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REVIEW PAPER

Orphan drug development: the increasing role of clinical pharmacology

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Abstract

Over the last few decades there has been a paradigm shift in orphan drug research and development. The development of the regulatory framework, establishment of rare disease global networks that support drug developments, and advances in technology, has resulted in tremendous growth in orphan drug development. Nevertheless, several challenges during orphan drug development such as economic constraints; insufficient clinical information; fewer patients and thus inadequate power; etc. still exist. While the standard regulatory requirements for drug approval stays the same, applications of scientific judgment and regulatory flexibility is significantly important to help meeting some of the immense unmet medical need in rare diseases. Clinical pharmacology presents a vital role in accelerating orphan drug development and overcoming some of these challenges. This review highlights the critical contributions of clinical pharmacology in orphan drug development; for example, dose finding, optimizing clinical trial design, indication expansion, and population extrapolation. Examples of such applications are reviewed in this article.

Keywords Orphan drugs · Rare diseases · Modeling and simulations · Model informed drug discovery and development

Background

The term orphan drug is used to designate any drug that has been developed to treat a rare disease or condition. In the US, rare disease is defined as a disease that affects fewer than 200,000 people [1]. In Europe, it is defined as a disease that affects less than 5 per 10,000 in a community, whereas in Japan and Australia, the numbers are fewer than 50,000 and 2000, respectively [2]. Although a specific rare disease affects small number of subjects, rare diseases collectively represent a significant public health concern. According to the NIH, over 7000 rare diseases are identified [3]. In the US and Europe alone, there are more than 60 million patients affected with one or more rare diseases. Most of these diseases are genetic in origin and affect children, resulting in death or significant developmental problems in the first few years of life. Thus, developing treatments for rare diseases is vital.

Challenges in orphan drug development

Development of drugs for rare diseases has been neglected in the past due to the considerable challenges and costs associated with orphan drug development [4]. These challenges mainly arise from the few number of patients affected with a specific disease, disease heterogeneity, and the limited understanding of the disease progression (i.e. natural history) and pathophysiology. The small number of individuals and the wide geographical distribution limits the opportunity to recruit sufficient number of patients; hence clinical trials pose a major risk of being underpowered. Additionally, replication and verification of study results might be difficult or impossible [5]. Multi-center or even multi-national collaboration is often considered to

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enhance recruitment, creating additional complexity to study conduct, feasibility and variability in the data.

For the majority of rare diseases, the natural history is poorly or incompletely understood. Although regulators do not require natural history studies to be conducted, absence of this information may halt the drug development process [6]. Because biomarker development and validation, and endpoint selections require a strong understanding of the natural history of a disease, clinical characteristics of the target population, disease pathophysiology and drug pharmacology. Such information is usually limited in rare disease settings. The limited understanding of disease pathophysiology also limits development of appropriate animal models. Besides these challenges in orphan drug development, the small market for orphan drugs may limit the ability of pharmaceutical companies to recover the high cost associated with launching a product into the pharmaceutical market through sales.

Stimulant to orphan drug development

In the US, the Orphan Drug Act (ODA) was enacted in 1983 to stimulate orphan drug development [7]. Subsequently, Japan and many European countries enacted similar regulations [8]. The ODA provides monetary and regulatory incentives to pharmaceutical companies. These incentives include waiver of the user fees associated with submission of new drug applications (NDAs) or biologic license application, market exclusivity, tax credits, and priority vouchers. In addition, a number of federal research grants are available to aid in the understanding of the natural history of a rare disease and in the development of a therapy, such as studies to develop or validate a drug development tool or to understand the full spectrum of the disease manifestations, including describing genotypic and phenotypic variability. Furthermore, patient registries are now available for several rare diseases. These registries are utilized to allow standardized observational data collection schemes such as information related to family history, demographics, environmental, laboratory, and genetic factors, as well as treatment and outcomes data. For example, the NIH Children's Oncology Group uses registries and national protocols to advance the development of new pediatric cancer treatments.

Basic research on orphan drugs has also been encouraged by the establishment of a global network and a platform that supports pharmaceutical companies in the development of orphan drugs. In addition, more academic institutions are conducting research on orphan drugs, and as a result, numerous target molecules have been identified; this is expected to lead to the development of innovative new drugs. Scientific advances have led to the identification of genetic causes of rare diseases and have the prospect of more targeted treatments for molecularly defined subgroups with different therapeutic profiles. The regulatory agencies have published several guidances and conducted workshops to summarize the current understanding and thinking of the agency and to assist sponsors of drug and biological products intended to treat or prevent rare diseases [4, 6, 9, 10]. These guidances were either general, such as guidance for pediatric rare disease development, or disease specific such as the guidances for Duchenne muscular dystrophy (DMD) and amyotrophic lateral sclerosis [11, 12]. As a consequence, there has been a marked increase in the development of orphan drugs globally. Since 1983, more than 2200 molecules have been designated as orphan drugs by the US Food and Drug Administration (FDA); about 400 drugs were approved and 200 rare diseases have become treatable.

Role of clinical pharmacology

Clinical pharmacology and quantitative clinical pharmacology (i.e. pharmacometrics) can play a critical role in designing efficient drug development programs and can contribute significantly to the totality of evidence required by the regulators for drug approvals. In this paradigm, regulators have encouraged drug developers to utilize clinical pharmacology and pharmacometrics in orphan drug development [12]. In 2012, the FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology unanimously voted to support the notion that modeling and simulation be considered for all pediatric drug development programs (14 March 2012, Gaylord National Resort and Convention Center, National Harbor, MD); pediatric rare diseases represent about 50–75% of all rare diseases. In this review, we focus on different areas of drug development and review several examples where clinical pharmacology aided effective drug development.

Dose finding, selection, or adjustment

Clinical pharmacology and pharmacometric analyses can leverage all available data to help reach an informed decision regarding the choice of dose for the pivotal efficacy trial. These analyses can substitute the conventional dose-finding study which is typically not feasible in rare diseases. Efforts to better define the optimal dose for a drug rely on adaptive dose-ranging and dose allocation studies. In this scenario, modeling and simulation provides a very important tool to characterize dose–exposure–response relationships. This information can then be utilized to design an adaptive clinical trial and understand the study operation characteristics. In addition, modeling and

simulations using population PK or physiologically based PK models and dose–exposure–response relationships can provide more complete information required for bridging dosing recommendations in special populations, such as pediatrics [13, 14], metabolizer phenotypes [15, 16], organ impaired patients, or in case of drug–drug interactions [17–22], where no or limited PK data is available.

