



Global Regulatory and Public Health Initiatives to Advance Pediatric Drug Development for Rare Diseases

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Abstract

The literature thoroughly describes the challenges of pediatric drug development for rare diseases. This includes (1) generating interest from sponsors, (2) small numbers of children affected by a particular disease, (3) difficulties with study design, (4) lack of definitive outcome measures and assessment tools, (5) the need for additional safeguards for children as a vulnerable population, and (6) logistical hurdles to completing trials, especially with the need for longer term follow-up to establish safety and efficacy. There has also been an increasing awareness of the need to engage patients and their families in drug development processes and to address inequities in access to pediatric clinical trials. The year 2020 ushered in yet another challenge—the COVID-19 pandemic. The pediatric drug development ecosystem continues to evolve to meet these challenges. This article will focus on several key factors including recent regulatory approaches and public health policies to facilitate pediatric rare disease drug development, emerging trends in product development (biologics, molecularly targeted therapies), innovations in trial design/endpoints and data collection, and current efforts to increase patient engagement and promote equity. Finally, lessons learned from COVID-19 about building adaptable pediatric rare disease drug development processes will be discussed.

Keywords Rare diseases · Pediatric drug development · Regulatory policy

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Abbreviations

AAV	Adeno-associated virus
AMED	Japanese Agency for Medical Research and Development
ASO	Anti-sense oligonucleotides

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CBER	Center for Biologics Evaluation and Research	PMDA	Japanese Pharmaceuticals and Medical Devices Agency
CDM	Common data model	PREA	Pediatric Research Equity Act
CFTR	Cystic fibrosis transmembrane conductance regulator	R2D2	Regulatory Review of Drugs and Devices
COMP	Committee for Orphan Medicinal Products	RACE Act	Research to Accelerate Cures and Equity for Children Act
COVID-19	Corona virus disease 2019	RDCRN	Rare Diseases Clinical Research Network
CTTI	Clinical Trials Transformation Initiative	RPD PRV	Rare Pediatric Disease Priority Review Voucher
DARWIN EU	Data Analysis and Real World Interrogation Network European Union	RWD	Real-world data
DIA	Drug Information Association	RWE	Real-world evidence
EHR	Electronic health record	SaME	Shared Molecular Etiology
EMA	European Medicines Agency	SAP	Special Access Program
FDA	US Food and Drug Administration	TGA	Therapeutic Goods Administration of Australia
FDARA	Food and Drug Administration Reauthorization Act	UDN	Undiagnosed Diseases Network
GTT	Gene-targeted therapy	US	United States
HTA	Health Technology Assessment		
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use		
INC	International Neonatal Consortium		
IRDiRC	International Rare Diseases Research Consortium		
IRUD	Initiative on Rare and Undiagnosed Diseases		
MAH	Marketing Authorization Holder		
MHLW	Ministry of Health, Labour and Welfare		
MLMT	Multi-luminance mobility testing		
NCATS	National Center for Advancing Translational Sciences		
NIH	National Institutes of Health		
NORD	National Organization for Rare Disorders		
OMOP	Observational Medical Outcomes Partnership		
PaVe-GT	Platform Vector Gene Therapy		
PCWP	Patients and Consumers Working Party		
PCORI	Patient-Centered Outcomes Research Institute		
PCORnet	National Patient-Centered Clinical Research Network		
PDAP	Pediatric Drug Action Plan		
PDCO	Paediatric Committee		
PDUFA	Prescription Drug User Fee Act		
PEAC	Patient Engagement Advisory Committee		
PEC	Patient Engagement Collaborative		
PEDSnet	National Pediatric Learning Health System		
PFDD	Patient-focused drug development		
PIP	Paediatric Investigation Plan		
PLS	Patient Listening Sessions		

Introduction

Most rare diseases (50–75%) affect children, with many disorders having serious, multisystemic, chronic, and/or progressive clinical manifestations [1]. Collectively rare diseases are one of the leading causes of death in children in both industrialized and developing countries [1–4]. Rare diseases (also termed orphan diseases) were first defined in the Orphan Drug Act of 1983 in the United States (US) [5]. Since then over 90 countries have established rare disease policies regarding access to and regulation of drugs and biologics for rare diseases [6]. The definition of a rare disease varies but includes either a specific proportion of the population [e.g., prevalence rate of ≤ 5 in 10,000 people in the European Union (EU)] or a specific population threshold (e.g., $< 200,000$ individuals in the US). There are an estimated 7000–10,000 rare diseases with approximately 80% monogenic (“single gene”) disorders as well as other chromosomal abnormalities, cancers, infections, toxic exposures, and degenerative and acquired conditions [1, 7–9]. Although small numbers of individuals are affected by one particular disease, collectively individuals with rare diseases account for a significant portion of the population. Despite this, unmet needs persist with fewer than 5% of rare diseases having approved therapies [10, 11].

