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Inclusion of Infants and Neonates in Pediatric Orphan Product Approvals

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Abstract

The Orphan Drug Act (ODA) of 1983 was enacted to provide financial incentives to drug sponsors to develop therapies for rare diseases. Although this act increased the number of orphan products approved, there are still a limited number of products available for the pediatric population because orphan drug products are exempt from the Pediatric Research Equity Act. The objectives of this study were (i) to evaluate the pediatric orphan drug studies submitted to the US Food and Drug Administration (FDA) in the period of 2007–2018 and (ii) to examine whether orphan drug products were fully labeled with a pediatric indication in infants and neonates. Out of the 468 indications evaluated, 171 (37%) were FDA-labeled for use in the pediatric population. Labeling for the 12 to < 18 years age group was most common (98%). Fifty-two percent of FDA-labeled pediatric indications included the newborn to < 2 years of age group. In this newborn to < 2 years age group, the indication was labeled without pivotal clinical trials in 43% of the programs. Of the 60 new indications not labeled down to birth, 50% were found to have an age of onset and diagnosis that occurs earlier than the age approved for use of the product for that indication. In summary, although the ODA has been successful in improving pediatric access to medications for rare diseases, our analysis identified the incomplete labeling for pediatric patients under 2 years of age. Strategies to include the birth to < 2 years old group of pediatric patients in orphan drug development programs should be explored.

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AUTHOR CONTRIBUTIONS

K.P., R.V., D.J.G., C.E., G.T.W., S.K.M., and G.J.B. wrote the manuscript. K.P., R.V., D.J.G., C.E., G.T.W., S.K.M., and G.J.B. designed the research. K.P., R.V., G.T.W., and G.J.B. performed the research. K.P., R.V., G.T.W., and G.J.B. analyzed the data.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

DISCLAIMER

The opinions expressed in this manuscript are those of the authors and should not be interpreted as the position of the US Food and Drug Administration.

CONFLICT OF INTEREST

All authors declared no competing interests for this work.

In order to encourage drug development in rare diseases, the United States Congress enacted the Orphan Drug Act (ODA) in 1983. This act provides financial incentives to sponsors to develop drugs and biologics for diseases that impact < 200,000 persons in the United States.^{1–3} The ODA also incentivizes the development of products that treat diseases that affect > 200,000 persons but with little expectation that the cost of product development will be financially recovered in the marketplace.^{1,2} Some of these financial incentives include tax credits on clinical trial expenses, research and development grants, waived drug application fees, and a 7-year marketing exclusivity period.^{2,4–10} These regulatory incentives aim to decrease the cost of drug development while providing new therapies to patients with rare diseases. According to the National Organization of Rare Diseases, there are ~ 7,000 rare diseases affecting up to 25–30 million Americans.^{9,11–14} Approximately 50% of this population are children under 18 years of age.^{12,14}

For a drug to qualify for orphan designation, both the drug and the disease or condition must meet certain criteria specified in the ODA and the US Food and Drug Administration (FDA)'s implementing regulations at 21 Code of Federal Regulations (CFR) Part 316, which includes a description of the rare disease or condition.¹⁵ The ODA provides for granting special status to a drug or biological product to treat a rare disease or condition upon request of a sponsor. This status is referred to as an orphan designation or orphan status. Prior to the enactment of the ODA, only 38 orphan drugs were FDA-approved in the United States.⁹ The ODA led to a significant increase in approved therapies, and other key markets, such as Japan and the European Union, followed suit and passed similar legislation.^{9,10,16} Although the ODA has substantially increased the number of therapies available for rare diseases, there still are unmet needs for drug development in some subgroups of pediatric patients. A recent report to Congress evaluating the pediatric labeling of orphan drugs illustrates a lack of comprehensive pediatric information in the labeling for orphan therapies with the youngest pediatric patient group being affected the most.¹⁷

