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ADVANCING RARE DISEASE DRUG DEVELOPMENT THROUGH REGULATORY REFORM

Policy Recommendations to Mitigate Unintended Barriers and Bring Rare Disease Treatments to Patients

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CONTENTS

EXECUTIVE SUMMARY

Despite the tremendous progress in rare disease drug development, the burden of rare disease remains enormous. As the science continues to evolve, so too must the regulatory environment. The U.S. Food and Drug Administration (FDA), legislators, drug developers, patients, and other stakeholders must work together to ensure the health care environment is prepared and suitable for advancing the medical breakthroughs for the next generation. This will require broader stakeholder outreach to continue to gain knowledge about rare diseases and education to raise awareness. Similarly, federal legislators should bolster incentives for rare disease drug development by maintaining and expanding the Rare Disease Priority Review Voucher program as well as tax credits for drug developers as established in the Orphan Drug Act. Regulators, meanwhile, should consider establishing a Rare Disease Center of Excellence, as well as establish a special engagement pathway to provide iterative feedback to rare disease drug developers to reduce uncertainty and spur development. Enacting these recommendations as well as others outlined below will help to speed the development, review, and access to new products for unmet medical needs. Implementing the appropriate incentives, proper tools, and sufficient funding to develop cures for rare diseases will benefit the millions of people diagnosed with one of the thousands of rare diseases without treatment options.

SUMMARY OF POLICY RECOMMENDATIONS

TOPIC	PROPOSAL	RECOMMENDATION
Enhance Incentives for Rare Disease Drug Development	Enhancements to the Orphan Drug Act	Maintain the tax credit incentive to ensure potential new indications can be realized with each approved drug. Increase funding and expand availability of grants to promote research and development of therapies to treat rare diseases.
	Maintain and Encourage the Use of the Accelerated Approval Pathway	Encourage the use of the accelerated approval pathway to a broader set of disease areas to provide greater opportunities for rare disease drug development and benefit more patients.
	Ensure Regulatory Integrity and Maintain Oversight of the Accelerated Approval Pathway	Strictly enforce post-market requirements to ensure the integrity and reputation of pathway is maintained by all stakeholders.
	Promote Greater Transparency of Accepted Surrogate Endpoints	Develop a public framework and report of validated surrogate endpoints to increase transparency and guide sponsors in development.
	Make Permanent the Voucher Program for Pediatric Rare Diseases	The pediatric rare disease Priority Review Voucher program should be made permanent and expanded to include adult rare diseases that are without treatments or require additional research.
Facilitate Greater Engagement Between Rare Disease Drug Sponsors and FDA Regulators During Drug Development	Establish a Rare Disease Center of Excellence (COE)	Establish a Rare Disease COE to facilitate greater regulatory efficiency and consistency for rare diseases.
	Ensure Ongoing Dialogue Throughout the Review Process	Establish a special engagement pathway for rare diseases that includes shortened timelines for regulatory feedback, additional milestone meetings to ensure sufficient time for discussion of issues, and opportunities for informal touchpoints to reduce uncertainty and risk during development.
	Leverage Outside Expertise in Rare Disease and Data Science, Especially the Patient Experience	Enable patients, caregivers, academia, health care providers and patient advocacy organizations to provide recommendations on focus areas for innovation, policies, and guidance related to the utilization of patient experience data.
	Promote Global Harmonization and Collaboration	FDA and global regulators will work together to harmonize rules for clinical trials targeting rare diseases.
Address Clinical Trial Design, Regulatory Flexibility and Leverage Existing Opportunities	Address Clinical Trial Enrollment Challenges	Utilize digital health technologies to enable the use of decentralized clinical trials and promote greater socioeconomic diversity among the clinical trial population.
	Utilize Existing Opportunities	Increase the use and regulatory acceptance of novel drug development tools and approaches, with consistent application across therapeutic areas and global regions.
	Provide Flexibility in Regulatory Review	Provide a framework to help establish efficacy endpoints for diseases with slow progression, small patient populations, and/or where the causes of the disease may not be known. Create an FDA priority review pathway for supplements for rare disease indications.
Rare Disease Cures Accelerator and Natural Studies	Strengthen and Support the Cures Accelerator and Study Design Efforts	Utilize new technology and break down data siloes to bolster the ability to conduct robust natural history studies to get a complete and personal understanding of these diseases.