Pediatric drug development for rare diseases poses a number of challenges. The literature thoroughly describes these ongoing challenges including: (1) garnering interest from sponsors, (2) small numbers of children affected by a particular disease, (3) difficulties with study design, (4) lack of definitive outcome measures and assessment tools, (5) the need for additional safeguards for children as a vulnerable population, and (6) logistical hurdles to completing trials, especially with the need for longer term follow-up to

establish safety and efficacy. In recent years, there has also been an increasing awareness of the need to engage patients and families in drug development processes and to address inequities in access to pediatric clinical trials. The year 2020 ushered in yet another challenge—the COVID-19 pandemic.

The ecosystem of pediatric rare disease drug development continues to evolve to meet these challenges. This article will focus on several key factors including recent regulatory approaches and public health policies to foster pediatric rare disease drug development, emerging trends in product development (biologics and molecularly targeted therapies), innovations in trial endpoints and data collection, and current efforts to increase patient engagement and promote equity in clinical trials. Finally, the article will discuss lessons learned from COVID-19 about building an adaptable pediatric rare disease drug development ecosystem.

Regulatory/Governmental Policy Framework

While global legislation has facilitated pediatric rare disease drug development, additional areas where regulatory policies could help address research gaps have been recognized. These actions to promote pediatric drug development for rare diseases have gained momentum in the past decade (Table 1). In the US, several key pieces of legislation were enacted to promote this area of drug development.

- In 2012, the Creating Hope Act established the rare pediatric disease priority review voucher (RPD PRV) program as an additional incentive for the study of rare pediatric diseases. Vouchers awarded through the program can be redeemed for a priority review (within 6 months instead of 10 months) of a subsequent marketing application for a different product [12]. Congress reauthorized

the program in 2016 for 4 more years and redefined rare pediatric diseases as those with serious or life-threatening manifestations that primarily affect children [13]. The FDA has interpreted the current definition of a rare pediatric disease as one that has clinical manifestations that uniquely or disproportionately affect children (e.g., abnormal growth or development) compared to adults [14]. As of September 2021, 31 vouchers have been granted; 74% of these products were the first approved therapies for the indicated disease(s).

- The Twenty-First Century Cures Act was enacted in 2016 and included several provisions pertinent to pediatric drug development for rare diseases [15]. The Cures Act created the Regenerative Medicine Advanced Therapies designation program, an expedited program for cell therapy, therapeutic tissue engineering products, human cell and tissue products, or combinations of these therapies [16]. The Cures Act also requires FDA to help advance the development of these therapies and clarified that marketing applications for targeted drugs for rare diseases can rely on data previously submitted (e.g., an approved New Drug Application or Biologics License Application) for which that same sponsor had right of reference.
- In 2017, Congress enacted the Research to Accelerate Cures and Equity (RACE) for Children Act [17]. This Act updates the Pediatric Research Equity Act (PREA) and permits FDA to require pediatric assessments when the molecular targets of cancer drugs under review are relevant to children's cancers. For example, the anaplastic lymphoma kinase (ALK) translocation that occurs in some forms of non-small cell lung cancer in adults is also seen in some forms of childhood anaplastic large cell lymphoma [18]. In addition, the RACE Act removed an exemption for cancer drugs that have

