



October 31, 2024

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061,
Rockville, MD 20852.

Re: Docket No. FDA-2024-N-3528 for “Advancing Rare Disease Therapies Through an FDA Rare Disease Innovation Hub; Public Meeting; Request for Comments.”

To Whom It May Concern,

On behalf of patients and families impacted by rare diseases, the EveryLife Foundation for Rare Diseases is pleased to offer the following comments to inform the Food and Drug Administration’s implementation of the Rare Disease Innovation Hub.

The EveryLife Foundation for Rare Diseases is a 501 (c)(3) nonprofit, nonpartisan organization dedicated to empowering the rare disease patient community to advocate for impactful, science-driven legislation and policy that advances the equitable development of and access to lifesaving diagnoses, treatments, and cures. Our comments reflect the insights and experiences of our diverse coalition comprised of patient organizations, industry leaders, and other relevant stakeholders who together inform our policy efforts.

Since convening a series of townhall meetings to assess the rare disease community’s priorities -- followed by our Scientific Workshop in 2018 -- our community has advocated for the creation of an inter-center institute for rare diseases. Working with rare disease scientific, clinical, regulatory, and patient organization experts, our community laid out a vision [Attachment A] for the inter-center, or Rare Disease Center of Excellence, to serve as the FDA’s coordinating office for the optimization of rare disease expertise, processes, and engagement with rare disease stakeholders across all therapeutic areas including drugs, cell and gene therapies, and medical devices.

While we recognize that the Rare Disease Innovation Hub will not be a formal organizational unit, we believe that the Hub can achieve similar goals as the formal inter-center institute if its foundational documents, leadership structures, operational guidelines, and metrics for community impact are thoughtful, thorough, and transparent. In the comments below, we lay out high priority regulatory challenges for the Hub to address, projects and infrastructure for the Hub to prioritize, and suggestions for enhanced engagement and transparency that are fundamental to the Hub’s sustainability.

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Highlighting Rare Disease Regulatory Science Challenges

The Hub can address rare disease regulatory challenges -- that despite the wide diversity in clinical symptoms and organ systems affected -- often apply across rare disease therapeutic development areas.

Regulatory challenges cutting across small populations include:

- How to understand, interpret and use the natural progression of disease for regulatory purposes;
- How to address phenotypic variability within a disease;
- The absence of well-characterized biomarkers and other surrogate endpoints to assess trials in rare populations;
- Limited diagnostic tools; and
- Limited access to and use of appropriate alternative clinical trial designs.

Despite many advances in FDA's approach to rare disease therapy evaluation, the challenges articulated have resulted in variability in the processes, approaches, transparency, and use of regulatory flexibilities between FDA offices, divisions, and centers. This inconsistency is magnified for communities with very-small populations, often referred to as ultra-rare diseases.

We urge the Hub to prioritize projects and infrastructure that will enhance consistency and improve the predictability of how any given office, division, or center will apply regulatory flexibilities to product applications.

Specific initiatives that the EveryLife Foundation recommend the Hub undertake include:

- **Establishing Cross-functional Consultation Processes**
- **Supporting the Creation of a Knowledge Management System**
- **Supporting the Dissemination of FDA Pilot Program Learnings & Data**
- **Advancing Ultra-rare Policy by issuing guidance that can operationalize consistent approaches to evaluating ultra-rare therapies within the FDA's existing authority.**
- **Enhancing Advisory Committee's Rare Disease Knowledge by establishing a Rare Disease Advisory Committee within the Hub**
- **Lead the Evolution of Patient Focused Drug Development**
- **Facilitating Pre-competitive Scientific and Regulatory Science Conversations**
- **Infusing Rare Disease Perspectives in Cross-cutting Guidance and Policy Making Across all Three Product Centers**
- **Enhancing Engagement and Collaboration with Rare Disease Stakeholders**

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Establishing Cross-functional Consultation Processes:

Establish processes that will enable internal experts to be efficiently consulted at the request of either FDA or sponsor staff.

We are grateful for the agency's efforts over the last several years to add internal rare disease capacity and mechanisms, such as the Accelerating Rare Disease Cures Program, to share expertise when challenging situations arise. We understand that rare disease team members can consult on rare disease new drug or biologic applications outside of their division, including by participating in sponsor meetings, but that these consultations are not required even when the sponsor has requested it.