FDA: ADVANCING RARE DISEASE DRUG DEVELOPMENT

Policy Recommendations to Mitigate Unintended Barriers and Bring Rare Disease Treatments to Patients

Nearly 30 million people — many of them children — are living with a rare disease in the United States.[1] A rare disease is defined as a condition that affects less than 200,000 people, making these conditions very difficult to research, diagnose, and treat.[2] According to the National Institutes of Health, there are more than 7,000 rare diseases,[3] with new estimates nearing 11,000 rare diseases.[4] Of these, only about 5% have an available treatment option, placing a significant health and economic burden on people living with a rare disease, their caregivers, and society.[5]

Several factors inherent to the nature of rare disease treatments play into this burden. First, due to the limited knowledge of rare diseases, there are few specialists who can readily diagnose and treat patients. This scarcity can delay diagnosis — which on average takes 4.8 years — and necessitates new or additional testing, procedures, and even hospitalization, delaying treatment and compounding the economic burden on patients from all walks of life.[6] Second, the indirect effects, such as the inability to work, time for travel to and from testing or treatments, and the unique needs of living with a rare condition weigh heavily on individuals. These factors are not insignificant; in the United States, the economic impact of the medical and indirect costs totaled $966 billion.[7] Finally, given the small patient populations, specialized research requirements, and lack of tools necessary to evaluate the effect of potential treatment in a clinical context, developing treatments for rare diseases is particularly challenging. The multitude of challenges unique to rare diseases requires tailored policy solutions that ultimately help patients.

Improving the regulatory environment for the development of rare disease treatments is a principal method to alleviate these burdens. Developing a broader understanding of how to diagnose and treat rare diseases, increasing partnerships and dialogues with patients and their caregivers, working more collaboratively with the U.S. Food and Drug Administration (FDA), and ensuring an environment supportive of innovation are key steps that can bring lifesaving and life-sustaining medicines to patients more efficiently and effectively.

THE RARE DISEASE POLICY LANDSCAPE:

How Far We've Come and How Far We Need To Go

> The rare diseases treatment community is proud of the work it has accomplished over four decades. The appropriate collection of policies can make the next four decades even better.

Given the lack of treatments available for thousands of rare diseases, there is a clear need to incentivize research and development in this area. Through federal legislation, regulation, and other policies and programs, significant scientific strides have been made, with FDA approving more than 6,000 orphan drug indications for more than 550 distinct products.[8] Most of these federal efforts have worked effectively to spur research into rare disease. As the science continues to evolve, so too must those efforts. As a key partner in the regulation and approval of rare disease treatments, FDA has taken significant steps in developing programs and initiatives in this area. Understanding the scope and breadth of these programs to date and considering policy recommendations will enable stakeholders to help FDA break down unintended barriers that slow scientific breakthroughs and impede access to life-changing medicines for patients.

FEDERAL LEGISLATION

Orphan Drug Act

In the rare disease policy space, all roads invariably lead back to the Orphan Drug Act's (ODA) enactment. In 1983, Congress passed the ODA to amend the Food, Drug, and Cosmetic Act — the U.S. law governing the approval of medicines — to include a definition of a rare disease or condition and to establish financial incentives to encourage the development of rare disease treatments, also known as orphan products. The ODA defines a rare disease as any disease or condition that

> **"...affects less than 200,000 people in the United States, or affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."[9]**

In addition to defining a rare disease in statute, policymakers purposefully built financial incentives into the ODA to enable access to these medicines, recognizing the challenges and risks in developing treatments for small patient populations. In particular, products developed for rare disease indications are eligible to receive an Orphan Drug Designation from FDA. This designation provides the drug developer, or company that submits an application for FDA review, with several important incentives:

- **ORPHAN DRUG TAX CREDIT.** The sponsor company receives a 25% tax credit to offset research and development costs (qualified clinical testing). It is intended to incentivize biotechnology companies to invest in the development of treatments that are not otherwise economically viable.
- **USER FEE WAIVER.** The application fee that is required for an FDA review (over $3.1 million,[10] depending on the type of clinical data required, in 2022) is waived for sponsors.
- **MARKET EXCLUSIVITY.** A new chemical entity typically has five years of market exclusivity, a guaranteed time period without generic drug competition for that indication. The orphan drug designation grants the sponsor company seven years of market exclusivity.
- **RESEARCH GRANTS.** Sponsors may be eligible for grants via FDA's Office of Orphan Products Development (OOPD), which determines whether medical products meet the criteria for certain incentives and provides funding through grants for research on rare diseases.[11] These grants are funded through Congressional appropriations and are used for clinical trials and natural history studies that advance rare disease medical product development and to develop nonprofit consortia to facilitate pediatric medical device development. In 2021, FDA awarded 11 different grants totaling $25 million to "meet the future and current health needs of those who suffer from a rare disease."[12]

The ODA's incentives have been essential in spurring rare disease drug development. Prior to its enactment in 1983, there were only 38 drugs approved to treat rare diseases;[13] however, FDA has approved over 550 individual drugs for more than 1,000 individual orphan drug indications and more than 6,000 orphan drug designations in the time since.[14] The ODA also has spurred the growth in research in rare diseases and the establishment of companies dedicated to helping patients to receive the medicines they need. The ODA's policies should be protected and enhanced so that innovators — and ultimately patients — can continue to benefit from its incentives and effects.

