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Therapeutic Orphan No More: Role for Clinical Pharmacology and Translational Science in Developing Therapeutics for Rare and Neglected Diseases

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Rare disease (a disease that affects fewer than 1 in about 2,000 people¹) and neglected disease (an infectious disease that is present in lower income countries) have very limited therapeutic options and can be considered as “therapeutic orphans.” Collectively, rare and neglected diseases are estimated to affect nearly 2 billion people worldwide – about 300 million people are estimated to be affected by rare diseases and 1.7 billion by neglected tropical diseases.^{2,3} However, it is reported that only <5% of rare diseases and a limited number of neglected diseases have therapeutic options available.^{4,5} That is, even though one in four people globally are affected by these diseases, very limited therapeutic options exist for these patients. In this special issue, we focus on rare diseases to highlight challenges and opportunities in developing therapies for these diseases and showcase the current and future role of clinical pharmacology and translational sciences in addressing the challenges and taking advantage of the opportunities. Additionally, the American Society for Clinical Pharmacology & Therapeutics (ASCPT) 2024 Annual Meeting Award and State-of-Art lectures

summarized in this issue also highlight the challenges and opportunities in developing effective therapies for the neglected diseases (e.g., tropical diseases including tuberculosis) and neglected populations (e.g., pregnant women or breastfeeding mothers). Our intention for this special issue of *Clinical Pharmacology & Therapeutics (CPT)* is that we can all collectively learn from these examples and experiences to accelerate drug development for these therapeutic orphans (**Figure 1**).

There are a number of challenges in developing therapies for rare diseases. Because each rare disease afflicts only a small number of patients, the market size is relatively limited, and consequently, developing drugs for many of these diseases may not be considered as being commercially attractive. Additionally, most rare diseases are poorly understood because limited longitudinal natural history data are available, and consequently, more information on disease etiology, pathogenesis, genotype-to-phenotype correlation, disease progression, and outcome is needed. Furthermore, the small patient population size can lead to difficulties in enrolling sufficient numbers of patients in clinical

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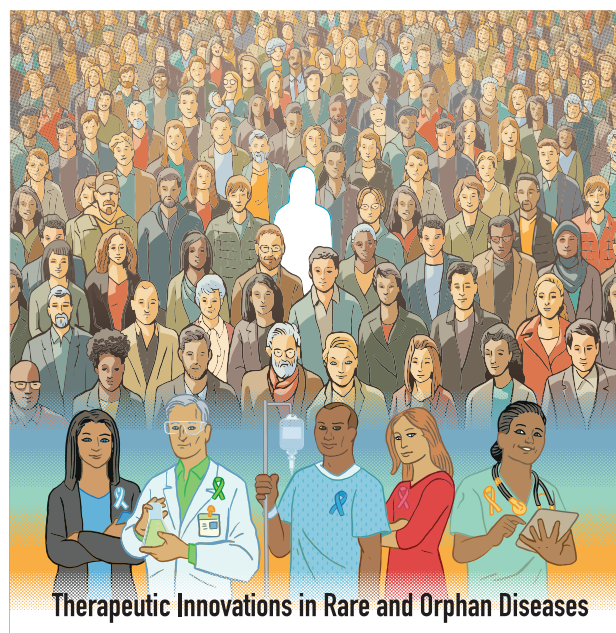


Figure 1 *Clinical Pharmacology & Therapeutics* December 2024 cover image: “Therapeutic Innovations in Rare and Orphan Diseases.”

trials and in generating adequate data to determine the benefit–risk profile of the drug. Compounding these challenges, there may be a lack of well-established biomarkers or animal models that can be leveraged during drug development. In sum, insufficient commercial interest and inadequate scientific research make it challenging to develop effective therapeutics for rare diseases.