Rare disease experts within the agency should be regularly leveraged to consult on specific regulatory science issues such as the endpoints being evaluated -- or consultation with specific experts who have previously led evaluations who could provide relevant subject matter expertise. The Hub should support the creation of a proactive process to facilitate these consultations and should define the circumstances in which a sponsor will be guaranteed the ability to include a consultation with a relevant expert from another team. Additionally, we appreciate the creation of two teams of roving experts within CDER focused on surrogate endpoints and clinical trial design. We look forward to learning more about these teams, how they are deployed, and how this can be expanded.

Supporting the Creation of a Knowledge Management System:

Increase access to - and awareness of - information on how FDA has applied regulatory flexibilities in rare diseases.

De-risking therapy development for rare indications requires consistency in approach across applications. While we recognize the many unique characteristics of a particular therapy under evaluation, the absence of consistency in how regulatory flexibility is applied in rare disease reviews leads to ambiguity, delays, and confusion that can prevent a promising therapy from reaching patients, especially those in ultra-rare communities.

Each challenging rare disease product review generates new evidence and insights that should be contributing to advancing reviewer and community understanding of how FDA approaches complex rare disease evaluations, yet no system currently exists to capture, aggregate, and communicate such information. We believe better information for therapy developers, clinicians, and patient communities regarding the basis for FDA decisions would benefit all rare disease stakeholders and support shared learnings across all relevant divisions and centers.

Support the Dissemination of FDA Pilot Program Learnings and Rare Disease Related Trends and Data:

Build infrastructure to enable rapid application of information to relevant rare disease work.

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The agency is currently operating numerous pilot programs and initiatives that will produce insights and evidence to improve rare disease policies, processes, and regulatory science approaches. These projects include the Rare Disease Endpoints Advancement pilot, Complex Innovation Trial Design, and the Support for clinical Trials Advancing Rare Disease Therapeutics (START) pilot. We are grateful for the agency's commitment to these and other initiatives that will move the rare disease therapy development field forward, however their impact will be proportional to the commitment made to disseminating the lessons learned and the evidence generated in ways that can be easily applied in the work of reviewers across centers. The Hub must also disseminate these findings to the rare disease community and identify the opportunities to scale programs when they are successful.

Additionally, the Hub is well positioned to scale the amount of available data that speaks to trends, successes, and challenges in rare disease therapy development. The Office of Orphan Products Development's (OOPD)¹ efforts to make timely data on rare disease indications, approvals, or other trends available has provided valuable information to support the rare disease community's understanding of where additional policy focus is needed. The Hub should support and enhance OOPD's efforts to enable the vast data that the agency holds to be analyzed and synthesized for publication. To support this effort, the Hub should work with the community to understand what additional data would be useful and ensure the community understands what data is already publicly available and how to access it.

Advancing Ultra-rare Policy:

Issue Guidance for Industry, operationalizing current and innovative approaches to developing and evaluating ultra-rare therapies within the FDA's existing authority.

In May 2024, EveryLife Foundation convened the **2024 Scientific Workshop: Therapy Development for Small Populations: Evidence, Implications, & Policy in Characterizing Ultra-Rare** where the foundation brought together patient advocacy organization leaders, product developers, and key voices from federal agencies, including FDA leadership.

Workshop participants identified key barriers in ultra-rare therapy development including too few patients, diagnostic challenges, lack of approved outcome measures, and lack of endpoints or biomarkers. A universal theme that emerged was the need to ensure that expertise and experiences with ultra-rare therapy development programs, both successful and unsuccessful, are formally captured to inform and optimize future regulatory science approaches. Expert panelists and attendees voiced the need for a more predictable and consistent framework for approaching the development and evaluation

¹ FDA Office of Orphan Product Development (OOPD). (n.d.-b). *Orphan Grants Scientific Publications*. U.S. Food and Drug Administration. <https://www.fda.gov/industry/orphan-products-grants-program/orphan-grants-scientific-publications>



of ultrarare therapies within the agency's existing statutory authorities. A framework targeted at ensuring consistencies and successes in ultra-rare therapy development is needed.

Enhancing Advisory Committee's Rare Disease Knowledge:

Establish a Rare Disease Advisory Committee within the Hub to serve in a consultative and disease agnostic approach, enabling external experts to support review committees across the centers, and provide guidance on emerging issues. Relatedly, provide additional training and support on FDA's approach to regulatory flexibility in rare diseases to all advisory committee members that participate in product reviews.