POLICY RECOMMENDATION — **Protecting Policies That Work:** Preserve and Enhance the ODA's Incentives

With leaps in scientific knowledge, such as genomic sequencing, there has been a tremendous increase in the number of treatments being submitted to FDA for ODA designation; more than 220 orphan drug products have been approved by FDA during the last two years alone. This growth in the number of products, along with the 40-year anniversary of the ODA, has sparked renewed interest from policymakers in making changes to the orphan drug financial incentives.

MAINTAIN THE ORPHAN DRUG TAX CREDIT

The 25% Orphan Drug Tax Credit has been continually at risk in recent Congressional negotiations to fund other policies, but the consequences of further limiting the credit negates the ODA's original purpose of bringing more treatments to rare disease patients faster. Specifically, policymakers have suggested narrowing the rare disease tax credit's availability to a subset of rare disease treatments, such as only for a product's first approved indication.[15] Yet policies that would arbitrarily restrict the Orphan Drug Tax Credit to only include qualified clinical testing expenses for the first approved orphan use or indication of a new drug would lead to less drug development as a drug developer may be less inclined to fund additional trials. If this limitation were enacted, the tax credit would not be available for clinical testing expenses beyond the first use or indication, for example, to evaluate whether an already approved therapy can treat children as well as adults, or whether an already approved therapy for one condition can treat additional rare conditions.

When a drug is approved, it has been deemed as a safe and effective treatment option for one disease. Though a company still must invest significantly to establish the drug's safety and efficacy for each additional use or patient population, it is both prudent and typical to determine if the drug is applicable to other disease states. Approximately 25% of rare disease therapies have been approved to treat two or more orphan indications.[16] Maintaining the tax credit is a vital incentive to ensure not only rare disease research for diseases without treatment, but also for new potential rare disease indications for existing drugs.

INCREASE FUNDING FOR OOPD GRANTS

The FDA's OOPD grants have spurred ongoing innovation into rare diseases, with over 700 grants resulting in more than 70 product approvals since the program's inception.[17] Increased funding and expanded availability of these grants can go even further to promote research and development of therapies to treat rare diseases.

Accelerated Approval Pathway

For rare disease patients, time is always of the essence. Many rare diseases progress quickly and, moreover, delayed treatment only increases the economic burden on families. However, many patients with rare conditions have obtained faster access to treatments that provide meaningful advantages through FDA's Accelerated Approval pathway. Congress established the pathway in 1992 to expedite the approval and availability of drugs and biologics intended to treat serious and life-threatening diseases and conditions for which there are unmet medical needs. Products seeking Accelerated Approval rely on surrogate endpoints, or markers, "such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit."[18,19] These endpoints can be measured effectively over a shorter period of time in smaller studies.

By comparison, FDA regulations require substantial evidence to support a sponsor's claims of effectiveness for new drugs. As defined by the Food, Drug, and Cosmetic Act, substantial evidence is "evidence consisting of adequate and well-controlled investigations"[20] that use a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. Historically, the gold standard of clinical trial design has been a double-blinded, randomized, placebo-controlled study.[21] For rare diseases, which are often life-threatening, it is not ethical to conduct a clinical trial with a placebo control arm, and there are often few patients who could be enrolled in a trial. Thus, approval based on surrogate endpoints is a vital approach for certain rare disease treatments.

Following Accelerated Approvals based on surrogate endpoints, drug developers also are required to conduct studies — phase 4 confirmatory trials — to confirm the clinical benefit of the medicine. Once confirmed, the FDA will grant traditional approval for the treatment. Since its inception, FDA has approved 282 products through the Accelerated Approval pathway, including numerous drugs for oncology, as well as for rare conditions like sickle cell disease, Fabry disease, and Duchenne muscular dystrophy.[22] A study published in ***Health Affairs*** that compared drugs approved from 1999 to 2012 through expedited versus conventional review processes found that drugs with an expedited review program offered greater health gains than drugs reviewed through a conventional process.[23] Similarly, researchers have recently estimated that 33% to 66% of products approved via the Accelerated Approval pathway may not be on the market at all due to prolonged development timelines and their associated impact on projected revenues.[24]