Considering the number of distinct rare diseases within the pediatric population, clinical studies of therapies are essential to establish safety and effectiveness for pediatric patients. The Pediatric Research Equity Act (PREA)¹⁸ of 2003 allows the FDA to require pediatric studies for certain drugs and biologics and was enacted to obtain pediatric labeling for more products. Because sponsors are not required to conduct pediatric trials for orphan drugs due to a PREA exemption, many therapies with orphan indications lack information for pediatric patients. This can lead to an increased potential for off-label use of the product when the product is not labeled for the full age range of affected pediatric patients.^{17,19}

Prior studies have evaluated orphan drug approvals and the impact of the ODA economically from the perspectives of both sponsors and patients.^{2,3,5–7,9–12,16,20} The objectives of this study were to (i) evaluate the extent to which the pediatric population was included in orphan drug studies in the period of 2007–2018 in relation to overall orphan drug approvals, and (ii) examine whether orphan drug products were fully labeled with a pediatric indication in infants and neonates.

METHODS

Orphan drug data are available through the Orphan Drug Designations and Approvals list that is made publicly available by the FDA.²¹ The original search included orphan indications that were designated and approved from 2007–2018. The primary search was analyzed by indication, and the data were further narrowed to include only those indications which were ultimately FDA-labeled (“labeled”) in the pediatric population. Other publicly available FDA sources used were Drugs@FDA, Center for Biologics Evaluation and Research (CBER) Licensed Biological Products with Supporting Documents database, and Reviews of Pediatric Studies Conducted under Best Pharmaceuticals for Children Act and/or Pediatric Research Equity Act (BPCA/PREA) database.^{22–24} Drugs@FDA and the CBER database were used to review the FDA-authored medical reviews and relevant product labels for the therapies.^{22,25} DailyMed was also used to locate archived labels.²⁶ The Reviews of Pediatric Studies database was used to identify if an indication had been evaluated in a study included in a Written Request,^{23,24} a specific document under BPCA in which the FDA requests submission of certain studies to determine if the use of a drug could have meaningful health benefits in the pediatric population. Unlike under PREA, conducting pediatric studies outlined in a Written Request under the BPCA process is voluntary.

This dataset of pediatric orphan indications (i.e., orphan indications labeled in the pediatric population) was stratified by labeled age group, type of studies conducted for the indication, therapeutic area, and the drug product approval year for the indication. By reviewing the product labels and the FDA-authored Medical Reviews, pivotal trials used to establish safety and effectiveness for the indication in the pediatric population were identified. The number of pediatric patients studied within these trials were summed and grouped in various categories by age (newborn to < 2 years, 2 years to < 12 years, and 12 years to < 18 years²⁷). Additionally, a literature search with Google Scholar and PubMed was conducted for the indications that were not labeled in the newborn to < 2 years age group to further examine the relation of the labeling status to the age of onset of the disease.

A literature search was conducted on the age of onset for those indications not labeled for use in pediatric patients under 2 years of age. This search was done to examine any difference between the age range of a known onset or diagnosis of a disease and the age range that was labeled for an indication. If a disease or indication was found to have an onset and diagnosis in newborn to < 2 years of age, but was not labeled in this age group, such a finding was referred as “not fully labeled” for the relevant pediatric age (newborn to < 2 years) range.

RESULTS

We identified a total of 468 orphan indications from 2007–2018 from the Orphan Drug Designations and Approvals database. This was further narrowed to 171 orphan indications that were labeled for pediatric use (37%), which represented 135 unique products. Within the 171 pediatric orphan indications that were evaluated, we identified 141 pivotal studies conducted for the drug product with the studied indications.

Stratification by labeled age group

The 171 orphan indications that were granted pediatric labeling were categorized based on age groups (Figure 1). Of the 171 indications, 168 (98%) and 143 (84%) were labeled for use in the 12 to < 18 years and the 2 to < 12 years groups, respectively, whereas 89 (52%) were labeled for use in the newborn to < 2 years age group.