We are aware of FDA's ongoing efforts to examine the role of its advisory committees and believe that Hub should prioritize efforts that ensure their use is serving the agency, patients, and the goal of safe and effective therapies reaching patients at the earliest opportunity. There are initiatives underway that can inform the Hub's efforts to enhance the use of rare disease expertise across advisory committees. These include provisions in FDORA requiring a GAO study on how the agency incorporates rare disease external experts in the regulatory review process, the recently released National Academies of Sciences and Medicine Report, *Regulatory Processes for Rare Disease Drugs in the United States and European Union* with an emphasis on improving consistency in decision making for rare disease product evaluations, and provisions in the FY2023 appropriations report explanatory statement that encourage the FDA to include no less than two expert members on each advisory committee when that committee is reviewing an orphan-designated drug².

While impractical to ensure there are experts in every rare disease on standing committees, one alternative to ensure consistent rare disease expertise is meaningfully incorporated into advisory committee discussions is to establish a standing rare disease advisory committee. A rare disease advisory committee can provide counsel to the agency on issues of importance in rare disease as well as possibly being convened jointly, as needed, with a human drug or device committee for the purposes of advising on a candidate therapy. The committee could also be called to provide guidance on emerging issues of importance to the field of rare disease, such as new approaches to conducting and reviewing small population trials, qualifying biomarkers, or establishing new or modified pathways. There is strong precedent for this approach within FDA.

While the Hub develops strategic priorities and infrastructure, some goals of a rare disease advisory committee could be met using an interim approach that could be implemented for immediate impact. The Hub could support leveraging appropriate members of the Genetic Metabolic Disease Advisory

² National Academies of Sciences, Engineering, and Medicine. (2024, September 12). *Regulatory Processes for Rare Disease Drugs in the United States and European Union: Flexibilities and Collaborative Opportunities*. The National Academies Press. <https://nap.nationalacademies.org/catalog/27968/regulatory-processes-for-rare-disease-drugs-in-the-united-states-and-european-union>



Committee in similar roles as suggested for proposed the rare disease advisory committee in the interim.

Coordinating Advisory Committee Training Needs Across Committees

Advisory committee members are chosen for their individual expertise, but many members lack a thorough understanding of the parameters that FDA operates in when considering rare disease products. Advisory committee members' contributions can be enhanced by providing them, in advance, with available information on the patient population, the impacts of living with the disease, patient preferences and risk tolerance, and other information commonly available in official documents like a previous Voice of the Patient Report or readouts from listening sessions.

Lead the Evolution of Patient Focused Drug Development:

Catalyze the continued momentum of PFDD, working across centers to drive evolution of Patient Focused Medicine Development.

As collaborative stakeholders, we have experienced a tremendous evolution of patient engagement and related areas since their infancy in PDUFA V -- to their continued development via 21st Century Cures and PDUFA VI -- and now their continued maturation today through the implementation of PDUFA VII. In this time, the landscape has shifted as the patient focused drug development movement evolved for the rare disease community. We've seen a deepened engagement and understanding of the patient perspective via numerous approaches such as the conduction of more than one hundred Patient Focused Drug Development meetings, the development of the FDA Benefit Risk Framework, and the implementation of the Patient Experience Data Checklist. We've had increased opportunities for meaningful participation in formal service on advisory committees, seen the formation of rare disease focused initiatives within CDER and CBER, seen the establishment of the patient engagement advisory committee (CDRH), and have benefited from reporting on the use of patient experience data within the regulatory review.

FDA's issuance of numerous guidances that are informing the inclusion of patient experience data within clinical trial and patient-focused product development activities are resulting in lives changed and saved through products approved to treat rare conditions, especially those that have benefited from the inclusion of more robust patient insights and patient experience data as part of the review process. By instituting a structured approach to listen to the voice of the patient in a meaningful way, the FDA has demonstrated its commitment to science and to ensuring appropriate processes are in place to quantify the perspective of the patient and caregiver.

The Hub can play a critical role in leading the evolution of this field, working across CDER, CBER, and CDRH, and co-creating processes that will build upon the impact of the Patient Focused Drug Development movement.