Table 1 Rare diseases regulatory environment 2010–2020

	USA	European Union	Canada	Japan	Australia
Orphan drug legislation	Yes	Yes	No	Yes	Yes
Other rare disease legislation	<ul style="list-style-type: none"> •Creating Hope Act (RPD PRV)-2012^a •Twenty-First Century Cures Act (Cancer Moonshot)-2016 •RACE Act-2017 				
Rare disease guidances/guidelines	Yes	Yes	No	No	Use EMA
Economic incentives	<ul style="list-style-type: none"> •Research grants •Tax credits •Reduced fees •Market exclusivity •Vouchers 	<ul style="list-style-type: none"> •Market exclusivity •Reduced fees •Incentives at member state level 	<ul style="list-style-type: none"> •Tax credits •Waived fees 	<ul style="list-style-type: none"> •Market exclusivity •Drug price premium 	<ul style="list-style-type: none"> •Reduced fees
Treatment access programs	Yes	Yes	Yes	Yes	Yes
National rare disease strategy	No	No	Under discussion	No	Plan published 2018

^aRPD PRV = rare pediatric disease priority review program. The RPD PRV program was reauthorized in 2016 and 2020

orphan status from PREA requirements for pediatric studies.

The US research programs targeting rare cancers (e.g., Cancer Moonshot—part of the Twenty-First Century Cures Act) aim to make more therapies available to more patients while improving cancer prevention and early detection [19]. While not limited to rare pediatric cancers, the Cancer Moonshot supports the study of some rare cancers that disproportionately affect children.

Other countries also employ regulatory strategies to provide access to drugs for rare diseases.

Canada

- Health Canada's Special Access Program (SAP) provides patients with serious or life-threatening illnesses access to drugs and medical devices that are currently unavailable on an exceptional case-by-case basis. SAP is accessible only when conventional therapies have failed, are unsuitable, or unavailable. Approximately 30% of requests submitted to SAP are for rare diseases [20].
- Health Canada initiated the Regulatory Review of Drugs and Devices (R2D2) project in 2017 to adapt their regulatory review processes to a changing health care system [21]. The intent of R2D2 was to increase access to drugs through regulatory improvements. The project focused on improvements of regulatory efficiency and timely access to drugs and medical devices, while promoting intra-network connections within the healthcare system. Certain sub-projects of R2D2 are especially relevant for drugs for rare diseases, including the renewal of the SAP, the introduction of aligned Health Canada—Health Technology Assessment (HTA) reviews to increase efficiency and information sharing, the expansion of the priority review pathways, and a plan for strengthening the use of real-world evidence (RWE) [22].
- In 2020, Health Canada introduced its Pediatric Drug Action Plan (PDAP) to address the challenges and barriers to accessing medicines for pediatric populations [23]. The program is designed to ensure that children in Canada have access to the medicines they need in age-appropriate formulations. To achieve this goal, the PDAP prioritizes three objectives: increasing the development of essential pediatric medicines, improving access to pediatric medicines and formulations, and providing more information and data to Canadians. Given that children are disproportionately affected by rare diseases, the PDAP is expected to promote drug development for rare diseases.

Japan

- In Japan, orphan drugs are defined in the Pharmaceutical and Medical Device Act (1993). Since the passage of this legislation, new regulations were added to promote research and development in children (e.g., financial aid, priority review, premium pricing, etc.). For example, a product can receive an extended period of marketing exclusivity (up to 10 years) only if the Marketing Authorization Holder (MHA) submits a pediatric trial plan and the pediatric trial is started as soon as the initial approval for adult indications has been granted (Notification No. 0831-16 of the PSEHB/PED dated August 31, 2020). In 2012, the Ministry of Health, Labour and Welfare (MHLW) implemented new pricing regulations for pediatric drugs, adding a premium (5–20%) to the drug price.
- Japan also has regulatory processes for approval of unapproved drugs or off-label uses of drugs that are approved in other developed countries, but not in Japan. In 2010, MHLW established a committee to evaluate whether a proposed drug or treatment meets high medical needs. Based on the committee's review, the MHLW determines the mode of regulatory authorization. Under certain conditions, sponsors can submit an abbreviated marketing application supported by existing foreign clinical data without a requirement for new clinical data. The MHLW has also established an academic research group that is directly collaborating with the Japan Pediatric Society to establish priorities for drug development.

European Union

- The EU provides several economic incentives for orphan drug development, including access to the centralized authorization procedure resulting in a single authorization valid in all EU member states, reduced fees for regulatory activities, and 10 years of market exclusivity. In addition, there are a range of national research and development incentives for orphan diseases. [24].
- The EU grants a 2-year extension of marketing exclusivity for medicine developments that have complied with an agreed pediatric investigation plan (PIP). A PIP is a development plan aimed at ensuring that the necessary data are obtained to support the authorization of a medicine for children. New products being developed for orphan diseases or those still under patent protection are not exempt from PIP requirements, even if the product is primarily intended to be developed for adults.

