in the form of additional marketing exclusivity for sponsors, for organisations that voluntarily conduct paediatric studies for therapies with a potential public health benefit in children. At the same time, the Pediatric Research Equity Act (PREA) requires sponsors to assess the safety and effectiveness of certain products in paediatric patients (excluding products with an orphan drug designation except products being developed under the Research Acceleration for Cure and Equity (RACE) for Children Act). Over the last 20 years, it is interesting that more than half of the new paediatric product labels have been secondary to PREA requirements and not BPCA incentives. In paediatric trials where adult efficacy has been demonstrated, one of the biggest hurdles is identifying appropriate paediatric endpoints. For example, younger children are not able to reliably perform the six-minute walk test. So, other endpoints must be developed for specific paediatric populations.

It is exciting that more therapies are being developed for paediatric-only diseases. However, the development programmes need to focus on the right dose, in the right population, with the right trial design and the right endpoints. Successful trials require the use of or the development of clinically meaningful endpoints and may benefit from innovative trial design approaches. These uncertainties in therapeutic development create challenges for sponsors. In addition, the limitations in financial incentives to develop products for use in children, generally hinder paediatric therapeutic development.

Q: Is the collaboration between the FDA and the EMA still ongoing, and do you think it adds value?

A: The collaboration between the FDA and the EMA is stronger than ever. The monthly and ad hoc international paediatric cluster calls are coordinated by the Office of Pediatric Therapeutics in the Office of the Commissioner at the FDA. These calls were initiated in 2007 to exchange information on therapeutic-specific study designs, waivers and deferrals, choice of comparator arms, efficacy endpoints, safety concerns, and general topics that are not product specific.

Following a call, feedback and sometimes a common commentary is provided to the sponsor. The common commentary provides non-binding comments to sponsors on paediatric development plans, which have been submitted to both the FDA and the EMA. Any of the collaborating agencies can request a specific discussion topic. Moreover, many companies do not realise that these meetings can also be requested by a therapeutic product sponsor.

Paediatric representatives from the FDA and the EMA have collaborated on several webinars. For example, representatives from the FDA and the EMA presented at the recent International Neonatal Consortium annual meeting and participated in panel discussions, on the topics of genetic testing technologies and real-world data. The FDA and EMA work with other international collaborators in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), where important paediatric documents are discussed, including the clinical investigation of medicinal products in the paediatric population ICH E11 and the nonclinical safety testing in support of development of paediatric pharmaceuticals ICH S11.

Q: What do you think has been (and will be) the impact of the RACE for Children Act on development?

A: The RACE for Children Act was incorporated as Title V Sec.504 of the FDA Reauthorization Act (FDARA). It was enacted on 18 August 2017 and amends PREA. It requires the evaluation of new molecularly targeted drugs and biologics that are "intended for the treatment of an adult cancer and directed at a molecular target FDA determines to be substantially relevant to the growth or progression of a pediatric cancer." The RACE for Children Act also eliminates the orphan exemption for paediatric studies for cancer drugs directed at relevant molecular targets. The act brings equity to children with cancer globally and will dramatically alter the landscape for paediatric cancer drug development. It will require earlier consideration of nonclinical assessments using paediatric-specific models.

Innovation in study design and the global coordination to study the relevant novel drugs are key to improving the cancer outcomes for children. The elimination of the orphan exemption for molecularly targeted paediatric cancer therapies, will promote the availability of new cancer therapies for children. The RACE for Children Act will not solve all the obstacles with respect to paediatric cancer drug development, as successful trial implementation depends on multiple stakeholder input and global collaboration. Unfortunately, the number of intercontinental paediatric cancer trials has been limited. Consequently, the ACCELERATE International Collaboration Working Group has been identifying obstacles and proposing solutions to improve global collaboration in paediatric cancer clinical trials.

Q: Several agencies have started to consider the inclusion of adolescents in adult studies. Do you think this is a positive move and do you think the trend will continue?

A: Historically, paediatric drug development has progressed sequentially, from adults to adolescents and then middle-aged children, toddlers, infants and neonates, based on concerns with respect to vulnerability. More recently, agencies have encouraged the inclusion of adolescents in adult Phase 3 trials for oncology, asthma, atopic dermatitis, hypertension, inflammatory bowel disease and SARS-CoV-2 infection. A central tenet to including adolescents in adult trials, is an understanding of the disease similarity and the expectation that the response to the therapy will be sufficiently similar in the two populations. For example, studies have shown that adolescents and adults with migraines do not have similar responses to therapy so these populations should not be consolidated within the same trial.

The inclusion of adolescents in adult clinical trials requires a conversation with the regulatory agencies, with respect to the data needed to support labelling in the adolescent population. For example, if efficacy is extrapolated, do a certain number of adolescents need to be studied, to obtain sufficient pharmacokinetic (PK) and safety data in that population?

Combined trials have been easier to conduct at institutions that clinically manage both adults and adolescents as it simplifies logistical issues. Some independent adult and paediatric sites have collaborated on studies. Paediatric experts also have been included on study steering committees and data safety monitoring committees.

It is important to recognise that the consent/assent requirements differ between the adult and adolescent populations. There are increasing efforts underway to include adolescents in the design of the clinical trials. I think this trend will continue; it has the potential to increase for those therapeutic areas, where the disease is similar and the expected response to therapy will be sufficiently similar between adults and adolescents.