Recognizing some of these challenges and limitations, several regulatory agencies and public-private partnerships have focused their efforts on rare and orphan diseases. Of note, recently, in the United States, the Food and Drug Administration (FDA) established the Rare Disease Innovation Hub to align regulatory efforts within FDA, identify and enable innovative approaches to treat rare diseases, and better serve the rare disease community.⁶ In 2022, the European Commission established the Rare Disease Moonshot with a goal to build rare disease centered public–private partnerships to aid optimization of translational research ecosystem, modernize clinical trials, and strengthen the infrastructure that can help shorten the path to diagnosis and subsequent treatment.⁷ In this issue, Ollivier et al.⁸ describe the purpose, strategies, and priorities of the Rare Disease Moonshot as well as the need for public-private collaborations to stimulate the integration of high-quality regulatory science into R&D, support the development of

large-scale sustainable infrastructures, and develop tools like the regulatory readiness scale. Also in this issue, Yu et al. describe the similarities and differences in postmarketing studies issued by the FDA and European Medicines Agency (EMA) while highlighting the need for harmonization between regulators and collaboration between the regulators and drug developers.⁹ The call for increased collaboration and harmonization between the FDA and the EMA is also echoed in a recent study by the National Academies that was commissioned by the FDA to focus on the processes for evaluating the safety and efficacy of drugs for rare diseases in the United States and the European Union.²

When developing therapies for rare diseases across different regulatory regions, as Larsson¹⁰ explains in a Mini Review in this issue, definitions matter. The definition of prevalence that deems a disease to be rare is different among different regulatory regions. This means that a disease that is considered rare in one region may not be considered rare in another region. In certain regions, rare disease may receive an orphan designation which then can confer additional incentives to the drug upon its approval; however, what the designation entails (e.g., see rituximab in¹⁰) and what the incentives are varies across regions. Another terminology that does not have a consistent definition across regions is the “ultra-rare” disease. Though

ultra-rare diseases are a subset of rare diseases that affect an exceptionally small number of individuals, the numbers are not codified in regulations as has been done for rare diseases. In literature, ultra-rare diseases are thought to affect fewer than 1 in 50,000 people.¹¹ Because an extremely limited number of patients are affected by the ultra-rare diseases, these diseases present unique challenges during diagnosis, drug development, and treatment. In terms of prevalence, even rarer are the “n-of-1” diseases that are thought to affect a single individual or at most a couple of individuals, and these are typically attributed to unique genetic variations. Though several “bespoke” therapies (e.g., Milasen) are being developed for these diseases, these therapies also face unique challenges during development and regulatory approval.¹²

In recent years, there has been an uptick in the approval of orphan drugs. In 2023 alone, more than half of all novel drugs and biologics approved by the FDA were intended to prevent, diagnose, or treat rare diseases.¹³ However, for some rare diseases even when multiple drugs have been approved, unmet medical need can still persist. For instance, several drugs for Duchenne Muscular Dystrophy (DMD) with different mechanisms of action (e.g., small molecule anti-inflammatory drugs, oligonucleotide therapeutics, gene therapy) have been approved either based on clinical outcomes or via the accelerated approval pathway based on dystrophin biomarker changes. In this issue, Konieczny describes the significant unmet medical need that still exists for DMD patients, given the disease's broad range of phenotypes and symptoms.¹⁴ Similarly for other rare diseases, Ullman et al.¹⁵ present data on a novel investigational agent with a mechanism of action (substrate reduction therapy) different from an already approved drug (enzyme replacement therapy) to address the unmet need in treating Pompe disease and Huang et al.¹⁶ review the progress in developing therapies for Huntington's disease by analyzing studies included in ClinicalTrials.gov. However, for many rare diseases, there are still no approved drugs. Using Shwachman–Diamond Syndrome as an example, a disease with no approved therapy, Hars and McReynolds¹⁷ share an approach for rare disease drug development that may be applicable for other rare diseases as well. They describe the need to develop non-clinical models, to develop/have dedicated ICD-10 code, to conduct longitudinal natural history studies (that can lead to a good understanding of the genetic etiology as well as clinical manifestation

of the disease), to collect patient-reported data, and importantly, to engage the patient community, researchers, and regulators to de-risk drug development.

Advances in genetic analysis have aided in rare disease diagnosis and drug development. In a Mini Review, Yee et al.¹⁸ describe the consequences of genetic mutations in vitamin B transporters expressed in the blood–brain barrier that result in rare neurologic diseases, and they highlight the potential development of pharmacologic treatments for these diseases. DeLeeuw et al.¹⁹ describe how emerging modalities, enhanced by the principles of translational science and clinical pharmacology, are addressing challenges associated with rare diseases using SLC6A1 pathogenic variants as an example. Hamdan et al.²⁰ use the Autosomal Recessive Cerebellar Ataxias (ARCAs) registry to point to how these data can facilitate planning future trials.