Multiple countries have developed national strategies for rare diseases [25]. Some regulatory authorities are creating an overarching national strategy to address rare diseases that

emphasizes a person-centered approach to the development of a national rare disease ecosystem. Recent examples of national rare disease strategies include

- In 2020, Australia published the National Strategic Action Plan for Rare Diseases, the first nationally coordinated effort to address rare diseases in Australia. The Australian government commissioned Rare Voices Australia (a patient advocacy group) to convene key rare disease stakeholders and draft the document [26].
- In 2021, Health Canada conducted national public stakeholder engagement events to solicit feedback on policy options to create a national strategy for rare diseases. The policy options were presented in a discussion document that was distributed online and Canadians were invited to respond by email, mail, or to participate in virtual town hall meetings [27]. The discussion document highlighted the benefits of a national strategy to address some of the challenges associated with drug development and access for rare diseases (e.g., consistency in access across the country, evidence and cost/sustainability). Feedback was compiled in a ‘What We Heard’ document which is available on the Government of Canada’s website [28]. Participants were generally in favor of a single framework for decision making for drugs for rare diseases. The discussion document identified strategies to address geographic accessibility issues, innovative approaches to approval and coverage (e.g., pay-for-performance models, early access and managed access), and regulatory approaches to expedite marketing approval of drugs for rare diseases (e.g., use of foreign decisions and an accelerated pathway for drugs already approved in the US and Europe). The clinical community and other stakeholders identified two main issues: (1) development of a database to monitor disease progression and treatment efficacy, and (2) improving diagnostic technologies for better long-term health outcomes. Canada is currently moving towards developing a national strategy for drugs for rare diseases based on the feedback received from the rare disease community across the country.

Regulatory authorities have increased efforts to promote global coordination of pediatric development programs for rare diseases. The Pediatric Cluster, established by the FDA and EMA in 2007, is an ongoing forum for international regulatory agencies to discuss product-specific pediatric drug development, especially topics related to product classes. Currently, Health Canada, the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, and the Therapeutic Goods Administration (TGA) of Australia participate in the Pediatric Cluster. Pediatric Cluster discussions may also prompt the FDA and EMA to issue a Common Commentary, an informal and non-binding document

with comments to sponsors on pediatric development plans that are under review by both authorities. FDA and EMA recently published a Common Commentary for pediatric oncology development plans [29]. An example of regulatory collaboration is the joint proposal for drug development for Gaucher disease published by EMA and FDA in 2014 [30]. It outlined approaches to facilitate international pediatric clinical investigations of products for Gaucher disease and was the result of extensive consultations with stakeholder groups that started in 2011. In 2008, EMA and FDA established a cluster to collaborate on orphan designation which was complemented in 2016 by the Rare Diseases Cluster, creating another forum for regulatory collaboration on rare disease product development [31].

Rare Diseases Research Networks

In parallel with these regulatory activities, there have been a number of public and private initiatives to improve the infrastructure for rare disease research. These include the National Institutes of Health (NIH)-funded Rare Diseases Clinical Research Network (RDCRN) and Undiagnosed Diseases Network (UDN) [32, 33]. More recently, the International Rare Diseases Research Consortium (IRDiRC) was launched with nearly 50 funding, research, industry, and patient organization members in 20 countries [34]. Other examples include Japan’s Initiative on Rare and Undiagnosed Diseases (IRUD) and the European Reference Networks for rare diseases [35, 36].

A common data-sharing system is a key element of clinical research networks. One example is the electronic health records (EHR) research networks system developed by the National Patient-Centered Clinical Research Network (PCORnet®) which is funded by the Patient-Centered Outcomes Research Institute (PCORI). PCORnet was created to enable the conduct of large randomized clinical trials and to address key challenges in building large, multi-institution study cohorts and outcomes analyses [37]. These networks provide economies of scale with efficiencies arising from having data for a large number of patients and institutions and using a common data model (CDM) and query infrastructure. There is also a focus on patient/family-centered study designs and reported outcomes. Over time, the networks can increase the number and quality of data elements in the CDM and can merge other data sources on a project-by-project basis (e.g., prospective cohort data assembled elsewhere) [38–40].