Further analysis was done for the 82 indications that were not labeled for the newborn to < 2 years of age group, and 60 of these were identified as new indications (Table S1). Drug products with more than one orphan indication designation, such as an orphan designation for a new formulation or new age group of the same drug product, or the exclusivity for the specific gene type within the same indication (e.g., CFTR gene mutation) were counted only once with the most recent labeling date. In addition, because the purpose of this part of analysis was to examine the age range of a known onset or diagnosis of a disease and the age range that was labeled for an indication, the indication was counted only once when a multiple drug product had the same indication designation. In such cases, the drug products with the indication labeled for the youngest age group, or with the most recent labeling update, were selected if the labeled age groups were the same between the different drug products. As a result of this subanalysis, a total of 30 of 60 indications (50%) were found to be not fully labeled (see Table S1 for the complete list).

Stratification by type of study

Of the 171 pediatric orphan indications that were studied and labeled between 2007 and 2018, 141 (82%) were studied in pivotal efficacy and safety clinical trials that included pediatric patients (Figure 1). In the 141 pivotal clinical trials that included pediatric patients, 128 (91%) and 120 (85%) included the 12 to < 18 years and the 2 to < 12 years groups, respectively, whereas 55 (39%) included the birth to < 2 years age group. Five of the 171 indications involved studies conducted under BPCA Written Requests. Of the 30 (18%) pediatric orphan indications that were not evaluated in new pivotal clinical trials in pediatric patients, 6 utilized efficacy data obtained from efficacy extrapolation from adults to pediatrics, 17 used prior evidence, such as literature data and/or data from other development programs, 2 were labeling changes (exclusivity protected indication update to include the specific mutations in the gene affected by the disease) without any new clinical trial information, and 5 conducted animal studies only due to ethical reasons.

The pediatric orphan indications labeled for the newborn to < 2 years age group were further classified based on inclusion of this age group in the pivotal efficacy and safety clinical trials that were identified for this analysis. As shown in Figure 2, of the 89 indications labeled in the newborn to < 2 years of age group, 51 had clinical trials conducted in this age group, 18 had clinical trials conducted in older pediatric age groups, and 20 did not have pivotal efficacy trials conducted in any pediatric age group. For the latter 20 indications, 12 utilized prior evidence, such as literature data and/or other development programs, 5 were studied in animal models only due to ethical reasons, and 3 used efficacy extrapolation from adults to pediatrics in providing the data to support pediatric labeling.

Stratification by therapeutic area

Seventeen different therapeutic areas were included in this analysis: anesthesia, antidotes/medical countermeasures, cardiovascular, dermatology, gastroenterology, hematology, infectious disease, medical imaging, metabolism/endocrinology/bone, neurology, oncology, ophthalmology, pulmonary, renal, reproductive, rheumatology/immunology, and transplant. The top five therapeutic areas that the pediatric orphan indications fell into were: hematology ($n = 30$), metabolism/endocrinology/bone ($n = 26$), oncology ($n = 24$), rheumatology/immunology ($n = 19$), and infectious disease ($n = 17$). The top 5 therapeutic areas among the 89 pediatric orphan indications labeled in the newborn to < 2 years age group were similar to those found in the overall analysis: hematology ($n = 21$), oncology ($n = 16$), metabolism/endocrinology/bone ($n = 14$), antidotes and medical countermeasures ($n = 9$), and infectious disease ($n = 8$).

Stratification by approval year

The indications were also stratified based on the drug product marketing approval year for the orphan indication (Figure 3). A striking increase in the number of orphan drug indication labeling has occurred in the last 5 years of analyzed data. The number of pediatric orphan indications labeled per year fluctuated over the 2007–2018 time period with the lowest number in 2007 and 2012 (5 pediatric indications) and the highest number in 2018 (36 pediatric indications). However, the percentage of pediatric orphan indication labeling has remained relatively stable and remains consistent despite the increasing overall drug products with orphan indications.