In the following section, we review two examples that demonstrate how clinical pharmacology, in conjunction with modeling and simulation, can help leverage all available information to support dose selection for Phase III studies without the need for conducting a conventional dose finding study. In addition, the example on Lorenzo's oil (LO) highlights the use of a Bayesian approach in designing an efficient dose finding study.

Domagrozumab

Domagrozumab is a monoclonal anti-myostatin antibody being developed by Pfizer for DMD. DMD is a genetic disorder characterized by progressive muscle degeneration and weakness. Inhibition of the myostatin pathway can benefit patients with DMD [23]. Myostatin is a member of the transforming growth factor-beta (TGF-β) family and is a potent negative regulator of muscle mass and growth [24].

Clinical development of this antibody started with a first-in-human (FIH) study with weight-based dosing in healthy adults followed by a Phase II study in children with DMD aged 6–10 years old. The FIH study generated safety profiles that supported its further development in children, with key emphasis on dose selection. The approach involved a combination of different analyses utilizing all available information, with the ultimate goal of reducing the likelihood of futile doses. A meta-analysis was first conducted to compare clearance and volume of distribution at steady state for monoclonal antibodies (mAbs), between adult and pediatric patients. This showed that body weight-adjusted dosing can bridge between adult healthy and pediatric patients with DMD. The next step involved building a population pharmacokinetic/pharmacodynamic (PK/PD) model using 1671 observations of drug and myostatin concentrations from 36 subjects who received a single dose of the antibody across a wide dose range (1–40 mg/kg) in the FIH PK/PD study. This model was then validated using data from nine subjects in the multiple-dose cohort. Body weight and myostatin levels were identified as two factors that could potentially account for variability between populations. Further meta-analysis to incorporate body weight-scaled PK parameters, and input from literature and experts, helped tackle these variabilities. The final step involved incorporation of species-based and fixed-exponent allometric scaling methods to ultimately inform the dosing decision [25].

Although the recommended dosing was accepted by seven regulatory authorities, the sponsor recently terminated two clinical studies using this antibody as it did not meet the primary efficacy endpoint [26]. However, Pfizer continues to review the data to better understand any insights they may provide for ongoing clinical development of other related compounds.

These analyses highlight how all available in-house data, literature, and input from external collaborators data were used to confidently estimate exposure of this mAb against myostatin in pediatric patients with DMD.

Emicizumab

Yoneyama et al. presented another example of adopting a pharmacometric approach that guided the Phase III dose selection of emicizumab (ACE910) in patients with severe hemophilia A, without conducting a conventional dose-finding study [27]. This was done by using the Phase I/II study data to develop a population PK and repeated time-to-event (RTTE) model.

Hemophilia A is an X-linked inherited bleeding disorder caused by a deficiency of coagulation factor VIII. Nearly 50% of affected patients are classified as having severe phenotype, defined as having $< 1\%$ of normal endogenous factor VIII activity [28, 29]. Moreover, $\sim 30\%$ of these patients with severe hemophilia will develop anti-factor VIII neutralizing alloantibodies ('FVIII inhibitors').

Emicizumab is a recombinant, humanized, bispecific antibody mimicking the cofactor function of activated coagulation factor VIII. Pre-clinical studies have shown that emicizumab can be administered subcutaneously, has an elimination half-life longer than existing treatments, is effective regardless of the presence or absence of FVIII inhibitors, and is not expected to induce FVIII inhibitors. In Phase I/II studies, emicizumab reduced the bleeding frequency in patients with severe hemophilia A, at once-weekly subcutaneous doses of 0.3–3 mg/kg.

The RTTE model quantitatively characterized the relationship between the PK of emicizumab and reduction in bleeding frequency. Simulations were then performed to identify the minimal exposure expected to achieve zero bleeding events for 1 year in at least 50% of patients and to select the dosing regimens to be tested in Phase III studies. Using this approach, a target efficacious exposure of plasma emicizumab of ≥ 45 μg/mL was identified and formed the primary rationale for selecting previously untested dosing regimens of 1.5 mg/kg once weekly, 3 mg/kg every 2 weeks, and 6 mg/kg every 4 weeks for Phase III studies. Thus, pharmacometric analysis leveraging early-

phase clinical study data substituted a conventional dose-finding study in a rare disease population.

Lorenzo's oil

We have utilized this approach to identify the exposure–response relationship of an investigational drug, LO, utilizing data collected from an open label expanded access trial in boys with X-linked adrenoleukodystrophy (X-ALD) [30]. X-ALD is a rare, progressive neurodegenerative disease caused by a mutation in a peroxisomal transporter, ABCD1, and affects cerebral white matter, peripheral nerves, adrenal cortex and testes. Biochemically the disease is characterized by elevated plasma and tissue levels of the saturated very long-chain fatty acids, $C_{24:0}$ and $C_{26:0}$. LO, a 4:1 mixture of triacylglycerol forms of oleic acid and erucic acid, is one of the few disease-modifying X-ALD treatments available. It has been shown that administering this oil with moderate reduction of dietary fat normalizes or significantly lowers the levels of $C_{26:0}$ in plasma. However, little was known about its clinical efficacy or indications for use.

Using data from 116 male asymptomatic pediatric patients who were administered LO as part of the open label trial, we developed a hierarchical Bayesian statistical method for evaluating LO PD and proposed a Bayesian adaptive design for a Phase IIa trial to determine a dose that is both safe and effective in terms of improvement in biomarker response. This design was adaptive to interim individual toxicity and efficacy results, a desirable trait when dealing with a rare pediatric disease like X-ALD [31]. It is to be noted that Bayesian methods are very helpful in efficiently using all available pre-existing and accumulating trial data and is being increasingly used in orphan drug development.