POLICY RECOMMENDATION — Give Patients the Gift of Time: Maintain and Encourage the Use of the Accelerated Approval Pathway Across Rare Diseases

Some policymakers have been considering changes to the Accelerated Approval pathway, which could potentially delay access to new treatments by requiring much longer timeframes for studying outcomes. The pathway should be protected to ensure that rare disease treatments, which have clinical study design limitations, can be reviewed in a flexible and efficient manner by FDA. The majority of the products approved under this pathway have been for oncology. However, the pathway's use should be expanded to a broader set of disease areas to provide greater opportunities for rare disease drug development to benefit even more patients. Policymakers and drug developers should educate FDA review staff on the benefits that this expedited pathway confers onto both developers and patients alike.

POLICY RECOMMENDATION — Ensure Regulatory Integrity and Maintain Oversight of the Accelerated Approval Pathway

While the Accelerated Approval pathway can benefit patients by ensuring earlier market access for new life-saving therapies, the pathway has been controversial due to delays in the completion of confirmatory studies and a failure to complete some studies by sponsors. A 2021 analysis of drugs approved via the Accelerated Approval pathway revealed that of this subset of drugs approved between 1992 and 2016, 76.5% of Accelerated Approvals were converted to traditional approvals, meaning that confirmatory, post-market commitments had been satisfied. These claims demonstrate the pathway's ability to bring drugs to market that otherwise would not reach patients, as well as result in traditional approvals following phase 4 studies.[25] Some payers have questioned the clinical benefit of drugs approved through this pathway. For example, the State of Oregon sought to deny Medicaid reimbursement of Accelerated Approval drugs under its extension of its Section 1115 Medicaid waiver.[26]

To address these issues, FDA needs to ensure that confirmatory trials are completed in a manner that is timely and considers the characteristics of a particular disease. During the development process it is important for sponsors and FDA to communicate and develop a post-market study plan that is tailored to each disease, specifically the disease progression.

As such, the FDA should create opportunities for sponsors to engage collaboratively to increase predictability of evidence requirements and how to best address uncertainty in these rare disease populations and programs at the post-marketing stage, leveraging sources of real-world data such as registries and other tools to render the efforts effective. Meanwhile, to ensure that both public and private payers do not deny coverage nor seek to reimburse these drugs at a lower percentage of reimbursement, a policy should be adopted requiring payers to fully cover these therapies, as was proposed in the Promising Pathways Act.[27]

POLICY RECOMMENDATION —
Promote Greater Transparency of Accepted Surrogate Endpoints

For rare diseases, sponsors using the Accelerated Approval pathway continually face a series of challenges in determining the appropriate efficacy endpoints resulting from the lack of regulatory precedent, limited understanding of the disease, and the small number of patients. FDA should provide a framework to help establish surrogate endpoints for diseases with slow progression, small patient populations, and/or where the causes of the disease may not be known. The qualification, validation, and continued public reporting of these endpoints could help advance rare disease drug development. The framework could provide a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process, while a public report of the accepted surrogate endpoints can lead to improved regulatory consistency, more acceptance among payers, and even greater utilization of the Accelerated Approval pathway.

Rare Pediatric Disease Voucher Program

In 2012, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA),[28] creating the Rare Pediatric Disease Priority Review Voucher (PRV) program. Under this program, a sponsor who receives an approval of a new drug or biologic for a rare pediatric disease, or a serious or life-threatening disease primarily affecting children, qualifies for a "voucher" from FDA. A sponsor can use the voucher to ensure FDA priority review (six months) for a future marketing application or sell it to another sponsor. The voucher only guarantees the timely review of the application and a decision by FDA, not an FDA approval. The FDA awarded 17 PRVs between 2014-2019. Of these designations, at least six rare disease PRVs have been redeemed,[29] and a number have been sold.[30,31] Congress must continually renew the PRV program before it expires in 2024, which creates uncertainty in the regulatory process.

POLICY RECOMMENDATION —
Create Permanent Solutions for Patients:
Remove the Sunset for the Voucher Program for Rare Pediatric Diseases and Expand to Include Adult Diseases

The current PRV program is set to expire, or sunset, in 2024 and must be renewed by Congress on a regular basis. Under the current statutory provisions, "after September 30, 2024, FDA may only award a voucher for an approved rare pediatric disease product application if the sponsor has rare pediatric disease designation for the drug, and that designation was granted by September 30, 2024."[32] Therefore, a company could receive a designation for a PRV from FDA, but the program might not exist when the PRV is awarded, creating business uncertainty. To fully optimize the PRV program, the incentive should be made permanent. In the interim, Congress and FDA should ensure that if the PRV program does sunset, previously awarded PRVs remain valid and applicable. Additionally, policymakers should consider expanding the voucher program to include adult rare diseases that are without treatments or require additional research.