Registries and real-world data can be instrumental for rare disease drug development by contributing to our understanding of the disease. In a Mini Review, Weberpals and Wang²¹ summarize the contemporary methodological approaches for the comparison of external control arm analysis in rare diseases and outline some of the criticisms and paths forward based on learnings from emulation challenges of randomized trials using real-world data.

Given the need to embrace various data sources to develop a totality-of-evidence approach, clinical pharmacology is in a unique position to integrate different pieces of information coming from various non-clinical, clinical, and in silico sources. As Ryder posits in this issue, clinical pharmacology is an integrative discipline that can bring together our understanding of disease, pharmacology, response, and response variability to support the development of drugs for rare and ultra-rare diseases.²² There is also a vital role for clinical pharmacology in getting the dosage right, particularly in the era of precision medicines as discussed in a recent *CPT* special issue.²³ While Project Optimus aims to reform the dose optimization and dose selection paradigm for cancer therapeutics, getting the dosage right is also critically important for both oncological and non-oncological rare diseases. In this issue, Ahmed et al.²⁴ describe some of the challenges and opportunities in selecting appropriate doses for novel and emerging modalities, including enzyme replacement therapies, cell and gene therapies, and oligonucleotide therapeutics. They discuss how data from various sources

including animal models, ex vivo and in vitro pharmacology studies, model-based predictions, and real-world data can be integrated to select appropriate doses.

Particularly, modeling and simulation approaches can help overcome certain challenges seen in rare disease drug development as these exposure-based, biological, and pharmacostatistical models can combine data from pre-clinical and clinical sources. Mitra et al.²⁵ discuss the application of novel quantitative approaches such as quantitative systems pharmacology (QSP), disease progression modeling, artificial intelligence (AI), machine learning (ML), and clinical trial simulations in accelerating drug development for rare diseases. Focusing particularly on QSP, Neves-Zaph and Kaddi²⁶ discuss the current state of the art in the application of QSP for rare disease drug development, including generating virtual digital twins of actual patients, simulating mechanistically the disease progression of rare diseases, and accounting for the phenotypic heterogeneity. They describe how QSP virtual populations can be developed to be more diverse than those often enrolled in clinical trials for rare diseases (representing mild, moderate, and severe phenotypes) and support prediction of therapeutic effects in underrepresented patient subpopulations. Additionally, Hamdan et al.²⁰ show how analyses of natural history data from ARCA registry can better inform trial designs by allowing for more effective characterization of disease progression.

Adding to the complexity, nearly half the rare diseases are pediatric rare diseases²⁷. To enroll children in clinical trials, the general expectation is that the potential treatment should provide a prospect of direct benefit. This unique setting (i.e., children with rare diseases) underscores the importance of leveraging clinical pharmacology principles and tools at our disposal. We can integrate knowledge of disease similarity between children and adults (when available) as well as physiological differences between the two populations to evaluate the safety and effectiveness of the investigational drug in children with rare diseases. In this issue, Krishna et al.²⁸ summarize the pharmaceutical industry experience in developing drugs for pediatric rare diseases focused on biomarkers and surrogate endpoints, statistical and development considerations, modeling and simulation, and public-private partnerships. They also highlight opportunities related to using master protocols, end-to-end quantitative integration, and sharing of trial level placebo data to understand

disease progression. Readers are referred to this White Paper and the one from Ahmed et al.²⁴ for further information on challenges and opportunities in the development of therapeutics for pediatric rare diseases.

Apart from rare diseases, neglected diseases and neglected populations often become therapeutic orphans. In a Perspective in this issue, Attipoe describes the role and contributions of Drugs for Neglected Diseases initiative (DNDi), a non-profit organization that has focused on developing new treatments for neglected diseases focused on patients in Africa, Asia, and Latin America.²⁹ In a Mini Review, Waitt et al.³⁰ expand on the 2024 Dolores Shockley Award lecture to discuss the ethical imperative to include women of child-bearing potential, pregnant, and breastfeeding individuals in clinical trials including pharmacokinetic studies, if there is an expectation that this patient subpopulation will use the drug. They highlight the importance of community engagement and capacity building within local communities. Mulubwa and Chibale³¹ highlight the need to build models while considering populations not typically enrolled in biomedical research in order to design doses tailored to that specific population. They describe how leveraging in vitro liver subcellular fraction data from Africans, incorporating information on African genetic variants (including considering the frequency of AI-predicted African prevalent drug-metabolizing gene variants to account for pharmacogenetic diversity across the continent), and including in vitro Mtb drug metabolism kinetic data can be used to promote personalization of therapeutics for tuberculosis, a neglected disease with great unmet medical need.