DISCUSSION

The overall number of orphan drug indication labeling has increased dramatically in the past 10 years, and pediatric orphan indications have maintained a consistent percentage of orphan drug programs. Although this report focused on the pediatric patients under 2 years of age, Kimmel *et al.* recently reviewed pediatric orphan drug indications from 2010–2018 with respect to novel drugs and breakthrough designations.²⁸ They found that most were not novel, breakthrough designations were uncommon (20%), and that a substantial unmet need remains for pediatric rare diseases.

The findings of this study mirror those of the FDA's Report to Congress on the Pediatric Labeling of Orphan Drugs,¹⁷ which found that 348 of 548 (64%) orphan indications were relevant to children between 1999 and 2018, and that a substantial number were not fully labeled for pediatric use.¹⁷ In the present study, of the 468 drug approvals with orphan indications, 171 indications (37%) representing 135 unique products for pediatric patients were identified. Although these represent a significant public health advance for pediatric patients, the percentage of orphan drug products with a pediatric indication is notable and remains consistent despite the overall increase in drug products with orphan indications (Figure 3).

In the Report to Congress, the FDA identified 127 orphan indications that were not fully labeled for pediatric patients with 81 labels having no pediatric information and 46 labels

with missing pediatric information for a portion of the full age range of affected pediatric patients, predominantly the youngest pediatric patients.¹⁷ The present study extended that analysis and focused on the labeling in infants and neonates. This study identified 60 pediatric orphan indications that were not labeled in the under 2-year-old age group, with 30 indications (50%) found to be not fully labeled for this age range. Although there are circumstances where the inclusion of the youngest population in clinical trials would not be appropriate for various reasons, they could not be considered in this analysis. Because these studies were exempt from PREA, it is unclear whether studies under 2 years of age would have been required by the FDA.

Drug safety considerations have occasionally led to a failure to label for pediatric use.²⁹ In a prior evaluation of safety information in drug development studies in neonates, 20 of 40 programs reported serious adverse events.³⁰ Because orphan drugs are exempt from the requirements of PREA, and Written Requests under BPCA are voluntary rather than required, there currently is no regulatory mechanism to require complete pediatric study programs for orphan-designated diseases (i.e., programs that study a product across the full age range of affected pediatric patients). However, there may be opportunities to improve on the current orphan drug program for pediatric patients.

A July 2018 FDA guidance identified a loophole in the interaction between granting orphan designation for a pediatric subpopulation and the PREA orphan exemption. This was because obtaining pediatric designation provided incentives to study a drug for an orphan indication in the pediatric population, but it did not mandate the conduct of those studies. As a result, a sponsor could use pediatric-subpopulation designation to obtain an exemption from PREA to conduct the very studies the designation program was meant to incentivize.⁸ In order to foster research in the pediatric population, the FDA has concluded that the pediatric subpopulation designation is no longer necessary to stimulate the conduct of studies in the pediatric population with the disease.⁸ To close this loophole, the FDA does not expect to grant any additional pediatric orphan designations for common diseases that are rare in pediatric subpopulations. The FDA will, however, continue to grant orphan drug designations as appropriate for the following: a rare disease that includes a rare pediatric subpopulation; a pediatric subpopulation that constitutes a valid orphan subset; and a rare disease that is a different disease in the pediatric population as compared with the adult population.⁸

There are regulatory approaches within the existing statutes that have enabled pediatric indications and labeling. Efficacy extrapolation can be utilized if there is scientific justification that the disease and the response to therapy are expected to be sufficiently similar between the target pediatric population and a reference population (i.e., adults or older pediatric patients). Six of the 171 indications evaluated in this study used extrapolation of efficacy from adults to establish effectiveness in children. Those six indications were: two for treatment of Merkel cell carcinoma (avelumab and pembrolizumab); one for treatment of moderate to severe hidradenitis suppurativa (adalimumab); one for treatment of angioedema (ecallantide); one for treatment of primary mediastinal B cell lymphoma (pembrolizumab); and one for a diagnostic for the clinical management of neuroendocrine tumors (Gallium (Ga-68)). In 5 of the 171 indications, data were used from animal studies, of which were