Leveraging information form one indication to the other indication

In some cases, information gained during developing a drug for one indication can be leveraged to support approval for a different indication. This is especially important when recruitment is a particularly challenging as in the case of ultra-rare diseases. The following two examples illustrate how clinical pharmacology tools were applied to accelerate drug development and approval for ultra-rare indications.

Eculizumab

Soliris® (eculizumab) is a first-in-class humanized mAb that inhibits the activation of the terminal part of the complement cascade by binding to the complement protein C5, which plays a key role in serious disorders like paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) [32]. Initially, it was approved for the treatment of PNH, a rare, progressive and life-threatening disease that causes destruction of red blood cells and excessive blood clotting. The US product label for Soliris includes a boxed warning: "Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early" [33].

Subsequently, Soliris® was approved for the treatment of aHUS, an ultra-rare, chronic, life threatening genetic disease, caused by chronic, uncontrolled, complement activation, leading to systemic thrombotic microangiopathy (TMA) and acute renal failure [32, 34, 35]. Initial accelerated approval of Soliris® for adults and pediatrics with aHUS was based on data from two prospective single arm studies in adults and adolescents and one retrospective single arm study in pediatric and adult patients receiving Soliris off-label. All three studies demonstrated a favorable effect of eculizumab therapy on renal function and TMA. Based on these three studies, the FDA clinical review team recommended that eculizumab be granted approval for the treatment of adult and pediatric patients with aHUS under Subpart E (accelerated) approval under 21 CFR 601.41. To gain regular approval, the FDA issued post-market requirement that requires the sponsor to finish the two additional open-label clinical trials in pediatrics and adults that were ongoing at the time of the submission, to verify the clinical benefit [36, 37]. Ultimately, Soliris received full approval for aHUS in pediatric and adult patients after fulfilment of the requirements [38].

The dosing regimen for these three studies was chosen based on a PK/PD model that was developed using data from PNH adult subjects [34]. This model was used to develop optimal dosing strategies for adult and pediatric aHUS patients [35]. Identification of the therapeutic dosing window for eculizumab in aHUS patients involved several steps. First, to ensure patient safety, the upper exposure limit had to be determined. As a safeguard against toxicity, the upper exposure limit was capped at what had been previously observed in adults. To ensure efficacy, the minimum drug exposure also had to be determined. Using the predicted concentration of the soluble C5 and the binding characteristics of the mAb to the C5, a minimum concentration threshold of 50 μg/mL was set to obtain close to full inhibition of the target. Then, trial simulations using a population PK model were performed to determine which doses would optimize the probability of obtaining the mAb within the window of target engagement in neonates, children, adolescents, and adult patient.

Eculizumab's example highlights how understanding of the disease pathophysiology and drug mechanism of action is important to leverage dose–exposure–response relationship across indications and provide dosing regimen recommendations for adult and pediatric aHUS patients without the need for dose ranging studies.

Ivacaftor

Ivacaftor (Vx-770; Kalydeco, Vertex Pharmaceuticals, Cambridge, MA) is the first disease modifying medication approved for treatment of cystic fibrosis (CF) in patients with certain mutation in the CF transmembrane conductance regulator (CFTR) gene. Nearly 2000 mutations in the CFTR gene have been identified, of which 312 mutations are identified to be associated with CF [39]. Ivacaftor is a CFTR potentiator that increases epithelial chloride transport across the CFTR ion channel by increasing channel-open probability in both normal and mutant CFTR [40, 41].

In 2012, the FDA originally approved ivacaftor for treatment of CF in patients with G551D mutation in the CFTR gene [42]. The G551D CFTR mutation is associated with severe disease in ~ 5% of CF patients worldwide. This amino acid substitution in nucleotide binding domain 1 (NBD1) results in a CFTR chloride channel characterized by a severe gating defect that can be overcome in vitro by exposure to a CFTR potentiator [40]. Consistent with the in vitro data, two randomized placebo-controlled, parallel group clinical trials in this subpopulation confirmed the safety and efficacy of ivacaftor. Both trials resulted in statistically significant and clinically meaningful improvement in forced expiratory volume 1 (FEV1), the primary endpoint, which was rapid and sustained [43]. Subsequently, the FDA approved expansion of indication for other nine mutations in the CFTR gene based on clinical trial data [42].

In 2017, the FDA approved an expanded indication for ivacaftor for 23 additional mutations by relying on evidence from laboratory-based in vitro pharmacology experiments [42]. A change in chloride transport above 10% of control in Fischer rat thyroid cells expressing mutant CFTR channels was expected to identify responding mutations to ivacaftor. The choice of the 10% threshold was consistent with previous clinical experience [44, 45]. It was confirmed that mature CFTR channels for each mutation were present in the epithelial cell membrane and, therefore, able to respond to ivacaftor.

While expansion of drug use to a new population is common, the basis for expansion of ivacaftor indication is unique. Typically, indication expansion is based on clinical data. However, such an approach was not feasible in the case of ivacaftor as several of the mutations that affects CFTR gene are extremely rare. The clear understanding of the disease pathophysiology and genetic basis, the full elucidation of the mechanism of action of the drug, and the safety profile of the drug paved the way for expansion of the indication based only on in vitro pharmacology studies [46].

Leveraging prior knowledge in guiding pediatric drug development

Pediatric extrapolation entails data leveraging across populations to derive evidence of the safe and effective use of drugs in the pediatric population. Such extrapolation requires evidence-based fundamental assumptions on the similarity of the course of the disease and the expected response to therapy in the adult and pediatric populations [47]. As outlined in the EMA concept paper, modeling and simulation can aid in systematic quantitative assessment of the data and in predicting the degree of similarity on various aspects including PK/PD and disease progression [48]. The following is an example where extrapolation provided a valuable tool in orphan drug development for the pediatric population.

Infliximab

Infliximab is an IgG mAb against the human tumor necrosis factor α (TNFα) [49]. This drug is used in the treatment of various autoimmune diseases including psoriasis, arthritis, Crohn's disease (CD), and ulcerative colitis (UC) [50].