With PCORnet, each participating institution extracts, transforms, and loads data from its local EHR repository into a common, standardized data mart model that is maintained locally. The data mart specifications are issued by the PCORnet Coordinating Center and address both format and content [41]. Although the harmonization of formats,

content, and processes creates substantial efficiencies, some inter-institutional variability in the data remains [41, 42]. Rare diseases that have not yet been studied or scrutinized in PCORnet are more likely than common diseases to pose difficulties with data quality or harmonization. Currently, PCORnet has nine clinical research networks (including the pediatric network PEDSnet) with approximately 80 million patients and two healthcare payer data marts with claims-derived data for approximately 60 million patients [43]. These networks include 70 data-contributing institutions with 337 hospitals, 170,000 physicians, and > 3500 primary care practices. The networks are especially valuable for rare disease researchers who struggle to achieve a large enough data set to statistically power study analyses. Since each data mart includes all of an institution's patients, most clinical research questions can be studied and the cohort size for a particular rare disease study may be sufficient.

PEDSnet is composed of a growing number of US children's hospitals. While it maintains a PCORnet data mart, PEDSnet has also designed and implemented a more robust CDM based largely on the Observational Medical Outcomes Partnership (OMOP) Common Data Model [44–46]. Using an OMOP-like approach has enabled PEDSnet to expand its pediatric research capabilities and data quality monitoring infrastructure while establishing learning health systems [44, 47–50]. It has also facilitated collaboration between subspecialists, generalists, and informaticians in multiple fields [48, 51]. PEDSnet includes one-fourth of the 0–17 year olds in PCORnet and a much higher proportion of those with rare diseases [43]. In 2021, expanding upon its portfolio of 35 funded rare disease comparative effectiveness studies, PCORI awarded three applications for PCORnet studies, with PEDSnet playing a key role in all three projects [52–54]. The aims for each of these projects include comparative effectiveness analyses as well as enhancement of the PCORnet data infrastructure for the respective rare disease domain.

Research Trends

Many of these research initiatives have occurred following the recognition that regulatory policy alone is not sufficient to move needed orphan drugs through the regulatory pipeline. Hence, many public health authorities have simultaneously provided research support to improve orphan drug research. In addition, advances in genomic and epigenomic analyses have accelerated research on drugs and biologics that act on disease-specific molecular pathways. Most rare diseases are monogenic (“single gene”) disorders and are more amenable to development of tailored therapies than are common diseases which generally have multifactorial pathways of injury. As a result, a “precision medicine” paradigm

for rare disease product development is increasingly framing both policy and scientific discussions [55–57].

Several gene-targeted therapies (GTT) have shown great promise for rare monogenic disorders. Given the urgent needs of rare disease patients, GTT are generating interest from the US NIH to accelerate drug development efforts for these disorders. This includes using many-diseases-at-a-time approaches, platforms, and master protocols to increase the logistical efficiencies in bringing these therapeutics to patients [58]. One example is the Platform Vector Gene Therapy (PAVE-GT) program which uses four adeno-associated virus (AAV) vectors for gene replacement therapies for four very low prevalence rare diseases to try to gain efficiencies in the research and development process [59, 60]. Another example is the Shared Molecular Etiology (SaME) program which is seeking to adopt similar strategies that have been used successfully to gain FDA approval for a cancer drug to treat multiple rare cancers with the same mutation [61]. SaME has recently been funded and is still in the translational research phase.

FDA and EMA have issued new guidances and scientific guidelines on emerging therapeutic trends including regenerative medicine therapies, gene therapies, and genetically modified cell-based therapies [62–65]. Regulatory authorities and public health research agencies have also sponsored scientific meetings on product development for these therapeutic classes and engaged in public–private collaborations to advance global drug development for rare diseases. One example is the Pediatric Strategy Forums which focus on developmental strategies to support regulatory decision making for various types of targeted therapies for pediatric cancers [66]. Another example is the International Neonatal Consortium (INC), a global public–private partnership formed to accelerate the development of therapies to prevent and treat a variety of neonatal conditions, most of which are rare diseases [67].