Q: What advice can you give to companies for engaging with agencies in their discussion around paediatric studies?

A: Discussions with agencies regarding paediatric studies can occur at different points in product development. For paediatric studies under PREA that are planned to be completed as part of a new drug application (NDA) for the adult programme, the initial paediatric study plan (iPSP) must be submitted no later, than either 60 calendar days after the date of the end of the Phase 2 meeting, or such other time as agreed upon between the FDA and the sponsor. An iPSP is not required if the drug has orphan designation. Based on the FDA Guidance on paediatric study plans, for studies planned under a written request (BPCA), it is important to submit a proposed paediatric study request (PPSR) asking the FDA to issue a written request.

Early meeting with the agency at the pre-IND phase is encouraged, as this can help prevent any clinical hold issues and identify (and avoid) unnecessary studies. The pre-IND meeting can help ensure that necessary studies are designed to provide useful information while obtaining regulatory insight, particularly, with respect to defining endpoints and goals for the development programme. A pre-IND meeting can be especially important when

the product is intended to treat a serious or life-threatening disease. That also is the case when there is a novel indication, the sponsors are new to drug development, the drug is a new molecular entity and/or there are concerning pharmacologic or toxicologic signals. These early conversations with the regulatory agencies can be critical in efficient paediatric product development, especially since new therapies are being developed for paediatric-specific diseases.

Q:When do you think companies should have those conversations? For example, is the end of Phase 2 early enough, especially given the EU requirement to occur at the end of PK?

A: The earlier the conversation begins with the regulatory agencies, the better. The EU requirement is that it occurs earlier in the development process. Therefore, having an earlier conversation with the FDA (sooner than 60 calendar days after the date of the end of Phase 2 meeting) may facilitate conversations between regulatory agencies if necessary, through the international paediatric cluster calls. Green et al. (2018) reported that trials succeeded in meeting their primary endpoint more often, when the adult and paediatric endpoints were the same. It is important to recognise if the clinical endpoints for studies in paediatric patients will be different, from those in adult patients. If new endpoints and biomarkers need to be developed for paediatric trials, having bridging data from adults in the earlier adult trials can help provide data to support the paediatric endpoints. So, early planning for paediatric studies, even during the planning for adult trials, may facilitate paediatric programmes in the long term.

Q: At a high level, what are any future trends/discussions that you think will continue/start to be brought into paediatric development?

A: I think that there are several exciting trends and future directions related to paediatric therapeutic development. More therapies are being developed for paediatric-specific diseases, including for the neonatal population. These new trends include: the development of new animal models, the development of paediatric-specific endpoints and biomarkers, the use of modelling and simulation, the development of digital technologies, the use of patient-centric sampling and the increased participation of the paediatric patient.

Q: Are there new nonclinical data that would be important in supporting paediatric trials?

A: New, robust animal models will be required as proof of concept to justify the initiation of Phase 2 trials in paediatric patients, with information to support the optimal dose/duration/frequency of drug administration. In some therapeutic areas, the development of animal models that can be replicated in humans has been more problematic. This is particularly true in the neurology therapeutic area. More sophisticated modelling and simulation paradigms are being developed, with respect to physiologically based pharmacokinetic (PBPK) models and model informed drug development (MIDD). These will increasingly be applicable to the paediatric population, as additional data become available, with respect to the development of metabolising enzymes and transporters.

More precise dosing strategies will be able to be developed based on increased data supporting the ontogeny of absorption, distribution, metabolism and excretion (ADME) of drugs. This will be particularly important in the neonatal population. The development of paediatric-specific endpoints and biomarkers will be critical. It would be important to provide bridging data from adult studies for these paediatric-specific endpoints and biomarkers, whenever possible.

Q: What role will digital strategies play in paediatrics?

A: Electronic health records, registries and other databases of digital data are rich sources of patient-level data. Future software solutions will facilitate linking data directly from patients to support safety and efficacy in studies. More robust natural history data can be leveraged to support the placebo arms of trials. The COVID-19 pandemic has required us to develop digital health strategies to minimise the need for in person visits. This digital strategy has been adopted for clinical trials and will continue to provide primary and supplemental data, even as we move out of the pandemic. Paediatric patients are particularly adept at utilising these digital strategies. Young persons' advisory groups (YPAGs) will play a key role in the incorporation of digital solutions into clinical trials.

Q: Are patient-centric sampling efforts being considered for paediatric trials?

A: Efforts have been underway to develop approaches to patient-centric sampling to improve patient convenience, as well as to collect samples near unpredictable clinical episodes or at the onset of an important adverse event. New devices have been developed to address the standardisation of sample volume and ensure sample quality. Efforts still need to be undertaken to validate the collection, conduct bridging studies, select the appropriate matrix, and identify stability, assay and operational issues related to sample processing. Like the digital solutions, innovative approaches to standardised blood sampling outside the clinic setting will be an important innovation in the future.

Q: Patient advocacy has been highlighted in adult trials. Is this true for paediatrics as well?

A: The voice of the patient is becoming an increasingly important aspect of clinical trial development and this is true for the paediatric population as well. There are groups of adolescents and younger children that have been working with sponsors to design trials globally, including several YPAGs that together constitute the International Children's Advisory Network (iCAN). The inclusion of the paediatric voice will continue to be critical, especially as increasing numbers of patient reported outcome and clinal outcome assessments are being developed, which will need to consider endpoints that are clinically meaningful to paediatric patients. ■

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