Infliximab has been approved for the treatment of UC in adults on the basis of results of two randomized, double-blind, placebo-controlled studies, the Active UC Trials 1 and 2 (ACT 1 and ACT 2) [51]. It was also approved for the treatment of CD in children utilizing the data from the randomized multicenter REACH study [52]. The drug was then considered for pediatric drug development for the treatment of UC [53]. This pediatric development program was based on extrapolating UC adult efficacy conclusions to the pediatric population. Therefore, it was required to demonstrate that the disease course and response to treatment are similar between adults and children with UC [53]. There is strong evidence available supporting the similarity of the disease course of UC in adults and pediatrics [54]; however, there was no clear understanding of the exposure–response relationship in pediatrics with UC, and how similar the relationship is to the respective adult population. Therefore, the pediatric efficacy and safety Phase III study (T72) was conducted in 60 pediatric UC patients [53, 55].

The T72 study was an open label, multicenter, randomized trial in pediatric UC patients aged 6–17 years. The study was composed of two phases, the induction

phase and the maintenance phase. The objective of the induction phase was to evaluate the clinical response after intravenous (IV) 5 mg/kg doses of infliximab at weeks 0, 2, and 6. At week 8 of the induction phase, only responders were randomized to one of the two maintenance arms: 5 mg/kg every 8 weeks (Q8W) or every 12 weeks (Q12W) and followed to week 54. The study primary endpoint of clinical response at week 8 was defined as a decrease in the Mayo score by at least 30% and 3 points, with a decrease in the rectal bleeding subscore of at least 1 point or a rectal bleeding subscore of 0 or 1. The validated Pediatric Ulcerative Colitis Activity Index (PUCAI) (non-invasive) scoring system was also measured and provided an assessment of efficacy maintenance at week 54.

The study achieved the primary endpoint of clinical response at week 8 in 44 of the 60 pediatric patients which translated to a response rate of 73.3%. Additionally, the median (90% CI) infliximab concentration at week 8 was 29 (12–48) μg/mL. Notably, the previous adult ACT 1 study induction phase results showed that 83 out of 121 were responders (69% response rate), and a median infliximab (90% CI) concentration at week 8 of 33 (7–64) μg/mL. Comparing the results of these two studies, it was concluded that the induction phase week 8 median concentrations and response rates were similar between adults and pediatric populations based on primary endpoint. The evaluation of the exposure–response relationship (probability of response vs drug concentration at week 8) supported the similarity conclusion as it showed superimposed results for both the adults and pediatric populations. These results supported partial extrapolation of efficacy from adults that supported pediatric labeling for induction with infliximab.

The results after the maintenance phase (week 54) demonstrated that Q8W arm has twice as many patients who achieved the PUCAI clinical remission compared to Q12W. Considering the Q8W results, 8 of 21 subjects (38%) were in remission at week 54. In comparison, the adults ACT 1 study showed that 42 of 121 subjects (35%) were in remission. Another observation at week 54 was that fewer patients randomized to Q8W discontinued the study or required a step up in comparison to Q12W maintenance therapy. Based on these clinical observations and combined with the exposure–response relationship of the induction phase, a maintenance dose of 5 mg/kg Q8W was approved for the pediatric patients.

The example above indicates that robust adult program is critical for facilitating a successful pediatric program. The choice of dose to be evaluated in pediatrics is typically informed by the adult data. A recent article discusses how Bayesian methods can be applied in the example above to help make a better-informed decision [56].

Identification of surrogate endpoints

A surrogate endpoint is an outcome measure used as a substitute for a clinically meaningful endpoint. Surrogate endpoints are useful in drug development as they can be measured earlier, more conveniently or more frequently than the clinical end points. When a surrogate endpoint is clearly shown to predict the clinical outcome, its use generally allows clinical studies to be conducted in smaller numbers of individuals over shorter periods of time [57]. For example, reduction of systolic blood pressure has been shown to correlate with reducing the risk of stroke in many clinical trials. Therefore, clinical trials evaluating the risk of stroke can utilize reduction of systolic blood pressure to claim such an indication.

Validating a surrogate endpoint requires providing an evidence-based justification that achievement of substantial effects on the surrogate endpoint reliably predicts achievement of clinically important effects on a clinically meaningful endpoint. This evidence is usually achieved by combining data across several randomized controlled clinical trials that evaluated both the surrogate and the clinical endpoint. Here we review two interrelated examples that utilized modeling and simulation approaches to validate a surrogate endpoint for use in pediatric trials for pulmonary arterial hypertension (PAH).

Pulmonary arterial hypertension (PAH)

PAH (World Health Organization (WHO) Group 1) is one of five groups of pulmonary hypertensions (PHs) [58]. It is a rare, progressive disorder characterized by elevation of pulmonary artery pressure and pulmonary vascular resistance in the absence of left-sided heart disease, lung disease, or pulmonary thromboembolic disease [59]. PAH can be classified according to the etiology into primary or idiopathic and secondary [60]. Idiopathic PAH occurs without any associated systemic diseases, while secondary PAH could occur secondary to drug/toxin exposure, congenital heart disease, or may be present in association with a variety of systemic conditions. Connective tissue diseases such as scleroderma, cirrhosis with portal hypertension, or HIV infection can contribute to a common pathophysiology at the level of the pulmonary vasculature [61]. Although, the pathobiology of PAH is complex and not fully understood, it is believed that PAH not only involves pulmonary vasoconstriction but also pulmonary vascular remodeling, which is an interplay of proliferation of endothelial and smooth-muscle cells, inflammation, matrix alterations, and thrombosis [62].

There are four classes of drugs approved for the treatment of PAH which modulate molecular pathways

implicated in the pathogenesis of the disease. These classes include: phosphodiesterase type 5 inhibitors (PDE-5i) (e.g., sildenafil, tadalafil); soluble guanylate cyclase agonists (e.g., riociguat); endothelin receptor antagonists (ERAs) (e.g., ambrisentan, bosentan and macitentan); and synthetic prostacyclins (e.g., epoprostenol, treprostinil, iloprost).