FDA PROGRAMS AND INITIATIVES

Rare Disease Staffing Enhancements at FDA

FDA has committed to developing its expertise in rare diseases by building out the Rare Disease Program. Over the past 10 years, FDA has increased the number of staff on the Rare Disease Program team in the Center for Drug Evaluation and Research (CDER) and established a Center for Biologics Evaluation and Research (CBER) Rare Disease liaison within the Office of the Center Director. The Rare Disease team is responsible for the development and dissemination of guidances and policies related to rare diseases, engaging with the biopharmaceutical industry and patient advocacy organizations, and conducting internal trainings for product reviewers to promote best practices and regulatory consistency.

Over the past five years, the Rare Disease Program team has been further integrated into CDER review teams in order to continue to familiarize review staff with the challenges associated with rare disease applications and the "flexible and feasible approaches to studying and reviewing such drugs."[33]

During the last decade, the Rare Disease Program team achieved a number of milestones that have improved regulatory consistency at the FDA, further developed the FDA's rare disease policy framework, and publicly elevated the challenges manufacturers and researchers face in rare disease drug development. For example, the Rare Disease Program team contributed to the 2015 draft guidance, ***Rare Diseases: Common Issues in Drug Development***, and hosted numerous public workshops and events, including a number of Rare Disease days. In 2020, CDER's Rare Disease Team consulted on the majority of rare disease programs in CDER's Office of New Drugs (OND), which houses all of the drug review divisions; staffed Rare Disease Cluster meetings with the European Medicines Agency (EMA) and Health Canada; and hosted the internal training, "Advancing Rare Disease Drug Development Through Innovative Thinking and Collaboration."[34]

The Rare Disease Program team also is responsible for the Accelerating Rare disease Cures (ARC) Program, launched in May 2022. ARC "harnesses CDER's collective expertise and activities to provide strategic overview and coordination of CDER's rare disease activities."[35] Its goal is to accelerate the development of effective and safe treatment options addressing the unmet needs of patients with rare diseases.

In 2021, FDA launched the Rare Disease Drug Development Council within OND to provide a forum to discuss cross-cutting issues and applications pertinent to rare disease drug review programs. Meanwhile, to support the review of biological products for rare disease, FDA participated in 166 outreach activities, including drafting presentations, publications, and abstracts.[36]

Collectively, FDA's efforts have enhanced the agency's ability to review products for rare diseases, raised awareness among broader health stakeholders and set clearer expectations for drug developers, lessening the uncertainty around the review process.

POLICY RECOMMENDATION — Empowering the Best: Establish a Rare Disease Center of Excellence at FDA

While FDA has made substantial strides in developing and strengthening the review function for rare diseases, many of these enhancements have been made within CDER, specifically OND. The Rare Disease Program team, the ARC, and the Rare Disease Drug Development Council are all housed within CDER, and this current structure does not consider nor address the diversity of rare diseases and the wide array of treatments and technologies being developed to treat these diseases. Similarly, due to CDER and OND's organizational structure according to human body systems, there are products for several rare diseases, such as neurological and hematological rare diseases, that are not reviewed by the Division of Rare Diseases and Medical Genetics (DRDMG), housed in the Office of Rare Diseases, Pediatric, Urologic, and

Reproductive Medicine (ORPURM). Bringing the review of all of these applications under one office would help generate regulatory efficiency as well as greater regulatory consistency.

It is imperative for FDA to take a cross-center approach to rare diseases. A Rare Disease Center of Excellence (COE) that encourages collaboration between CDER, CBER, and the Center for Devices and Radiological Health is needed to help FDA prepare for the next generation of rare disease therapies, which include cell and gene modalities, as well as digital devices and diagnostics.

POLICY RECOMMENDATION — Promoting Coordination: Facilitate Greater Engagement Between Rare Disease Drug Sponsors and Regulators During Drug Development

FDA SHOULD ENSURE ONGOING DIALOGUE WITH SPONSORS THROUGHOUT THE REVIEW PROCESS

To ensure decisions are not made in a vacuum, FDA has made a concerted effort to enhance the knowledge and number of staff engaged in rare disease programs. Additionally, FDA is obligated to provide advice on clinical and non-clinical design for orphan drugs;[37] however, it is important to further break down communications barriers between the agency and rare disease drug sponsors so that questions can be appropriately considered and addressed throughout all phases of the review and approval process. Given the unique nature of rare diseases, there is a need for continual and timely feedback from FDA, especially during the early drug development phase to aid with identifying appropriate endpoints, utilizing clinical trials for small populations, and addressing other complex issues that arise during development and review. Early and ongoing consideration of these issues provides sponsors the opportunity to efficiently and effectively advance new treatments for unmet or underserved medical needs.