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The next generation of Patient Focused Medicine Development would include opportunities such as:

- Transforming PFDD meetings from a single point in time, to a pathway for ongoing engagement.
- Enabling enhanced transparency in how patient experience data is utilized in regulatory decision making for rare disease therapies.
- Establishing opportunities for earlier payer engagement to reduce barriers to access to life-alerting therapies once approved.

Facilitating Pre-competitive Scientific and Regulatory Science Conversations: *Implement a formalized forum for addressing disease clinical and regulatory challenges impacting the development of rare disease therapies.*

Again, building on the success of the Externally-led PFDD Workshop model, the establishment of the Hub provides an opportunity to further evolve the processes for community engagement around key scientific and regulatory challenges. The Hub should facilitate the creation of a mechanism to convene medical experts, drug sponsors, scientific organizations, and patient organizations to align on novel approaches for development of products, including considerations around clinical trial design, patient populations, endpoints, the use of biomarkers and surrogate endpoints, the use of natural history as a control, and more, with a goal of expediting rare disease therapy development.

Infusing Rare Disease Perspectives in Cross-cutting Guidance and Policy Making Across all Three Product Centers: *Establish communication and review processes for Hub experts to contribute rare disease perspectives to agency guidance and policy documents with implications for rare disease device, biologic and drug innovation.*

Across the agency's product centers, guidance documents, or other policies are regularly created or updated that, while not rare disease specific, have significant implications on rare disease products. Policies that apply agency-wide such as topics related to PFDD, companion diagnostics, accelerated approval withdrawal processes, and others, likely have nuanced effects on the rare disease space that must be considered during the guidance creation process. The Hub can play a supportive role in bringing that nuanced perspective into the teams working on such guidance creation.

One current example demonstrating the need for increased collaboration with non-rare disease specific guidance creation, and the need for robust integration of CDRH into the Hub activities, is the changes to the enforcement discretion in the regulation of laboratory developed tests³. The guidance represents a major change to diagnostic regulation that will have significant and unique implications for the rare

³ Laboratory Developed Tests: Small Entity Compliance Guide Guidance for Laboratory Manufacturers and Food and Drug Administration Staff (2024). <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/laboratory-developed-tests-small-entity-compliance-guide>



disease space. For example, while created with good goals in mind, the new rules severely inhibit the ability to quickly and cost-efficiently develop innovative newborn screening tests for a state-run, public health program that has a long history of developing safe, accurate tests. If the Hub existed while this rule was under development, this unintended consequence may have been identified and mediated through simple changes addressing the timing and cost implications for state newborn screening programs, while recognizing the difference in risk presented by tests developed in state labs with the support of the CDC.

Enhancing Engagement and Collaboration with Rare Disease Stakeholders

The creation of the Hub is an opportunity to streamline and enhance FDA's engagement throughout the rare disease community. We are encouraged by comments made during the October 16th public meeting that indicate a desire for a single front door approach to community engagement. Providing a simple, easy to navigate mechanism for engaging with FDA can help ensure efficient and effective communication occurs, removing unnecessary delays. However, this approach should not create additional gatekeepers between the community and the agency staff. The Hub should work closely with the Patient Affairs Staff, as well as the center-level teams that frequently engage with patient groups (e.g., PFDD and outcome measure teams) to identify opportunities for enhanced collaboration, reduced redundancies in outreach efforts, and common challenges different teams have faced when supporting community engagement.

Similarly, we recommend that the new Hub Director organize a series of discussions with key stakeholder groups as a follow-up to the October 16th public meeting. We are grateful for the initial forum and the chance to submit written comments, however, meaningful engagement must include more dedicated time to hear from community members about their experiences and dialogue between Hub personnel and the community members. These sessions will provide the context necessary to shape a strategic plan for the Hub and they will build trust between the agency and the community.

Additional Considerations and Success Metrics

As the agency develops foundational policies and processes for the Hub, there are a few additional considerations to integrate.

Transparency

We were pleased to hear the agency's commitment to transparency during the October 16th public meeting. For the community, a commitment to transparency means more than making plans, processes, and pre-set metrics available to the public. We urge the Hub team to be as specific as possible about the initiatives the Hub will prioritize and their intended outcomes. Most importantly, we urge the Hub team to focus on providing transparency into *how* the Hub's efforts are changing processes that occur out of

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sight of the community. For example, from recent public remarks, we were pleased to learn of the existence of the Rare Disease Policy and Programs Council and the effort to create roving expert teams centered around surrogate endpoint and clinical trial design challenges that are available to drop into reviews as needed.