Sildenafil Sildenafil is a selective PDE-5i that results in the degradation of cyclic guanosine monophosphate, thereby causing a vasodilation effect. Revatio® (sildenafil) 20 mg tablets was initially approved in 2005 for treatment of adults with PAH to improve exercise ability. The basis for approval was based on a single pivotal study, SUPER-1. SUPER-1 was a randomized placebo-controlled study that aimed to evaluate the efficacy and tolerability of three oral doses of sildenafil (20, 40 and 80 mg) three times a day (TID) in 278 adult patients with PAH [63]. In all the dosing groups, the distance walked in 6 min (6MWT) exercise capacity test increased significantly compared to placebo. In all sildenafil groups, the distance walked in 6 min increased significantly from baseline where the mean placebo-corrected treatment effects were 45 m (+ 13.0%), 46 m (+ 13.3%), and 50 m (+ 14.7%) for 20, 40, and 80 mg of sildenafil, respectively ($P < 0.001$ for all comparisons). Based on this study, Revatio® (sildenafil) was approved for the treatment of PAH at a dose of 20 mg TID as no greater efficacy was achieved with the use of the higher dose. Since the 20 mg was the lowest studied dose in the pivotal trial, a post-market commitment was issued by FDA to study the efficacy of a lower dose [64]. In 2009, an efficacy supplement to expand the Revatio® indication of PAH to include a "delay to clinical worsening" claim was approved. Later, an IV formulation was approved for use in the treatment of adult PAH patients who are currently prescribed oral Revatio® and who are temporarily unable to take oral medicine [65].

In 2011, Pfizer submitted a NDA to market a new dosage form (powder for oral suspension) and expand the indication to pediatrics. The pediatric development program started in parallel with the adult development program but took a significantly longer time.

Pfizer conducted a dose ranging STARTS-1 trial (blinded) and an open-label extension trial to evaluate sildenafil in pediatric patients with PAH. The STARTS-1 trial was conducted in pediatric population with PAH, aged 1–17 years old (N = 235). The study was a 16 week, randomized, double blinded, placebo-controlled dose ranging study that evaluated safety and efficacy of sildenafil [66]. One-third of patients had primary PAH; two-thirds had secondary PAH (systemic-to-pulmonary shunt in 36%, surgical repair in 30%).

In STARTS-1, 3 sildenafil dose levels (low, medium, and high) were selected to achieve maximum plasma concentrations of 47, 140, and 373 ng/mL, respectively, at steady state after oral administration three times a day. These target concentrations were selected so that the concentrations of unbound sildenafil would be expected to be similar to sildenafil concentrations that produced ~ 53%, 77%, and 90% inhibition of phosphodiesterase type 5 activity in vitro, respectively.

The doses that are predicted to achieve these target concentrations were predicted based on allometric scaling principles [67, 68]. To provide a practical dosing scheme, 3 body weight categories were specified: ≥ 8–20 kg, > 20–45 kg, and > 45 kg. In this study, the marketed tablet formulation of sildenafil tablets (Revatio®) were used. For pediatric patients unable to take the tablet, an extemporaneously prepared formulation based on the intact tablet was used. Given the available marketed sildenafil tablet dosing strengths, there was no low dose level for subjects with body weight < 20 kg; consequently, these patients were not randomized to the low-dose sildenafil. Depending on body weight and dose level, doses were 10 mg, 20 mg, 40 mg, or 80 mg TID.

As prolonging exercise (like 6MWT) endpoint is not well reproducible and difficult to evaluate in children, especially those under 7 years of age, a different exercise capacity primary outcome endpoint was used in this trial for children between 7 and 17 years old in the study; the percent change in the peak oxygen consumption (pVO_2) as a measure of exercise tolerance. The secondary hemodynamic endpoints, including pulmonary vascular resistance index (PVRI), were used to evaluate efficacy, in children of all ages who participated in the study (1–17 years old) [66]. At the end of the study, patients were rolled over into a long-term extension study in which all subjects received the active treatment [69].

The strategic question in the pediatric drug development process that evolved after conducting these trials was whether it's possible to establish sildenafil's efficacy in children and select a dose without the need to conduct any further studies. The ability to extrapolate the adult efficacy data to the pediatric population was faced with two issues. First, the adults and pediatric population were assessed via different primary endpoints, i.e., 6MWT versus pVO_2 in adults and pediatric, respectively. Second, the primary endpoint (i.e. pVO_2) was not assessed in the younger children (< 7 years old), and instead it was assessed via the secondary PVRI hemodynamic endpoint. Therefore, the ability to extrapolate the adult data depends on whether it is possible to relate pVO_2 to 6MWT and PVRI to pVO_2.

An FDA meta-analysis, based on data from 13 PAH trials conducted in adults across 3 drug classes, indicated that drug-induced changes in exercise capacity is associated with drug-induced hemodynamic measure changes in adult patients with PAH [70]. Essentially the analysis

showed the existence of a relationship between the placebo corrected change from baseline in the 6MWT (ΔΔ 6MWT) and the placebo corrected change from baseline in the hemodynamic endpoint pulmonary vascular resistance index (ΔΔ PVRI) in the adult PAH population, and it also showed that this relationship is consistent across the three different drug classes. It was demonstrated that 10–15% increase in ΔΔ 6MWT is associated with 30% decrease in ΔΔ PVRI. Based on these analyses, the FDA concluded that a treatment effect on PVRI can be used to demonstrate effectiveness and to derive dosing information in the pediatric PAH population [71].

When the sildenafil pediatric drug development team compared the results, it was noted that the adult 6MWT and PVRI data submitted within sildenafil NDA were consistent with the relationship established by the FDA model. Modeling was then conducted to characterize relationships between exposure, PVRI changes and associated changes in 6MWT and pVO_2. Once the models were validated, simulations were done to find the pediatric doses that achieve the exercise capacity outcomes that are comparable to those seen in adults. Simulation results supported pediatric dosing regimen of 10 mg TID for children $\leq$ 20 kg, and a dose of 20 mg TID for children above 20 kg [72, 73].