Given the costs of developing rare disease products and the limited market they serve, it is not financially feasible to proceed throughout each phase of drug development without the continuous input and approval of regulators. FDA has established new pathways for promising therapies or specialized products that offer additional opportunities for sponsors to engage with regulators during development. The Breakthrough Therapy (BT) designation is for drugs intended to treat serious conditions where preliminary data indicate a substantial improvement over existing therapies.[38] In the program's first 10 years, the BT designation led to over 250 approvals of new products.[39] Similarly, FDA established the Regenerative Medicine Advancement Therapy (RMAT) designation for regenerative medicines, or cell therapies, therapeutic tissue engineering products, and cell and tissue products, that address unmet needs for serious and life-threatening diseases.[40] Both BT and RMAT are similar in that they provide sponsors with opportunities for early interaction with reviewers, intensive development guidance from FDA starting as early as Phase 1, and engagement with senior management at FDA throughout the development process. Similar to these two expedited programs, a special engagement pathway also could be established for rare diseases that includes shortened timelines for regulatory feedback, additional milestone meetings to ensure sufficient time for discussion of issues, and opportunities for informal touchpoints to reduce uncertainty and risk during development, essentially expanding the BT and RMAT framework to rare diseases.

FDA SHOULD LEVERAGE OUTSIDE EXPERTISE IN RARE DISEASE AND DATA SCIENCE, ESPECIALLY THE PATIENT EXPERIENCE

FDA utilizes a Patient-Focused Drug Development Approach to facilitate the incorporation of patient input into decision-making. This approach is used "to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation."[41] Incorporating patient experiences

and providing additional guidance on rare diseases is integral to expanding scientific knowledge and understanding of rare diseases. Rare disease patients and caregivers are the strongest advocates for their needs and the primary source of information and data on treatments for their diseases. There needs to be focused regulatory support for incorporating patient experiences and a willingness to collaborate with the rare disease community to advance rare disease drug development.

There is more that can be done, especially by broadening outreach to outside voices and experts. Patients, caregivers, academia, health care providers, and patient advocacy organizations have unique perspectives and experiences that can better inform the benefit-risk profile of rare disease products. These external stakeholders can help identify and address barriers to development and provide solutions to promote greater access to rare disease treatments. Specifically, they could work with and through the FDA Rare Disease Council to provide recommendations on focus areas for innovation, policies, and guidance related to the utilization of patient experience data as well as elevate rare disease issues at FDA Advisory Committee meetings.

FDA SHOULD TAKE A LEADING ROLE TO PROMOTE GLOBAL HARMONIZATION, COLLABORATION, AND RELIANCE

FDA also could tap into expertise across the globe, particularly on clinical trials. Many rare diseases have patient populations that are too small to conduct a clinical trial in a single regulatory jurisdiction. Global harmonization and collaboration between regulators could enable patients from across geographical regions to participate in clinical trials, making research and development more viable. Although there are legislative and logistical obstacles, FDA and other regulatory bodies such as the European Medicines Authority, Health Canada, the United Kingdom Medicines and Healthcare products Regulatory Agency, and Japan's Pharmaceuticals and Medical Devices Agency can work together to harmonize rules for clinical trials targeting rare diseases. For example, FDA could assemble a global council on rare diseases comprising regulatory authorities from around the world to address common rare disease drug development and regulatory issues and draft harmonized recommendations and solutions. Similarly, FDA could spearhead an initiative to establish "Clinical Trial Sites of Excellence" and construct a standing clinical trial infrastructure responsive to the unique needs of rare disease drug development. If successful, these strategies could lead to a more streamlined and efficient development process of new rare disease treatments to enable timelier approvals and access to treatment options throughout the world. We also encourage the FDA to explore and facilitate reliance in marketing authorization applications globally based on the U.S. approval, particularly in emerging countries, to ensure patients globally have the fastest access possible to life-saving medicines.

Innovative Clinical Trial Designs

To address the difficulties in studying medical products for small patient populations with rare diseases, FDA has demonstrated a commitment to regulatory flexibility, encouraging the use of innovative trial designs. For example, FDA's draft guidance, ***Rare Diseases: Common Issues in Drug Development***,[42] notes that when concurrent controls are impractical or unethical — which is often the case in the study of rare diseases — historical controls, or the use of historical data to substitute for an active control arm, is permissible.

