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Surrogate Endpoints in Pediatric Studies Submitted to the US FDA

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Abstract

The 21st Century Cures Act was passed in December, 2016, and included a number of provisions to facilitate drug approval. Considerable discussion was generated related to some aspects of the Act, especially to the use of surrogate endpoints (SEs) as a means to shorten the time required prior to receiving US Food and Drug Administration (FDA) approval.¹ The objective of this analysis was to identify the use and outcomes of SEs and clinical endpoints in pediatric drug development trials.

SEs are commonly used in all of drug development. The opposing views were weighing the value of expediting drug approval vs. the risks of more rapid drug approval. These considerations would be particularly important for drug development programs that suffer from prolonged development time² and high trial failure rates,³ as is the case with pediatric studies.

Pediatric drug development is a relatively new science. Very few drug development studies were conducted before 1997, when an incentive program for sponsors conducting pediatric studies under a Written Request from the FDA was included as part of the Food and Drug Administration Modernization Act (FDAMA). The Best Pharmaceuticals for Children Act (BPCA) was enacted by Congress in 2002, followed in 2003 by the Pediatric Research Equity Act (PREA). PREA required the conduct of pediatric studies when the indication of

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CONFLICT OF INTEREST

The authors declare no competing interests for this work.

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Additional Supporting Information may be found in the online version of this article.

the drug in adults also existed in pediatric patients. Both BPCA and PREA were renewed in 2007 under the FDA Amendments Act (FDAAA), and were made permanent in 2012 under the FDA Safety and Innovation Act (FDASIA). Subsequently, over 1,200 pediatric trials have been submitted to the FDA, with most of those trials submitted since 2007. Only one previous discussion of SEs for pediatric clinical trials has been published.⁴

To perform this analysis, FDA-authored reviews of pediatric pivotal efficacy trials from drug development programs submitted to the FDA under FDAAA (September 2007 to June 2012; 133 trials) and FDA-SIA (July 2012 to July 2016; 101 trials) were surveyed. Pivotal trials were defined as trials that were deemed critical in supporting a labeling claim for efficacy in pediatric patients. Of the pediatric pivotal trials, 1) only those for which there was a corresponding adult trial for the same indication studied, and 2) only those that did not rely on “full extrapolation” of efficacy from another population (e.g., adults) to support pediatric marketing approval in the US were included in our analysis.

FDA-authored reviews of each trial were used to extract the following data: drug name, indication studied in children, therapeutic area, age group studied, primary efficacy endpoint, time of measurement of primary efficacy endpoint, trial outcome, and drug approval status.⁵ For a given indication studied in children, information regarding the primary efficacy endpoint measured in the corresponding adult trial was extracted from the FDA-approved drug label obtained from the Drugs@FDA database.

An endpoint was considered a clinical outcome if it directly measured how a patient functions, feels, or survives, while an endpoint was considered a surrogate if it was a biomarker intended to substitute for a clinically meaningful endpoint. Endpoints that were considered both included a combination of endpoints measures (e.g., SEs and clinical endpoints, CEs). When it was not clear whether the endpoint was clinical or a surrogate, the appropriate FDA Center for Drug Evaluation and Research (CDER) review division was contacted, and their interpretation was accepted as the classification for the endpoint.

Trial outcome was categorized as a “success” or “failure” based on whether or not the trial met or did not meet its primary efficacy endpoint, respectively. Drugs that were approved in an age subset of the pediatric patients studied in the trial were considered a success. Statistical evaluation was performed using Blaker’s exact method,⁶ which was chosen as a method suitable for the range of observed values. Computations were performed using R v3.4.3⁷ and employed the R packages Blaker confidence interval (CI) and exact 2×2. The 95% CI was calculated as appropriate. No adjustment for multiple testing was made, as this analysis was exploratory.

Of the original 234 trials, 121 pivotal pediatric efficacy studies were identified, where no pediatric extrapolation was applied at the time of marketing approval by the FDA. None of these trials were part of an accelerated approval program. Forty-five of these studies (37%) measured SEs, 66 (55%) measured CEs, and 10 (8%) measured an endpoint containing both CEs and SEs. There were several therapeutic areas that exclusively used SEs, and they included hematology, inborn errors, metabolic/endocrine, and oncology (Figure 1).

Pulmonary had the largest number of trials, and ~70% of pulmonary trials used SEs. A complete list of the SEs and CEs that were used are provided in Supplementary Table S1.

The pediatric clinical trials that were successful vs. those that failed to achieve their primary endpoint were not different between those that:

- Used SEs (82% success, 95% CI 68.2–91.8);
- Used CEs (77% success, 95% CI 65.4–86.0); and
- Used both an SE and a CE (80% success, 95% CI 44.4–96.3).

Eighty-five pediatric trials (70%) used the same endpoint in the pediatric trial as was used in the corresponding adult trial (86% success, 95% CI 76.8–92.2). Thirty-six trials (30%) used a different endpoint in the pediatric trial than was used in the adult trial (64% success, 95% CI 47.2–78.4).

Surrogate endpoints are frequently used in adult drug development trials. Previous work found that the FDA approval of novel therapeutic agents for adults from 2005–2012 used SEs for approval as pivotal endpoints in 45% of the indications. Our finding that 37% of pivotal endpoints for pediatric drug development studies between 2007 and 2016 were SEs is very much in line with that finding. Seventy percent of the time, the same pivotal endpoint was used in the pediatric trial as was used in the corresponding adult trial for the same indication studied. The use of endpoints in pediatric trials that are not the same as has been used in adult trials increases the chance that the study will fail to obtain the pediatric indication.⁸ This observation has been made generally for pediatric endpoints, and was found to be true in this subset of trials that used no extrapolation of efficacy data from adults. One possible explanation for this observation is that the unique pediatric endpoints have not been validated for use in a drug development program, in contrast to endpoints that have been previously used in adult studies.

In drug development, the use of a validated surrogate can clearly establish the effectiveness of a drug. However, when an SE is used to support approval under accelerated approval regulations, approval is based on an SE that is “likely to predict clinical benefit.”⁹ Using an SE has enabled the FDA to approve these drugs faster.¹⁰ When products are approved under accelerated approval regulations, a postmarketing confirmatory trial is required. These regulations have allowed drugs for serious conditions that filled an unmet medical need to be approved based on an SE.

The use of SEs is strongly divided by therapeutic area. For example, pediatric trials in the hematology, inborn errors, metabolic-endocrine, and oncology therapeutic areas are very dependent on SEs. While clinical outcomes for the pediatric indications in these areas can be measured, the clinical outcomes of interest for some of these indications either take a prolonged amount of time to occur (e.g., overall survival depending on the tumor type) or occur infrequently in children (e.g., death with diseases that are not serious or life-threatening). In other therapeutic areas like allergy, dermatology, neurology, ophthalmology, and psychiatry, clinical outcomes comprise all of the pivotal endpoints.

In conclusion, pediatric trials that did not rely on the use of extrapolation of efficacy from adults were assessed for the use of SEs over the time period of 2007–2016. Thirty-seven percent of these studies used only SEs as the pivotal endpoint for the trial, and an additional 8% used both CEs and SEs. The success rates for achieving the primary pivotal endpoint were the same for pediatric trials measuring SEs, CEs, and both endpoints. The use of SEs in pediatric trials is effective, but validation of uniquely pediatric SEs is critical and continues to be a challenge for pediatric drug development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Number of trials measuring surrogate, clinical, or both endpoints by therapeutic area.