Unfortunately, sildenafil was not approved by FDA. While there were no major safety findings during this 16-week study and no deaths were reported, an unexpectedly increased risk of mortality with the high sildenafil dose (i.e. 20 mg, 40 mg or 80 mg) and the little efficacy associated with the low dose (i.e. 10 mg) had major negative implications for sildenafil approvability in pediatric patients with PAH [74]. In fact, sildenafil's current label states a warning of increased mortality in pediatric patients and does not recommend the chronic use in children. Notably, sildenafil is approved in Europe and the guidelines of the European Society of Cardiology for PH recommend sildenafil therapy in children, for those aged 1–17 years old using the low dose (i.e. 10 mg for 8–20 kg, and 20 mg for > 20 kg) [75].

Bosentan Bosentan is approved for the treatment of PAH in adults and pediatric patients. Bosentan exerts its vasodilatory effects through competitive inhibition of endothelin-1 receptor (ET-1) [76]. ET-1 concentrations are elevated in plasma and lung tissue of patients with PAH, suggesting a pathogenic role of ET-1 in this disease [77].

In 2001, Actelion Pharmaceuticals received FDA approval for Tracleer® (Bosentan) film coated tablets for the treatment of adult patients with PAH. The basis for approval was based on two double-blinded, placebo-controlled trials (Studies AC052-351 and AC052-352). Study AC052-351 was a 12 weeks study to evaluate the clinical effects of bosentan as a long-term oral treatment for idiopathic PAH or PAH related to scleroderma [78]. All patients were NYHA Class III at baseline. Over 12 weeks, oral bosentan (62.5 mg twice a day for 4 weeks, then 125 mg twice daily) improved placebo-adjusted Δ 6MWT (+ 76 m, P value = 0.021), PVR (−415 dyne s/cm^5, P-value < 0.001), and NYHA Class. Study AC052-352 (BREATHE-1) was a 16-week study using 62.5 mg BID for 4 weeks, followed by a maintenance dose of either 125 mg or 250 mg twice daily [79]. At the end of the maintenance period, there was a significant improvement in the placebo-adjusted Δ 6MWT (+ 44 m, P < 0.001). The study also showed that bosentan also improved the Borg dyspnea index and WHO functional class and increased the time to clinical worsening. However, a dose-dependent abnormal hepatic function was observed. Taken together, these studies supported bosentan film-coated tablets approval for the treatment of patients with PAH at initial dose of 62.5 mg BID for the first 4 weeks followed by 125 mg BID with a warning of potential liver injury [80].

Later, Actelion Pharmaceuticals submitted NDA seeking approval for a dispersible tablet formulation (32 mg) of bosentan in pediatric patients with PAH. The efficacy of bosentan was evaluated in BREATHE-3 study [81]. BREATHE-3 was an open-label, single-arm, uncontrolled study in pediatric patients (N = 19; aged between 3 and 15 years). Patients had primary PH (n = 10) or PAH related to congenital heart diseases (9 patients) and were WHO functional class II (n = 15, 79%) or class III (n = 4; 21%) at baseline. In this study, patients received weight-based dosing, based on different weight tires, of bosentan tablets (∼ 2 mg/kg BID) for 12 weeks. The applicant also submitted results of two additional studies but were not considered pivotal for this submission [82–85].

While the Cardiovascular and Renal Drugs Advisory Committee, when discussing Revatio® (sildenafil) for the treatment of pediatric PAH, agreed that there seems to be a relationship between PVRI (PVR adjusted to the body mass index) and exercise capacity in adults with PAH [71], there were concerns with the generalizability of this observation across different PAH disease type, etiology, pathogenesis and pathophysiology in adults as well as across different drug classes. Despite the fact that the etiologies of PAH are different in children than adults, and the clinical course has some inconsistencies, the committee members agreed that they were similar enough, with the caveat of subgroups but recommended additional work to validate the proposed hemodynamic endpoint using the data available in adults. Therefore, a meta-analysis was conducted by the FDA review team utilizing data from 12 randomized adult clinical trials evaluating the efficacy of 9 approved drugs across the 4 different classes (see above) and BREATHE-3 pediatric clinical trials submitted within bosentan package.

The meta-analysis focused on the following questions: (1) is there a consistent relationship between Δ PVR and Δ 6MWT across drug classes in adult patients with PAH, (2) does bosentan have a significant effect on Δ PVR and Δ 6MWT in adults, (3) can bosentan treatment effect on 6MWT explained by PVR, and (4) does bosentan treatment have a significant effect on Δ PVR in pediatric patients with a magnitude similar to the treatment effect in adults. The first three questions were basically asked to evaluate the adequacy of the PVR as a surrogate endpoint for 6MWT based on Prentice's surrogate endpoint's criteria [86].

The linear regression analysis indicated that there was an association between improvement in 6MWT and a reduction in PVR, using pooled adult data of 12 trials of 9 approved drugs (adjusted R^2 value = 0.121). Most importantly, the relationship between Δ PVR and Δ 6MWT using pooled treatment and placebo arms is consistent across drug classes and the slope is statistically significant for each drug class with P-values < 0.0001. The pooled analysis also showed that bosentan has a significant effect on Δ PVR and Δ 6MWT. After adjusting for placebo, the ΔΔ 6MWT was + 35 m (P-value = 0.0005), and the ΔΔ PVR was – 250 dyne s/cm^5 (P-value < 0.0002). Additionally, a univariate analysis indicated that Δ PVR is a significant predictor of Δ 6MWT. The final regression model included both the baseline 6 MWT and Δ PVR as the significant predictors for Δ 6MWT. This model indicated that Δ PVR explains 52% of the bosentan treatment effect on Δ 6MWT [85].

To establish the similarity of the bosentan treatment effect on Δ PVR in adults and pediatric patients, the FDA review team compared the distribution of the Δ PVR in adults and pediatrics across the placebo-treated arm and bosentan-treated arm. Since there was no placebo data for pediatrics submitted within the bosentan NDA, the PVR data in pediatrics taking placebo for 16 weeks were obtained from STARTS-1, a Phase III, placebo controlled, parallel group, dose ranging study in patients aged 1 to 17 years that was submitted within the *Sildenafil* NDA [65]. This comparison revealed that after administration of 2 mg/kg BID bosentan (film-coated tablets) to pediatric patients with PAH, Δ PVR was − 389 (95% CI − 682, − 96) dyne s/cm^5 at week 12, which was similar to the Δ PVR measured at 12 to 24 weeks in adult patients with PAH treated with bosentan 125 mg BID.