Innovation in Study Endpoints

A lack of established study endpoints is a major challenge in pediatric drug development for rare diseases. Pharmaceutical companies and regulators are collaborating to develop practical, clinically appropriate, and patient meaningful endpoints for rare diseases. Some examples include the use of the lung clearance index ($LCI_{2.5}$) for cystic fibrosis transmembrane conductance regulator (CFTR) modulators in young children with cystic fibrosis and multi-luminance mobility testing (MLMT) scales in patients with inherited biallelic *RPE65* mutations.

There is an urgent need to develop appropriate study endpoints in pediatric rare diseases that are measurable and patient specific while being clinically meaningful for children, parents, clinicians, nurses, and regulators. Medical

geneticists can play a pivotal role in this area, given their knowledge of disease natural histories, the underlying molecular pathways involved, and the application of emerging technologies such as exome and genome sequencing in trial design and endpoint development [68–71].

There is increased interest in using real-world data (RWD) to generate RWE in the rare disease space [72–74]. Historically, FDA has utilized RWE as a key component of its efforts to assure post-marketing surveillance and evaluation of medical product safety. The Twenty-First Century Cures Act mandates FDA to develop a framework that expands the use of RWD and RWE to support approval of a new indication for an already approved drug. By leveraging data generated through normal clinical practice, signals of safety and efficacy for new indications can be identified in already approved therapies. However, as most existing RWD was generated without regulatory standards in mind, significant challenges exist to ensure RWD is high quality and fit-for-purpose to generate RWE capable of informing regulatory decisions. Efforts to use existing RWD to generate actionable RWE to answer regulatory questions can identify these challenges and corresponding solutions. However, this endeavor requires a significant amount of data and regulatory science expertise to fully optimize the use of RWD.

PCORI is funding “pragmatic clinical studies” to explore the use of RWE to compare treatment options, including a study in children with moderate to severe Crohn’s disease [74]. The PCORnet infrastructure also supports pragmatic trials such as Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness study [39, 75]. PCORI has also developed guidance on conducting research under real-world clinical care conditions [76]. EMA is establishing a data coordination center, the Data Analysis and Real World Interrogation Network (DARWIN EU), to provide timely and reliable evidence on medicines for human use (including vaccines) from real-world healthcare databases across the EU. EMA is currently exploring how RWE approaches can specifically support the work in the area of medicines for rare pediatric conditions. There is also increasing interest in the use of innovative study designs such as adaptive studies, *n*-of-1 studies, and platform trials to increase efficiency and reduce the number of patients needed for enrollment. [77].

Patient Engagement

There has been significant interest in engaging patients and families in pediatric drug development. Patient representatives serve on FDA advisory committees and provide input to review staff early in regulatory review processes. EMA has patients on several scientific committees and holds meetings of the Patients and Consumers Working Party (PCWP), established as a forum for exchange of information with

patients and consumer groups in 2006. EMA’s Committee for Orphan Medicinal Products (COMP) and the Paediatric Committee at EMA (PDCO) include patients organizations who are involved in the assessment of orphan designations and PIPs. Patients are also involved in the review of EMA documents developed for the public, such as package leaflets, safety communications, and medicines summaries. In Japan, patients are members of several committees in the MHLW (e.g., the Cancer Control Promotion Council) or PMDA. In the past 5 years, Japanese regulatory authorities have implemented new legislative mandates and agency processes to expand the scope of patient involvement in the development of regulatory policies. PMDA published a patient engagement guidance document in September 2021. There is also ongoing global collaborations in the private sector. The Drug Information Association (DIA) has a Patient Advisory Council that focuses on enhancing patient engagement. The council’s current membership includes regulators, industry representatives, patient advocates, and physicians from Europe, US, China, and Japan [78].

In the US, patient-focused drug development (PFDD) is the cornerstone of the Twenty-First Century Cures Act, which requires the FDA to include an assessment of patient experience data in the marketing application review process. Specifically, this Act:

- Directs FDA to develop PFDD guidance documents for collecting patient experience data,
- Details FDA’s anticipated use of these data in a benefit-risk framework,
- Directs FDA to publish a report regarding the use of patient experience data in regulatory decision making.

The 2017 FDA Reauthorization Act (FDARA) included reauthorization of the Prescription Drug User Fee Act (PDUFA VI) which requires FDA to use patient experience data in its benefit risk framework. This includes holding meetings to gather stakeholder input and establishing a timeline for evaluating implementation of the benefit risk framework process. In 2017, FDA conducted 24 PFDD meetings.