approved under the Animal Rule regulations (21 CFR 314.600–650 for drugs³¹; 21 CFR 601.90–95 for biologics³²), to obtain pediatric labeling in the presence of ethical dilemmas that prohibited pediatric studies. Those five indications and their strategies for dose selection³³ were: treatment of anthrax (raxibacumab); treatment of exposure to *B. anthracis* spores (oblitoxaximab); treatment of inhalational anthrax (anthrax immune globulin-human); treatment of acute exposure to myelosuppressive doses of radiation (sargramostim); and treatment of smallpox (tecovirimat). Another approach that was used for pediatric labeling was to utilize prior evidence for support (17 of the 171 indications).

An additional regulatory approach to orphan indications in pediatric cancer is now available through the Research to Accelerate Cures and Equity (RACE) for Children Act.³⁴ This Act was part of the FDA Reauthorization Act of 2017, and was effective on August 18, 2020. The RACE for Children Act requires pediatric assessment for oncology drugs developed for adults that target molecular alterations relevant to the growth or progression of pediatric cancers and eliminates the orphan drug PREA exemption for these products. The FDA has published a draft guidance for industry regarding pediatric studies for molecularly targeted oncology drugs.³⁵

One limitation of the present study was that only the pivotal efficacy trials were analyzed. Therefore, pediatric patients that were studied in secondary supportive trials were not accounted for. Another limitation is that for those indications that were not labeled in the birth to < 2 years old age group, the present study only considered disease onset and diagnosis to determine whether this group should have been considered for labeling. As stated previously, because these studies were exempt from PREA, it is unclear whether studies under 2 years of age would have been required by the FDA.

