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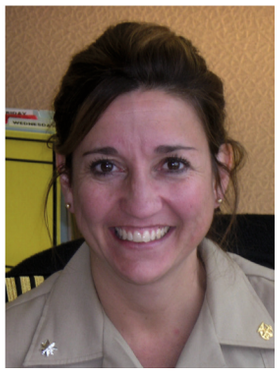

"One important area for further development is the understanding of biomarkers and surrogate markers and their applications to pediatric clinical trials and drug development."

Pediatric drug development: unmet medical needs and opportunities for collaboration between industry, academia and the US FDA

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The needs and advances in pediatric drug development have burgeoned since Shirkey initially referred to children as 'therapeutic orphans' [1]. Owing to requirements and incentives to investigate and develop therapeutic classes of molecules in children, drug development involving pediatric patients has risen steadily. The requirements are the result of the Pediatric Research Equity Act and the incentives are from the Best Pharmaceuticals for Children Act, two pieces of legislation that are set to expire in 2012 [101]. Pediatric Research Equity Act and Best Pharmaceuticals for Children Act have resulted in a total of 335 written requests issued (1998–July 2011), 323 marketing applications approved with postmarketing requirements (through May 2011) and 415 labels changed (1998–July 2011).

From a global development perspective, ongoing collaborations between the US FDA and the other regulatory agencies, including the European Medicines Agency, facilitate these advances in pediatric product development. The significant role of personnel exchanges (short-term), working groups between both agencies, European Medicines Agency Non-clinical and Formulations Working Groups and expert meetings and workshops (including FDA representatives) and WHO initiatives, are helping to facilitate critical involvement and participation. Other collaborative networks between global regulatory partners include the Pediatric Regulators Network and Essential Medicines for Children Activities, Japan's Pharmaceuticals & Medical Devices Agency as observers in the FDA's and European Medicines Agency's pediatric collaboration and the FDA and NIH collaboration to develop a publicly available framework on pediatric formulations.

One important area for further development is the understanding of biomarkers and surrogate markers and their applications to pediatric clinical trials and drug development. The lack of appropriate parameters for pediatric clinical trials in children with gastrointestinal disease has resulted in the lack of appropriate end point identification and delays in pediatric product development. This is an area that would benefit from earlier attention in the overall development process.

A renewed commitment to identify appropriate drug candidates and plan a process for approval for children is needed. Of the total products studied and labeled under US pediatric legislation, drugs with pediatric gastroenterology labeling account for only 8.6% (n = 11). Drug classes studied included treatment of hypercholesterolemia, inflammatory bowel disease, vomiting, obesity and hepatitis B and C and acid blockade

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therapy [2]. Notable areas for new drug development based on the paucity or absence of treatments include treatments for eosinophilic esophagitis (EoE) and related disorders, motility disorders including gastroesophageal reflux disease in infants, gastroparesis and irritable bowel syndrome, to name a few.

EoE is a disorder that has become increasingly recognized in the medical community over the past decade [3], affecting a significant percentage of the pediatric population, and has resulted in an increased reported prevalence over the years [4]. This gastrointestinal disease is a clinicopathologic condition characterized by symptom presentations that vary significantly among different age groups [5]. EoE symptoms are atypical in nature, but the predominant ones in infants and toddlers are usually feeding difficulties and failure to thrive, while in school-aged children symptoms are vomiting and abdominal pain; whereas adolescents and adults are most likely to present with dysphagia and food impaction [3–7]. Aside from the nonspecific EoE symptoms, symptom frequency can vary from daily to every couple of months [7]. Currently, however, there are no FDA-approved pharmacologic therapies for children with EoE.

Identification and use of patient-reported outcome (PRO) measures is one example of alternative end point models that may accelerate development of new therapies in the pediatric population. According to Burke and colleagues, PRO measures provide an important perspective on how patients feel and function [8]. This perspective cannot be adequately captured by clinical measures. A PRO is any report that comes directly from a patient about a health condition, or its treatment, without interpretation of the patient's response by a clinician or anyone else [102]. Histologically, EoE is defined by eosinophil-predominant inflammation [5]. Current evidence on the correlation of symptoms to histology includes conflicting research findings [6,9–11,102]. Therefore, the proper diagnosis of EoE and assessment of treatment efficacy may benefit from a multifactorial approach including the symptom experience captured from the patients' perspective, as well as endoscopic and histologic evaluations of the esophageal mucosa. Understanding the relationship between these parameters is critical to accelerating drug development in this area.

A well-developed symptom measure is urgently needed for use in clinical trials to support treatment efficacy, and to accelerate drug development for EoE. Despite efforts to develop questionnaires that assess symptoms of pediatric EoE [6,7,10], there are currently no psychometrically well validated self- or caregiver-PRO instruments [5]. The development and psychometric validation of patient and parent proxy reported outcomes for pediatric EoE have faced many challenges. For example, pilot-testing of instruments in the target population is difficult to accomplish because the disease is rare (i.e., the number of children with EoE is relatively small). In addition, there is a lack of appropriate control-cohorts. Finally, crucial aspects affecting the reliability of self-report measures, such as determining appropriate recall periods and effective response scales for children self-report of symptoms, have not been well established in EoE.

The FDA guidance for industry entitled 'Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims', encourages using PRO instruments for children and adolescents that relate to objectively measured outcomes [10]. With specific regard to the pediatric population, the guidance discourages proxy-reported outcomes and recommends that parent/caregiver reports only of observable events and behaviors for children who cannot respond for themselves. Since the natural history of EoE in the pediatric population has not been well characterized, the identification of an appropriate severity index remains a major challenge.

Overall, the availability of an EoE PRO instrument that can discriminate changes attributable to pharmacological therapy, and that has been properly validated psychometrically and clinically, would be critical for development of new therapies for pediatric patients with this rare disease. Challenges in the development of such an instrument include: the small pediatric population diagnosed with EoE, which limits the ability to conduct robust pilot testing of the instrument; the variability in symptoms experienced between individual patients, as well as among the different age groups of children; the lack of an appropriate control cohort; the lack of research evidence regarding optimal recall period; the lack of evidence regarding the most appropriate response scale for self-report of symptoms in young children and adolescents with EoE.

"The stakeholders involved in [pediatric] drug development ... must continue to work collaboratively and proactively for the benefit of public health."

In the case of EoE and for the multitude of other diseases affecting children, collaboration between stakeholders is critical. The stakeholders involved in drug development, including academia, industry and the FDA, must continue to work collaboratively and proactively for the benefit of public health. The goal of development and facilitation of reaching these milestones is mutually important for all stakeholders, and especially for the children of the world.

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