In addition to legislatively mandated activities, FDA has encouraged dialogue between patients and regulators. FDA and EMA created the Patient Engagement Cluster in 2016 to share information on involving patients in regulatory activities. FDA and the Clinical Trials Transformation Initiative (CTTI), a public–private partnership of stakeholders in the clinical trial arena, launched the Patient Engagement Collaborative (PEC) in 2018. The PEC is modeled upon the EMA’s PCWP [79]. FDA also established the Patient Engagement Advisory Committee (PEAC) which is the only advisory committee whose members are all patients, caregivers, and representatives of patient organizations. The FDA also hosts informal Patient Listening Sessions (PLS) and participates

in externally led PFDD meetings. PLS are an opportunity for patients and the advocacy community to share their experiences and perspectives directly with FDA; PLS can be FDA requested or patient led. Although these models were not specifically designed to address rare diseases, they have been adopted by rare disease patient groups. For example, rare diseases were the focus of 41% (10 of 24) of the PDUFA-mandated PFDD meetings [80]. In addition, a majority of PLS and externally led PFDD meetings attended by FDA are for rare diseases with significant pediatric populations. [81].

The issues of diversity and equity in patient participation in health research have also been highlighted in recent public and regulatory policies for rare diseases. Examples include the Australian National Strategic Action Plan for Rare Diseases and FDA's draft guidance on enhancing diversity of clinical trial populations [23, 82]. These documents specifically highlight the role of patient engagement in ensuring that under-represented communities are involved in drug development for rare diseases.

On-Going Challenges

Pediatric drug development for rare diseases is increasingly challenged by clinical trial infrastructural requirements and ethical considerations. These barriers frequently result in a lack of available and eligible/willing participants for clinical trials, leading to unknown or understudied safety and efficacy profiles of new drugs for pediatric populations. In addition, employment of traditional clinical trial designs may not be feasible due to small sample sizes and limited or non-existent knowledge regarding the natural history of the disease. Therefore, innovative/adaptive trial designs and methodology are frequently necessary to produce valid measurements of the safety and efficacy of these products. Furthermore, the resource intensive nature of these projects and the smaller market continue to be disincentives for sponsors.

Patient/Family-Centered Research

Long-standing paradigms in drug development are shifting, starting with the role of patients and families throughout the drug development cycle. There is a growing literature on the value of involving patients and patient advocacy groups in all aspects of clinical research including: securing research funding, development of outcome measures that are meaningful to clinicians, regulators, and patients/families, and improving recruitment and retention in clinical trials [83–89]. This paradigm shift is reflected in the incorporation of patient-focused drug development in regulatory policy and the increasing focus on patient-centered outcome measures by researchers conducting clinical trials on rare diseases. INC routinely invites parents to participate in all

drug development activities including leadership and annual meetings as well as discussions with regulators, physicians, and other key stakeholders.

Access to Diagnostic Tests

Most individuals with rare diseases will not receive a causal diagnosis due to the limited availability of valid and accurate diagnostic tests. However, with 80% of rare diseases having a genetic component, the use of whole genome sequencing and other diagnostic technologies is changing the paradigm for patients with rare diseases [90, 91]. The development of these diagnostic tests for rare diseases is a cornerstone of future drug development efforts. One of the principal goals of IRDiRC is that all patients with a suspected rare disease receive a diagnosis within 1 year of the onset of their disorder. IRDiRC also set a goal that all individuals who do not receive a diagnosis are enrolled into a globally coordinated diagnostic and research network. IRDiRC reports that since 2010, more than 4000 genes have been linked to rare diseases [92].

Regulatory Flexibility

Regulatory authorities continue to evaluate ways to facilitate rare disease drug development under existing regulatory approval pathways. One example is the use of pediatric extrapolation to minimize the number of pediatric studies required for regulatory submission and/or to supplement and support data generated from smaller studies. Although it may be appropriate to extrapolate data from studies in a reference population (e.g., adults) to children, there needs to be similarity of disease between children and the reference population as well as similarity of drug response. In addition, regulatory authorities have varying criteria for what data may be extrapolated. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is updating its guidance on extrapolation in pediatrics [93].