FDA's 2019 draft guidance, ***Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products,*** confirms that support for a drug's effectiveness can be generated from external controls if certain criteria are met.[43] This flexibility has been effectively utilized by sponsors studying treatment for rare disease; a 2021 peer-reviewed study identified 36 products with rare disease indications wherein the approval relied upon a trial using an external control.[44]

In addition, FDA has advanced a number of programs and initiatives to support innovative approaches to evidence generation for small patient populations, such as:

- **REAL WORLD EVIDENCE (RWE) PROGRAM.** FDA is developing a framework that provides sponsors the ability to establish safety and efficacy of a drug based on data derived from sources other than clinical trials, including electronic health records (EHR) data, registry data, and medical claims and billing data. Considering challenges in patient recruitment for clinical trials, this program increases the ability of manufacturers to use new data sets to study innovative products for rare disease indications.
- **COMPLEX INNOVATIVE DESIGN PILOT PROGRAM.** This pilot program facilitates the use of novel trial designs, such as adaptive trials or trials that incorporate specific approaches to data analysis, such as Bayesian elements.
- **THE RARE DISEASE ENDPOINT ADVANCEMENT PROGRAM IN THE PRESCRIPTION DRUG USER FEE ACT (PDUFA) VII.** This program is intended to encourage collaboration between FDA and sponsors on the development of endpoints for rare diseases. Ideally, this program will spur the development of new methods to determine a rare disease drug's success at improving symptoms, many of which are difficult to measure.

POLICY RECOMMENDATION — Casting a Wide Net: FDA Should Address Clinical Trial Enrollment Challenges Inherent with Small Patient Populations

We can only treat what we can measure. While FDA has worked on making tools available to sponsors to help mitigate the challenges of recruiting participants for rare disease clinical trials, the biopharmaceutical industry is hampered by a lack of guidance from FDA on how to implement existing tools in trials. One particular tool, digital health technologies (DHTs), is "a system that uses computing platforms, connectivity, software, and/or sensors, for health care and related uses." A clinical investigation can use multiple DHTs to collect a range of information that may include clinical, physiological, psychological, behavioral, or functional data.[45] More importantly, DHTs can be utilized to collect data remotely during a trial, which alleviates the need for patients to be centrally located near a testing site and allows for more frequent and continuous data collection from trial participants. Although there is a strong desire to ensure greater diversity in clinical trials, with rare disease, there may be as few as one patient per testing site at each location across the country.

While DHTs enable the use of decentralized clinical trials and greater socioeconomic diversity among the clinical trial population, there is limited stakeholder experience with these novel approaches and a lack of predictability in utilizing them in drug

development programs for rare diseases. To enhance the efficiency of clinical trials in small and hard-to-study populations, methodologies for evaluation and validation of DHTs need to be formulated via collaboration between regulators and drug and biologic sponsors, with specific input and attention given to the experiences and expertise of rare disease product developers. In addition, more robust guidance and support from regulators is needed to help ensure standardization of processes and consistency of application across product types and therapeutic areas.

POLICY RECOMMENDATION — Unlocking Innovation Across the Rare Community: FDA Should Utilize Existing Opportunities

FDA provides regulatory flexibility for rare disease drug development due to the limited ability to design adequate and well-controlled studies to demonstrate the substantial evidence required for approval.[46] The increased use and regulatory acceptance of novel drug development tools and approaches, with consistent application across therapeutic areas and global regions, can significantly improve efficiency of the research and development process and ensure new rare disease medicines are available in a timely manner to meet patient needs.

The natural histories of rare diseases — how they progress over time, without treatment — are not well understood in most cases, and it is difficult to detect the rate of occurrence and variability. Utilizing real-world data (RWD) and real-world evidence (RWE), including patient registries, and using complex trial designs can be effective at streamlining the development and availability of rare disease therapies. To enhance the effectiveness of RWD/RWE for rare disease development, the FDA must provide greater clarity on the types of data that are suitable and streamline the processes for submitting the data and evidence for review. Consistently using the same approach across therapeutic areas and products is also imperative to ensure predictability. Ultimately, there need to be greater assurances that the data will be accepted by FDA and used to make regulatory decisions.

Rare disease registries, which collect information related to patients, diseases, and/or conditions, can be useful tools to generate RWD/RWE. A registry can be established through state, federal, or non-profit channels and be used to enable or enhance the ability to connect researchers with patients and help connect potential clinical trial participants with new studies being conducted. Registries also can support the development of new therapies and generate patient experience data and patient-reported outcomes (PROs). The National Center for Advancing Translational Sciences at the National Institutes of Health (NCATS) provides information and guidance on setting up registries and collecting data;[47] however, this data may not be applicable to regulatory decision-making. Additional guidance and support from regulators are needed to expand the use of rare disease registries, where appropriate, and enable the collection of information about efficacy and safety of rare disease treatments.