These analyses were significant in bridging the efficacy data between the adult and pediatric studies and supported labeling recommendations in pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve PVR, which is expected to result in an improvement in exercise ability.

While PVR qualified as a surrogate endpoint for the 6MWT in PAH, two deaths and three severe adverse events during the right heart catheterizations to obtain PVR measurement made this an unacceptably high-risk surrogate. Therefore, this surrogate endpoint as currently performed is not acceptable for any further pediatric drug development programs.

Drug-disease-trial models

Traditionally, drug development involves 10–40 clinical trials enrolling thousands of participants. The pivotal trials are usually randomized controlled clinical trials (RCTs). The pivotal studies for orphan drug approvals are more likely to be small, heterogenous, and in many cases are nonrandomized, un-blinded trial design, e.g. single arm designs [87–90]. It has been shown that for new products entering Phase III trials, an average 761 patients were enrolled in orphan drug trials versus 3549 in non-orphan drug trials [91]. Observational studies are typically not a valid replacement for randomized clinical trials. Therefore, alternative trial designs and statistical approaches that aim at addressing these limitations are considered. These alternative designs include: crossover, factorial, randomized withdrawal, early-escape, and adaptive designs [92–94].

The crossover design compares two or more treatments by randomly assigning each participant to receive study treatments in a different sequence. Once participants finish a treatment, they are switched to another one. With the randomized withdrawal design, participants who respond positively to a study treatment are randomized to continue receiving that treatment or receive a placebo. The early-escape design is another way to minimize participants' duration of exposure to a placebo by removing them from the study if they do not respond to a defined extent. Single-subject (N-of-1), sequential, and adaptive designs have been developed for small-size studies. The N-of-1 trial design is a randomized multi-crossover study of an individual patient's responses to a set of treatments (usually two). Treatments are randomly assigned individually or within paired periods and given to the patient. The patient's disease status is measured at set time intervals, corresponding to different treatment periods. After several crossover periods, comparisons are made between the outcomes obtained for each drug. In adaptive design assignment probabilities are skewed to favor the best-performing treatment in ongoing trials. The "play-the-winner" rule is the major advantage of the adaptive design because more patients will be assigned to the more successful treatment over time. In other possible designs (randomized placebo phase, stepped wedge trials) either the time spent on placebo is minimized or all patients receive the active

treatment at the end of the trial. This is very important when studying treatments for life-threatening rare diseases, especially with the ethical issues involved (i.e. the need to minimize placebo administration in severe patients).

The choice of a specific study design should be based on the trial objective(s), number of patients needed and anticipated, recruitment duration, duration of the trial, knowledge about the treatment and the intervention, and how the variability is handled. It is possible that several trial designs can be identified for a specific research question. In that case, it is important to consider building an integrative model of the drug-disease-trial model and simulate the results from each design before selecting the best design [95]. Simulation of in silico trials requires mathematical models of the disease pathophysiology and progression, drug effect (i.e. PK/PD), and the experimental design(s) [96].

We review below a drug-disease-trial model developed for dornase alfa in CF [96, 97]. This work was done as part of the Child-Rare-Euro-Simulation (CRESim) project. The CRESim aims at creating a platform for performing trial modelling and simulation. The platform expects to assess different RCT designs in silico to identify the optimal trial design in terms of trial duration and precision of the estimation of the treatment effect for drug evaluation in children with rare diseases [98].

Clinical trial simulation of dornase alfa in cystic fibrosis

Dornase alfa (Pulmozyme®) is a recombinant human deoxyribonuclease I (rhDNase) that selectively cleaves the DNA present in sputum/mucus of CF patients and reduces viscosity in the lungs, promoting improved clearance of secretions [99, 100]. An in silico approach with modelling and simulation has been proposed in the CRESim project to find the most appropriate design in CF.

A PD model was initially developed to describe the effect of dornase alfa on mucociliary clearance in CF, which takes into account the differential deposition of dornase alfa after inhalation and its effect on sputum viscosity [101, 102]. Several experimental designs were then simulated to identify the optimal design, in terms of precision of the estimation of treatment effect, statistical power, and trial duration. The treatment effect of dornase alpha in CF patients was assessed by using the mucociliary clearance as the main endpoint. The simulated clinical trial designs included the gold standard parallel design as well as cross-over, randomized withdrawal, early escape, N-of-1, and adaptive randomizations such as "play the winner" (PW) and "drop the loser" (DL). One thousand trials were simulated for each design with a sample size of 50 patients. Patients were randomized from a simulated virtual patient population.

Result of these in silico trials indicated that the cross-over design has the best estimation of treatment effect with 87% statistical power, a low coefficient of variation (36%) although a large trial duration (2 years). Parallel, PW and DL designs all had a similar power (about 60%) and coefficient of variation (about 45%) but PW and DL had a larger trial duration (2 years vs. 1.5 years). The N-of-1 design had the lowest power (22%) [96, 97].

These simulations are intended to allow investigators to make informed decision on the choice of the trial design. According to the trial objectives, which can include a high precision, a high power, and/or a reduced time for patients, investigators can choose the most appropriate design. This work was done under the CRESim initiative. There are several other international initiatives sharing the same objective of improving small population clinical trial methodologies, and clinical trials in rare diseases (see for review [103]).

Contribution to the totality of evidence for drug approval

Regulatory approval dossiers often lack full evidence on drug effectiveness. Sponsors and regulators can sometimes accommodate gaps in data by utilizing a totality of evidence approach. Examples of this include accelerated or conditional approval of new active substances in general. We review an example where FDA approval relied on totality of evidence and how dose–response relationship contributed to such evidence.

Tetrabenazine

Tetrabenazine is an orphan drug that is approved by the FDA for the treatment of Huntington's disease (HD)-related Chorea [104]. HD is a progressive devastating and disabling neurodegenerative disorder characterized by movement disorders, incoordination, cognitive decline, and personality and behavioral changes [105]. The most striking and common symptom is chorea, or involuntary dance-like movements that seem purposeless and abrupt [106]. As the severity of symptoms progresses, patients are at a higher risk of dying because of complications, such as falls and aspiration. The typical period between diagnosis and death of the patient is 20 years [107].