CONCLUSIONS

One hundred seventy-one orphan indications labeled in pediatric patients were identified from 2007–2018. The total number of pediatric indication labeling have been increasing per year and reached a maximum in 2018 ($n = 36$). However, 60 indications were found to not have been labeled down to birth, and 30 (50%) of them were considered to be not fully labeled in the relevant age group when considering the age and diagnosis of the disease in infants and neonates. Therefore, although the ODA has been very successful in improving pediatric access to medications for rare diseases, our analysis identified a current status of incomplete labeling of the full relevant pediatric age range with pediatric patients under 2 years of age being primarily affected. Strategies for ensuring the inclusion of the infants and neonates in orphan drug development programs, when appropriate, should be explored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. US Food and Drug Administration. Orphan drug act - relevant excerpts <<https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts>>. (2013) Accessed April 9, 2020.
2. IQVIA Institute for Human Data Science. Orphan drugs in the United States: growth trends in rare disease treatments <<https://www.iqvia.com/insights/the-iqvia-institute/reports/orphan-drugs-in-the-united-states-growth-trends-in-rare-disease-treatments>> (2018). Accessed April 9, 2020.
3. Haffner ME, Whitley J. & Moses M. Two decades of orphan product development. Nat. Rev. Drug Discov. 1, 821–825 (2002). [PubMed: 12360259]
4. Institute of Medicine. Rare diseases and orphan products: accelerating research and development <<https://www.nap.edu/catalog/12953/rare-diseases-and-orphan-products-accelerating-research-and-development>>. Accessed January 14, 2021. (Washington DC, 2010).
5. Wellman-Labadie O. & Zhou Y. The US Orphan Drug Act: rare disease research stimulator or commercial opportunity? Health Policy 95, 216–228 (2010). [PubMed: 20036435]
6. Miller KL & Lanthier M. Investigating the landscape of US orphan product approvals. Orphanet J. Rare Dis. 183 (2018). Article Number 183.
7. Seoane-Vazquez E, Rodriguez-Monguio R, Szeinbach SL & Visaria J. Incentives for orphan drug research and development in the United States. Orphanet J. Rare Dis. 3 (2008). Article Number 33.
8. US Food and Drug Administration. Guidance for industry: clarification of orphan designation of drugs and biologics for pediatric subpopulations of common diseases <<https://www.fda.gov/media/109496/download>> (2018). Accessed April 9, 2020.
9. EvaluatePharma. Orphan drug report <<https://www.evaluate.com/thought-leadership/pharma/evaluatepharma-orphan-drug-report-2019>> (2019). Accessed April 9, 2020.
10. Melnikova I. Rare diseases and orphan drugs. Nat. Rev. Drug Discov. 11, 267–268 (2012). [PubMed: 22460117]
11. Braun MM, Farag-El-Massah S, Xu K. & Cote TR Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years. Nat. Rev. Drug Discov. 9, 519–522 (2010). [PubMed: 20531273]
12. Attwood MM, Rask-Andersen M. & Schioth HB Orphan drugs and their impact on pharmaceutical development. Trends Pharmacol. Sci. 39, 525–535 (2018). [PubMed: 29779531]
13. National Organization for Rare Disorders. NORD rare diseases facts page <<https://rareaction.org/about/rare-diseases>>. Accessed April 9, 2020.
14. Wu J, Wang C, Toh S, Pisa FE & Bauer L. Use of real-world evidence in regulatory decisions for rare diseases in the United States-Current status and future directions. Pharmacoevid. Drug Saf. 29(10), 1213–1218 (2020). [PubMed: 32003065]
15. Code of Federal Regulations: 21 CFR Part 316—Orphan drugs subpart C—Designation of an orphan drug <https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=718f6fcbc20f2755bd1f5a980eb5eed&mc=true&n=sp21.5.316.c&r=SUBPART&ty=H&TML#se21.5.316_120> Accessed March 22, 2021.
16. Miller KL & Lanthier M. Trends in orphan new molecular entities, 1983–2014: half were first in class, and rare cancers were the most frequent target. Health Aff. (Millwood) 35, 464–470 (2016). [PubMed: 26953301]
17. US Food and Drug Administration. Pediatric labeling of orphan drugs <<https://www.fda.gov/media/130060/download>>. Accessed February 19, 2020.
18. US Food and Drug Administration. Pediatric Research Equity Act <<https://www.fda.gov/drugs/development-resources/pediatric-research-equity-act-prea>>. Accessed September 12, 2020.
19. Balan S, Hassali MAA & Mak VSL Two decades of off-label prescribing in children: a literature review. World J. Pediatr. 14, 528–540 (2018). [PubMed: 30218415]