Standard clinical trial designs are not always appropriate for diseases with small patient populations to generate adequate safety and efficacy data. Alternative approaches offer great potential to inform the efficacy and safety of rare disease treatments by reducing the size or number of trials, while also reducing development program time. Innovative trial designs can include complex adaptive designs, enrichment trials, multi-arm multi-stage trials, seamless trials, and N-of-1 studies. Drug developers can benefit from greater clarity on the development of alternative clinical trial designs and how they will impact regulatory decision-making. Innovative trial designs require an infrastructure effort that includes significant investment from multiple stakeholders. To be most effective, regulators, developers, and clinicians need to align on what constitutes a valid innovative trial design across therapeutic areas and product types.

Rare Disease Cures Accelerator and Natural History Studies

A key pillar in FDA's strategy to further enhance knowledge of rare diseases is the Rare Disease Cures Accelerator. Established in 2019, the Accelerator consists of two components: a data analytics platform, the Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP), and a core-set of patient-focused measures. The first component, RDCA-DAP, led by the Critical Path Institute (C-Path), is a secure centralized database that integrates and standardizes data from a wide array of global sources, including clinical trials, registries, natural history studies, electronic health records, and genomic databases, among others. The goal of RDCA-DAP is to "generate solutions to drug development bottlenecks"[48] by advancing the understanding of disease progression through developing longitudinal datasets, identifying novel biomarkers, or supporting new disease models.

The second component of the Rare Disease Cures Accelerator is the development of a core set of patient-focused clinical outcome measures and endpoints intended to be incorporated into rare disease drug development programs. The core patient-focused measures are developed by researchers and clinicians under the CDER-led grant program, Standard Core Clinical Outcome Assessments and their Related Endpoints.[49] This initiative has been essential in helping clinicians, sponsors, and regulators better understand how a patient experiences the progression of a number of rare diseases.

In May 2020, FDA issued a Request for Information (RFI) for a Rare Disease Clinical Trial Network, which the Agency suggested would be the third component of the Accelerator.[50] Per the RFI, FDA intends for the Rare Disease Clinical Trial Network to be a resilient global network that will improve the design, conduct, and completion of rare disease trials. FDA has not yet announced the next steps for this program.

FDA considers natural history studies to be the cornerstone of rare disease drug development, continually emphasizing their importance in gaining a full understanding of a rare disease. To underscore this point, FDA issued in March 2019 the draft guidance, ***Rare Diseases: Natural History Studies for Drug Development***.[51] The guidance notes the importance of natural history studies in identifying the relevant patient populations, understanding the current standard of care, and providing demographic data to support estimates of prevalence and disease characteristics. FDA also notes the important role natural history studies play in the identification and development of clinical outcome assessments, identifying and developing biomarkers, and running externally controlled studies.

POLICY RECOMMENDATION — Removing Firewalls, Implementing Collaboration: Strengthen and Support the Cures Accelerator and Study Design Efforts

Enhanced coordination and harmonization across FDA review centers is imperative to ensure consistency, efficiency, and predictability for product development and the utilization of innovative tools and approaches. Collaborative, multi-disciplinary programs aimed at cataloguing the variety of rare diseases and investigating the progression and patient experience are essential in advancing the rare disease knowledge base. Harnessing the power of technology and breaking down data siloes can bolster the ability to conduct robust natural history studies to get a complete and personal understanding of these diseases.

FDA programs such as the Rare Disease Cures Accelerator, as well as the Agency's policies and guidance documents on natural history studies and preferred study designs, are important contributions towards this effort, which need to be continuously strengthened, supported, and financed by government and the biopharmaceutical industry alike.

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FDA/REGULATORY ACRONYMS

ARC	Accelerating Rare disease Cures
BT	Breakthrough Therapy
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Reasearch
COE	Center of Excellence
DRDMG	Division of Rare Diseases and Medical Genetics
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
ODA	Orphan Drug Act
OND	Office of New Drugs
OOPD	Office of Orphan Products Development
ORPUM	Office of Rare Diseases, Pediatric, Urologic, and Reproductive Medicine
PRV	Priority Review Voucher
RDCA-DAP	Rare Disease Cures Accelerator-Data and Analytics Platform
RMAT	Regenerative Medicine Advancement Therapy
RWD	Real-World Data
RWE	Real-World Evidence