These initiatives hold great promise to remove roadblocks facing rare disease therapy development, however they do not involve public-facing interactions for the most part. It will be essential that the Hub regularly reports on the types of conversations occurring in the council, the policies that were changed because of those conversations, the types of challenges the roving teams drop into, and how their involvement shaped decisions. We recognize that in some cases, the nature of the work will mean some detail is left out of reporting, but we encourage the agency to aggregate info and take all available avenues to show the Hub's activity and what specific impact the efforts are having.

The EveryLife Foundation and the broad rare disease community are enthusiastic about the establishment of the Rare Disease Innovation Hub and progress represented at the October 16th Hub meeting convened by FDA. We are grateful to all the community members who have worked tirelessly for many years to ensure that the needs, priorities, opportunities, and urgency of our rare disease community is strongly reflected in these recommendations. The EveryLife Foundation and its partners are eager to continue to work with the agency to ensure that the agency's robust launch and implementation of the Hub is fully supported and ensures ultimate impact for our collective communities. It is our hope that the FDA will commit to sustained and robust cross-agency collaborations, inclusive of all three product centers – emboldened by meaningful engagement with rare disease stakeholders and agency experts.

Thank you for the opportunity to provide comments and for your ongoing commitment to addressing the unmet needs of the rare disease population. If we can provide additional information to support your process, please contact Annie Kennedy, Chief of Policy, Advocacy and Patient Engagement, akennedy@everylifefoundation.org.

Sincerely,

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A Community Vision for a Rare Disease Center of Excellence at the FDA

MEETING THE URGENCY OF RARE DISEASES IN THE U.S.

EVERYLIFE FOUNDATION FOR RARE DISEASES

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Contents

Abstract.....	3
A Vision for an FDA Rare Disease Center of Excellence	6
Background	6
The Proposal	9
Following Precedent: The First Center of Excellence.....	10
Expanding the Concept: Digital Health and Compounding Pharmacies	11
How a Rare Disease COE Complements CDER’s Office of New Drugs Reorganization	14
Structure, Function, and Responsibilities of a Rare Disease COE	15
Supplementing Internal FDA Expertise: A Rare Disease Advisory Committee	19
Stakeholder Engagement Coordination.....	20
Conclusion.....	21
References	22

Abstract

Background

Over the past four decades, tremendous strides have been made in treating some rare diseases and disorders, those conditions that affect less than 200,000 people in the United States. Individually, rare diseases may affect relatively small populations compared to highly prevalent conditions such as heart disease, but collectively they take a major toll with estimates suggesting one of every 10 Americans is living with a rare disease.

While scientific breakthroughs have been key to developing these treatments, two changes to law and policy were essential ingredients: the enactment of the Orphan Drug Act and the development of the field of patient engagement. The Orphan Drug Act (ODA), enacted in 1983, transformed orphan diseases from a desert with little to no industry interest in developing therapies to a robust ecosystem.

Before the ODA was enacted, there simply was not an economic case to justify the tremendous time and monetary costs needed to develop therapies for such small patient populations. The ODA helped to address this problem by creating the incentives needed to attract and sustain industry interest. If anyone doubts the impact of the ODA, two numbers tell the story: 38 and 1,036. Thirty-eight was the number of drugs approved by the Food and Drug Administration to treat orphan conditions prior to the ODA, and 1,036 is the number of drugs indicated to treat rare diseases approved since 1983, providing hope for approximately 330 rare diseases. [1]

If the ODA initially catalyzed the rare disease innovation field, the development and refinement of patient engagement has advanced it markedly over the past decade, stretching back to the FDA Safety and Innovation Act or the 5th update of the Prescription Drug User Fee Act in 2012. This combination of legislation as well as actions undertaken by the FDA have and are continuing to produce the structure, processes and tools needed to ensure that patient and caregiver perspectives – including the patient's views on the potential benefits of a therapy juxtaposed with the perceived degree of acceptable risk – are listened to by FDA reviewers and incorporated into regulatory decision making.