Health Canada is currently updating its Food and Drug Regulations to create a more agile system with the intent of better supporting drug oversight, both before and after sale. The updated regulations are expected to support rare disease drug development by providing more streamlined processes (e.g., aligned Health Canada–HTA reviews) and establishing a framework for the adoption of foreign decisions to expedite drug access to patients [94]. Updates are also being proposed for clinical trial regulations including [95]:

- Proportional risk-based approach,
- Single authorization of a trial,
- Agile lifecycle across product lines,
- Enabling decentralized trials,

- Registration and public disclosure of results.

Creation of these flexible and risk-based regulations is expected to promote the conduct of more trials with greater representation of patients in national and global trials. This should ultimately improve access to new drugs including those for rare diseases.

Economic Incentives

Market considerations remain a major factor in drug development activities. Economic incentives for drugs for rare diseases include reduced marketing application fees, marketing exclusivity, price premiums, and priority review vouchers (Table 1). There has been a significant increase in the number of products approved for rare diseases since the implementation of orphan drug legislation and other policies [6]. However, as noted previously, only 5% of rare diseases have an approved treatment. Furthermore, although 50–75% of rare diseases affect children, fewer than 50% of FDA-approved new drugs for rare diseases have pediatric indications [96]. As of 2020, 12% ($n=286$) of EU orphan designations have been granted for pediatric only developments.

Impact of COVID on Rare Disease Research

The COVID-19 pandemic has had an immediate and sustained impact on patients with rare diseases. Multiple reports worldwide have documented the extent of this impact, with most patients reporting interruptions in their regular health care. Disruptions have also extended into research in rare diseases as significant amounts of funding and personnel have been diverted to COVID-19 research efforts. Approximately 80% of non-COVID-19 clinical trials were stopped or temporarily interrupted and the long-term consequences of COVID-19 on rare disease populations (who can have many associated co-morbidities) have yet to be determined. RDCRN (with its network of 20 rare disease research teams) has collected comprehensive survey data with some programs planning to incorporate survey findings into natural history studies [97–100]. The pandemic has also resulted in significant changes in the current rare disease drug development infrastructure. Telemedicine has been successfully implemented to improve access during the pandemic to research staff and regulators. FDA has issued guidance regarding clinical trial conduct during COVID-19 that allows virtual visits in certain circumstances [101]. A patient survey conducted by the National Organization for Rare Disorders (NORD) found

that nearly 90% of patients accepted telemedicine when offered [102]. Although patients favor telemedicine as a visit option, there are limitations for completing trial activities (e.g., sample collection). In addition, some patients with rare diseases may not have access to computers and broadband capacity for remote access. The pandemic also highlighted other vulnerabilities in the research infrastructure including drug shortages and supply chain issues.

Although the response to COVID-19 continues to unfold, it has already provided lessons for strengthening future infrastructure for rare disease drug development. First, the pandemic has generated practices that many stakeholders advocate to be the “new normal” (e.g., telemedicine). There are also lessons to be learned from experiences of rare disease patients during the pandemic that may contribute to the rare disease knowledge base. For example, studying the association between COVID-19 and rare diseases may provide important insights into underlying physiological processes in rare diseases and other relevant conditions [97]. In addition, examining the impact of COVID-19 on the natural history of rare diseases is essential. Finally, there are many parallels between the integrated response to the pandemic and rare disease drug development, including the creation of global clinical trial networks and open access data platforms. The rapid development of COVID-19 vaccines affirms the power of collaboration when applied to a public health priority. The pandemic has facilitated greater collaboration between sponsors, industry, families, and international regulatory authorities which can only improve drug development efforts going forward.

Conclusions

Pediatric rare diseases are a significant global public health issue. Despite landmark legislative efforts as well as the institution of multiple regulatory and financial policies/incentives in many countries, drug development in this area remains limited. However, the pediatric rare disease ecosystem is evolving to address these challenges. Key elements that have contributed to a more robust ecosystem include novel approaches to product development made possible through the availability of enhanced genetic and diagnostic testing, innovations in trial design/endpoints and data collection, and increased efforts in the area of patient engagement and health equity. It is essential that these changes continue with a focus on drug development processes that are collaborative and patient centered.

Declarations

Conflict of interest

No conflicts of interest to disclose relevant to this manuscript.

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