Prestwick Pharmaceuticals, conducted two pivotal double-blinded controlled clinical trials (Studies 004 and 005) to establish tetrabenazine safety and efficacy for its indication, (15). In addition, the sponsor conducted two open-label extension trials of the two controlled trials (Studies 007 and 006, respectively).

Study 004 was a placebo-controlled, 12-week study in which patients were randomized to placebo (n = 30) or

tetrabenazine (n = 54). Weekly dose titration was allowed until week 7 followed by maintenance dose for the following 5 weeks. The study demonstrated that tetrabenazine significantly reduced the total chorea score (the primary endpoint) from baseline to week 12 ($P < 0.001$).

On the other hand, Study 005, was a placebo-controlled 5-day study in 30 patients already stabilized on tetrabenazine for at least 3 months. In this study, patients were randomized in a 2:2:1 ratio to receive placebo for 5 days (Cohort 1, n = 12), receive tetrabenazine until after the assessment on day 3 (Cohort 2, n = 12), or receive tetrabenazine for all 5 days (Cohort 3, n = 6). The primary outcome, the mean change form baseline in the chorea score between the placebo group (n = 12) and the tetrabenazine groups combined (n = 18) on day 3, didn't achieve statistical significance ($P = 0.078$). The sponsor claimed that the protocol was not followed for Cohort 2. Specifically, patients were to be assessed on day 3 in the morning after receiving tetrabenazine, however, patients received placebo on day 3 morning before assessment. Since patients stopped their medication the night before assessment, and as tetrabenazine has a short half-life ($\sim$ 5 h), the sponsors believed that the drug was getting completely washed out on the day of assessment and thus did not meet the study endpoint.

With one of the two controlled trials failed, the pharmacometric group at FDA conducted a dose–response analysis to gain insights on tetrabenazine effectiveness. The dose–response analyses revealed that there was adequate evidence of tetrabenazine effectiveness which was consistent across trials. This effect was sustained upon continuous tetrabenazine administration and reproducible upon tetrabenazine re-administration.

Specifically, the dose–response analyses were conducted utilizing the data across the two controlled and open-label extension (Study 007) clinical trials. Study 004 demonstrated a significant dose–response using data across all visits (titration and maintenance phases). This effect was maintained over the 5 weeks of maintenance period. A consistent sustained change in the chorea score was also observed in Study 007. Since this study was extension of Study 004, re-titration of the patients to the same tetrabenazine dose demonstrated a reproducible effect of tetrabenazine as patients re-gained similar effect on chorea score to what was initially observed in Study 004. Study 005 dose–response analysis demonstrated that in patients in whom tetrabenazine was withdrawn on day 1 (placebo group, n = 12) or day 3 (n = 12), the total chorea scores significantly increased by day 5 ($P < 0.001$). Likewise, the mean chorea score changes in Study 006 were similar to Studies 004, 005, and 007.

Based on the totality of evidence, the FDA agreed that tetrabenazine demonstrated a significant lowering effect on chorea scores and that these effects were sustained.

Concluding remarks

The FDA Office of Orphan Products Development states that "approval of orphan designation does not alter the standard regulatory requirements and process of obtaining marketing approval," and that "safety and efficacy of a compound must be established through adequate and well-controlled studies." Adequate and well-controlled studies are defined according to Section 314.126 of Title 21 of the Code of Federal Regulations (21 CFR 314.126) as a "design that permits a valid comparison with a control." The control may be a placebo, dose comparison, active treatment, or historically derived. Concurrent controls should be randomized.

The current statutory and regulatory framework provides the FDA with the flexibility needed to make science-driven decisions to "waive in whole or in part any of the criteria" regarding adequate and well-controlled studies. Clinical pharmacology can have implications on study's reliability, generalizability, and capacity to substantiate

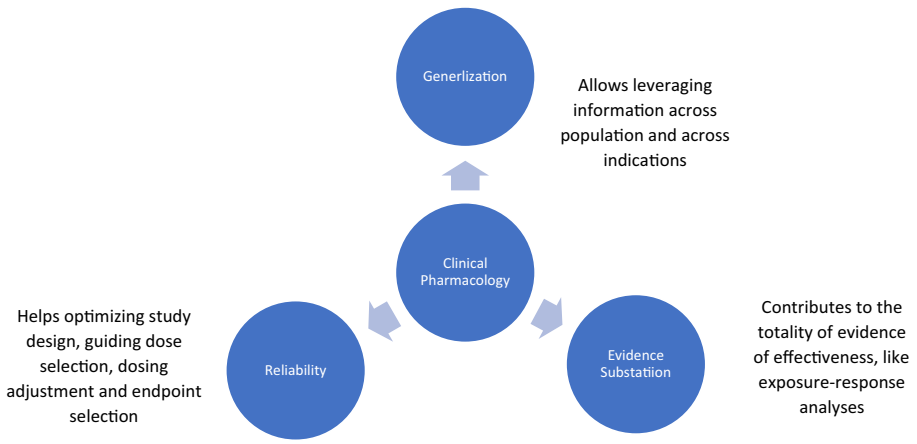

Fig. 1 The increasing role of clinical pharmacology in orphan drug development and approval

effectiveness, therefore, adding to the rigor and the scope of orphan drug development and approval (Fig. 1). The examples described here clearly demonstrate the role of clinical pharmacology in these aspects. Pharmacometric approaches can combine PK and PD with statistical inference methods to allow drug developers to generalize and leverage information across trials, populations, or diseases, to reach informed decisions regarding the appropriateness of the selected dose, and requirements of dosing adjustments based on intrinsic and/or extrinsic factors. Disease progression and placebo response models could be combined with drug-trial models to simulate clinical trial outcomes and select the most efficient and reliable study design. In addition, dose–exposure–response analyses can substantiate the evidence of effectiveness and adding to the totality of evidence for drug approvals. Obviously, these tools have limited utility when there is a deficiency of clinical trial data, lack of full understanding of the disease mechanisms, or lack of qualified biomarkers of drug response.

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