As we look back at the nearly 40 years since the ODA and forward to the looming PDUFA VII renewal deadline in September 2022, we have much to build upon but also so much more work to be done. The achievements of the past decades should be celebrated, but any celebration is tempered by the reality that most rare diseases – 93-95% – lack any FDA-approved treatments as the 1,036 therapies include several diseases with multiple therapies.

In thinking about what needs to happen next to advance rare disease drug and medical product development, several public policy ideas are on the table. These include both actions that the FDA can take directly as well as updates to laws that need to be passed by Congress to enable broader FDA engagement. Several meritorious rare disease policy proposals are in the works, and one of these ideas enjoys tremendous support from the community – establishing an FDA Center of Excellence in Rare Diseases.

As the name suggests, a Center is an administrative mechanism for collecting and organizing all the FDA's scientific, clinical and regulatory expertise on a therapeutic area. Given that rare diseases often cut across multiple organ systems and share common drug development challenges, rare diseases would be an ideal candidate for such coordination and organization.

The 21st Century Cures language authorizing FDA to create Centers was not overly prescriptive as Congress recognized that Centers may have different characteristics. For example, given that rare disease products are currently reviewed by different Centers and several review divisions, a rare disease Center would not necessarily be tasked with product reviews. However, the Center would be a place where all FDA expertise on rare diseases could reside to support the various review divisions handling applications.

Today, rare disease expertise is dispersed throughout FDA. For example, the recently completed reorganization of the Office of New Drugs created a Division of Rare Diseases and Medical Genetics within the Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine but divisions such as the Division of Neurology have considerable responsibility for rare diseases. The Center for Drug Evaluation and Research has a [Rare Disease Program](#), and other Centers have programs or initiatives focused on rare diseases, too.

A Center of Excellence would help organize all FDA resources – such as statisticians, regulatory scientists and experts in clinical trial design for small populations – within a single structure to avoid duplication and disciplinary silos as well as to make concentrated resources available to multiple review divisions. It would recognize that despite the wide diversity in clinical symptoms and organ systems affected by rare diseases, the barriers to effective therapeutic development are similar for all rare diseases.

It would also complement the recent OND reorganization and enable FDA to build an agency-wide team to meet current and future rare disease needs.

Despite the strong support that exists within the rare disease community for such a Center, including bipartisan and bicameral legislation pending in Congress, some skeptics have misinterpreted or mischaracterized the proposal. For starters, some detractors have suggested that a Center is not needed

because of the recent CDER reorganization. But the reorganization pertains only to the Office of New Drugs within CDER, meaning it is contained in a single Center. The reorganization will not touch the significant and growing rare disease work performed by the Center for Biologics Evaluation and Research (CBER), which regulates gene therapy and cell-based therapies, nor does it touch the Centers for Devices and Radiological Health (CDRH). If we want to ensure rare disease expertise permeates all relevant corners of FDA, we need an FDA-wide Rare Disease Center of Excellence.

Others have suggested that the field of rare disease is not yet mature enough for such a Center. This argument fails to recognize the progress of the past half-century and the pressing opportunities on the horizon. It also misses the point in that a rare disease Center is intended to help further refine and build the regulatory science framework for accelerating rare disease therapeutic development – including the rare disease workforce – and that the goal of a fully mature field cannot be an argument against a Center.

The field of rare diseases is poised for continued progress. But at the same time, gaps and challenges – particularly in rare disease regulatory science and related areas – threaten to impede these gains. A Rare Disease Center of Excellence will build upon the advancements of the past several decades and open the next chapter in rare disease innovation and medical product development.

The following is a proposed vision for the establishment of an FDA Rare Disease COE. It was created by a group of key opinion leaders thinking about the possible ways such a COE could be implemented. In no way is it prescriptive but rather an opening for further discussion.

Conclusions

A Rare Disease COE would complement and build upon recently implemented organizational changes at the FDA, foster a culture of collaboration and consolidate and strengthen expertise in the science of small trials. This Center would develop inter-center resources and provide support to review staff while also developing and furthering policies and stakeholder engagement to support rare disease therapy development. The Center would be cross-cutting, capacity-building and consultative in order to support review of rare disease applications and would not supplant any authority of the existing Centers and their delegated signatory authorities.