THERAPEUTIC ORPHAN, NO MORE—A CALL TO ACTION

Patients with rare and neglected diseases often face a long, difficult, and expensive journey to diagnosis and subsequent treatment. As patient and patient advocates share in this issue, it takes a village to develop drugs for these diseases.^{17,19} Academic institutions, biopharmaceutical companies, patients, patient advocacy groups, regulatory agencies, and healthcare providers will all need to join forces in advancing the treatment of these therapeutic orphans (Figure 1). Addressing the challenges of rare and neglected diseases requires a united effort across multiple disciplines. We call upon the clinical pharmacology and translational science community to collaborate across sectors

and disciplines so that we can collectively transform the landscape of rare and neglected diseases, offering hope to millions of patients worldwide.

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CONFLICT OF INTEREST

Islam Younis is an employee of Merck and Co. Inc may own stocks in Merck and Co. Inc. Ya-Feng Wen is an employee of Gilead Sciences and may own stocks in Gilead Sciences. All other authors declare no competing interests for this work.

DISCLAIMER

Anuradha Ramamoorthy is currently serving on the ASCPT Board of Directors. This article reflects the views of the author and should not be construed to represent the views of FDA.

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1. The Lancet Global Health. The landscape for rare diseases in 2024. *Lancet Glob. Health* **12**, e341 (2024).
2. National Academies of Sciences, Engineering, and Medicine. 2024. Regulatory Processes for Rare Disease Drugs in the United States and European Union: Flexibilities and Collaborative Opportunities. Washington, DC: The National Academies Press.
3. Global Report on Neglected Tropical Diseases 2023 (World Health Organization, Geneva, 2023). <<https://www.who.int/teams/control-of-neglected-tropical-diseases/global-report-on-neglected-tropical-diseases-2023>>. Accessed September 2024.
4. Fermaglich, L.J. & Miller, K.L. A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the orphan drug act. *Orphanet J. Rare Dis.* **18**, 163 (2023).
5. World Health Organization. Neglected tropical diseases: treating more than one billion people for the fifth consecutive year. <<https://www.who.int/news/item/16-07-2020-neglected-tropical-diseases-treating-more-than-one-billion-people-for-the-fifth-consecutive-year>>. Accessed September 2024.
6. FDA Rare Disease Innovation Hub to Enhance and Advance Outcomes for Patients. <<https://www.fda.gov/news-events/fda-voices/fda-rare-disease-innovation-hub-enhance-and-advance-outcomes-patients>>. Accessed September 2024.
7. Rare Disease Moonshot <<https://www.rarediseasemoonshot.eu/news/translational-research-needs-recommendations/>>. Accessed September 2024.
8. Ollivier, C. et al. The rare disease moonshot: paradigms shift, translational medicine, and regulatory science for the World's rarest conditions. *Clin. Pharmacol. Ther.* **116**, 1387–1390 (2024).
9. Yu, J.H., Lee, S., Kim, Y.J., Kim, W.Y., Lee, M.J. & Kim, Y. Assessing post-marketing requirements for orphan drugs: a cross-sectional analysis of FDA and EMA oversight. *Clin. Pharmacol. Ther.* **116**, 1560–1571 (2024).
10. Larsson, K. What Is Rare and What Is Orphan? A Guide to the Regulatory Terminology. *Clin. Pharmacol. Ther.* **116**, 1395–1397 (2024).
11. Harari, S. Why we should care about ultra-rare disease. *Eur. Respir. Rev.* **25**, 101–103 (2016).
12. Pacanowski, M., Vitarello, J., Hyun, I., Yu, T. & Zineh, I. A multistakeholder perspective on advancing individualized therapeutics. *Clin. Pharmacol. Ther.* **114**, 994–1001 (2023).
13. FDA Novel Drug Therapy Approvals for 2023 <https://www.fda.gov/drugs/novel-drug-approvals-fda/novel-drug-approvals-2023>. Accessed September 2024.
14. Konieczny, P. Systemic treatment of body-wide Duchenne muscular dystrophy symptoms. *Clin. Pharmacol. Ther.* **116**, 1472–1484 (2024).
15. Ullman, J. et al. First-in-human evaluation of safety, pharmacokinetics and muscle glycogen lowering of a novel glycogen synthase 1 inhibitor for the treatment of Pompe disease. *Clin. Pharmacol. Ther.* **116**, 1580–1592 (2024).
16. Huang, C., Zheng, X., Yan, S. & Zhang, Z. Advances in clinical therapies for huntington's disease and the promise of multi-targeted/functional drugs based on Clinicaltrials.gov. *Clin. Pharmacol. Ther.* **116**, 1452–1471 (2024).
17. Hars, E.S. & McReynolds, L.J. From challenge to opportunity: how Shwachman–Diamond syndrome became a promising target for therapy development. *Clin. Pharmacol. Ther.* **116**, 1377–1380 (2024).
18. Yee, S.W., Wang, J. & Giacomini, K.M. Rare diseases linked to mutations in vitamin transporters expressed in the human blood–brain barrier. *Clin. Pharmacol. Ther.* **116**, 1513–1520 (2024).
19. DeLeeuw, M.B., Tiller, J., Kang, J.-Q. & Freed, A. Ongoing pharmacological developments in SLC6A1 research & treatment. *Clin. Pharmacol. Ther.* **116**, 1381–1384 (2024).
20. Hamdan, A. et al. Longitudinal analysis of natural history progression of rare and ultra-rare cerebellar ataxias using item response theory. *Clin. Pharmacol. Ther.* **116**, 1593–1605 (2024).
21. Weberpals, J. & Wang, S.V. External controls to study treatment effects in rare diseases: challenges and future directions. *Clin. Pharmacol. Ther.* **116**, 1521–1524 (2024).
22. Ryder, S. Integrated applied clinical pharmacology in the advancement of rare and ultra-rare disease therapeutics. *Clin. Pharmacol. Ther.* **116**, 1485–1495 (2024).
23. Minichmayr, I.K., Shebley, M., van der Graaf, P.H. & Venkatakrishnan, K. Getting the dosage right: a vital role for clinical pharmacology in the era of precision medicine. *Clin. Pharmacol. Ther.* **116**, 491–496 (2024).
24. Ahmed, M.A. et al. Getting the dose right in drug development for rare diseases:

- barriers and enablers. *Clin. Pharmacol. Ther.* **116**, 1412–1432 (2024).
25. Mitra, A. et al. New horizons of model informed drug development in rare diseases drug development. *Clin. Pharmacol. Ther.* **116**, 1398–1411 (2024).
 26. Neves-Zaph, S. & Kaddi, C. Quantitative Systems Pharmacology Models: Potential Tools for Advancing Drug Development for Rare Diseases. *Clin. Pharmacol. Ther.* **116**, 1442–1451 (2024).
 27. Batshaw, M.L., Groft, S.C. & Krischer, J.P. Research into rare diseases of childhood. *JAMA* **311** (2014). <https://doi.org/10.1001/jama.2013.285873>.
 28. Krishna, R., Sebastien, B., Corriol-Rohou, S., Cheung, S.Y.A., Liu, J. and Suryawanshi, S. Pediatric rare diseases development in the pharmaceutical industry: an international consortium for innovation and quality in pharmaceutical development, clinical pharmacology leadership group-pediatrics working group, rare diseases subteam whitepaper examining the current landscape and recommendations for the future. *Clin. Pharmacol. Ther.* **116**, 1433–1441 (2024).
 29. Attipoe, D. The promise of health for all: a collaborative model to close treatment gaps for neglected diseases **116**, 1385–1386 (2024).
 30. Waitt, C., Asiimwe, S.P., Ojara, F.W., Nakijoba, R., Kawuma, A.N. & Castelnuovo, B. Attaining equity of access to research: perspective on research in pregnancy and breastfeeding following Dolores Shockley lecture at ASCPT2024. *Clin. Pharmacol. Ther.* **116**, 1506–1512 (2024).
 31. Mulubwa, M. & Chibale, K. Model-informed approaches to optimizing therapeutics in the African patient populations. *Clin. Pharmacol. Ther.* **116**, 1391–1394 (2024).