20. Rodriguez-Monguió R, Spargo T. & Seoane-Vazquez E. Ethical imperatives of timely access to orphan drugs: is possible to reconcile economic incentives and patients' health needs? *Orphanet J. Rare Dis.* 12 (2017). Article Number 1.
21. US Food and Drug Administration. Search orphan drug designations and approvals <<https://www.accessdata.fda.gov/scripts/opdlisting/oopd/>>. Accessed April 9, 2020.
22. US Food and Drug Administration. Drugs@FDA: FDA-approved drugs <<https://www.accessdata.fda.gov/scripts/cder/daf/>>. Accessed April 9, 2020.
23. US Food and Drug Administration. Reviews of pediatric studies conducted under BPCA and PREA from 2007–2012 <<https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2007-2012>>. Accessed April 9, 2020.
24. US Food and Drug Administration. Reviews of pediatric studies conducted under BPCA and PREA from 2012–present <<https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present>>. Accessed April 9, 2020.
25. US Food and Drug Administration. Licensed biological products with supporting documents <<https://www.fda.gov/vaccines-blood-biologics/licensed-biological-products-supporting-documents>>. Accessed April 9, 2020.
26. National Institutes of Health: U.S. National Library of Medicine. DailyMed <<https://dailymed.nlm.nih.gov/dailymed/>>. Accessed April 9, 2020.
27. US Food and Drug Administration. E11 clinical investigation of medicinal products in the pediatric population <<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11-clinical-investigation-medicinal-products-pediatric-population>> (2000). Accessed on April 12, 2020.
28. Kimmel L, Conti RM, Volerman A. & Chua KP Pediatric orphan drug indications: 2010–2018. *Pediatrics* 145, e20193128 (2020). <10.1542/peds.2019-3128>.
29. Kim C, Park K, McMahon AW, Green FG, Green DJ & Burckart GJ Drug safety in labeling for pediatric drug development and dose selection in submissions to the US Food and Drug Administration. *J. Clin. Pharmacol.* (in press) (2021).
30. Avant D. et al. Neonatal safety information reported to the FDA during drug development studies. *Ther. Innov. Regul. Sci.* 2017, 1–9 (2017).
31. US Food and Drug Administration. Code of Federal Regulations Title 21, Part 314, Subpart I; Approval of new drugs when human efficacy studies are not ethical or feasible <<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.600>>. Accessed April 6, 2021.
32. US Food and Drug Administration: Code of Federal Regulations Title 21, Part 601, Subpart H: Approval of biological products when human efficacy studies are not ethical or feasible <<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=601.90>>. Accessed April 6, 2021.
33. Wu K, Choi SY, Bergman K. & Seo S. Antimicrobial dose selection under the animal rule. *Clin. Pharmacol. Ther.* 109, 971–976 (2021). [PubMed: 33565088]
34. Fletcher EP, Burckart GJ, Robinson GW, Reaman GH & Stewart CF The RACE to develop new targeted therapies for children with CNS tumors. *Clin. Pharmacol. Ther.* 108, 434–436 (2020). [PubMed: 32638364]
35. US Food and Drug Administration. Guidance for industry: FDARA implementation guidance for pediatric studies of molecularly targeted oncology drugs: amendments to sec. 505B of the FD&C act <<https://www.fda.gov/media/133440/download>> (2019). Accessed April 22, 2020.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Although more therapies have become available for rare diseases under the Orphan Drug Act (ODA) of 1983, there still are unmet needs for drug development in some subgroups of pediatric patients.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ To what extent were infants and neonates included in orphan drug studies in the period of 2007–2018 in relation to overall orphan drug approvals?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Although 98% of the 171 pediatric orphan indications were approved for age 12 years and above, only 52% were indicated for use in infants and neonates. For the 60 new orphan indications not included in infants and neonates, 50% were not fully labeled for the entire age of occurrence of the disease.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Exploring strategies to include infants and neonates in orphan drug development programs would help to bridge the gap in knowledge and expand the benefits to pediatric patients across all ages.

Figure 1.

Pediatric indication labeling classified by age groups. The 171 pediatric orphan indications that were granted labeling were categorized based on age ranges. Within the 171 pediatric orphan indications that were labeled, 141 (82%) conducted pivotal clinical trials that included pediatric patients. The grey bars are total number of indications labeled and the dark bars are numbers of pivotal clinical trials.

Figure 2.

Labeled orphan indications in newborn to < 2 years of age. A total of 89 indications were labeled in the newborn to < 2 years of age. Of these, 51 had clinical efficacy trials conducted in this age group, 18 had efficacy extrapolated from clinical trials conducted in an older pediatric age group, and 20 did not have any clinical trials conducted in any pediatric age group for this indication. Of these 20 indications, 12 utilized prior evidence, 5 were studied in animal models only due to ethical reasons, and 3 used efficacy extrapolations from adults to pediatric patients.

Figure 3.

Marketing approval year for drug products with orphan indications from 2007 to 2018. The drug products with pediatric orphan indications approved from 2007–2018 were identified by year and compared to the total number of drug products with orphan indications labeled. The solid line represents the percentage (%) of pediatric orphan indications labeled in comparison to the total. The grey bars represent the total number of drug product orphan indications whereas the dark bars represent pediatric orphan drug indications.