A Vision for an FDA Rare Disease Center of Excellence

Background

While rare disease innovators and stakeholders have long believed that a Rare Disease COE could provide the necessary resources and support to allow Centers, Offices, and Divisions across FDA to more consistently and efficiently review novel products for these conditions, this proposal grew from the discussion and learnings at the 10th Annual EveryLife Foundation Scientific Workshop on “Conceptualizing an FDA Rare Disease Center of Excellence” held on September 13, 2018. [2] At that meeting, senior FDA officials, patient advocates, pharmaceutical/biotechnology industry representatives, and researchers shared insights and examples to inform the conceptualization of an FDA Rare Disease COE. The need for that 2018 discussion, and development of this proposal, can be summarized through the words of then-FDA Commissioner, Dr. Scott Gottlieb:

“In many cases, developing a treatment for a rare disease can be especially hard and present unique challenges. Each success is the end of a long uphill climb. It requires the concerted efforts of stakeholders, including scientists, product developers, regulators, policy makers, and of course, the energy and organization of patient advocacy groups.”
[3]

Since the enactment of the Orphan Drug Act in 1983, which incentivizes developing drugs for rare diseases, there has been increased investment in the research and development of medical products (drugs, biologics, and medical devices) to prevent and treat rare diseases, also known as orphan conditions. This influx has created unique regulatory challenges for the FDA in providing oversight and in reviewing marketing applications. [4] Understanding the natural history of a disease is foundational to a rare disease therapy development program; however, because of the small numbers of patients affected and with clinical expertise dispersed among a small number of clinical sites, the natural history of rare diseases is often poorly described and the dispersion of expertise and resources at the FDA makes it more difficult to engage the agency consistently in the development of overarching standards,

putting these programs at a disadvantage. Similarly, general knowledge about a rare disease's pathophysiology is frequently incomplete, creating another challenge for developers of such products. Little, if any, medical product development work has been done for most rare diseases, so there are not well-developed assays to identify potential biomarkers, nor are there well-characterized disease-specific clinical outcome assessments to assess how a patient feels or functions to better evaluate a treatment's efficacy.

Furthermore, the ability to detect clinically meaningful outcomes requires understanding of their rate of occurrence, variability, importance to patients, and the amount of change that would be considered clinically meaningful. All of these contribute to difficulties in powering a study in an already small population. Standard trial designs cannot be optimized to obtain adequate safety and efficacy data from small numbers of patients, especially with the substantial phenotypical variability that exists in many rare disorders. On top of these scientific issues, the affected patients can be challenging to identify, especially early in the course of their disease, are generally geographically dispersed, and are often children, creating additional challenges for their inclusion in clinical studies. Many of these challenges are acknowledged by FDA in its Draft Guidance for Industry, *Rare Diseases: Common Issues in Drug Development* (January 2019). [5]

There is no separate, lower or lesser legal or regulatory standard for approval of orphan products, so researchers, product developers and FDA alike must confront these issues throughout all phases of development and employ creative approaches to product development and review. For example, rather than traditional clinical trials conducted in large populations, alternative clinical trial designs (enrichment, crossover, adaptive, N of 1) are still nascent and in need of further consideration and refinement. Furthermore, the applicability of programs that afford some type of regulatory flexibility, such as single study approval or acceptance of a surrogate endpoint, need to be explicitly considered. While FDA has a track record of applying reasonable flexibility when it approves orphan products [6][6]-

[7], myriad challenges in rare disease medical product development remain. [8] Navigating these issues requires its own set of expertise in rare disease product development and review, expertise and experience that is inconsistently distributed within currently existing organizational structures (Centers, Offices, review divisions) and which a Rare Disease COE would help optimally organize, formalize and expand.

To further complicate matters, exciting new therapeutic approaches such as combination therapies, gene and cell therapies, and novel diagnostics, are emerging and require multi-disciplinary expertise by regulators, the type of expertise a Center model can help provide. Some rare diseases, for example, may have a gene therapy and a small drug in development at the same time, meaning different divisions within the FDA would be involved. A Center could further help coordinate and inform the historically siloed review and approval processes occurring in these different Centers.

It is important for the FDA to recognize that the organ-based model of reviewing new therapies does not necessarily work for rare diseases in the 21st Century. Instead, genetic diseases require a systems approach to drug development. In many cases, the underlying genetic mechanism of a disease affects processes across multiple organ systems and thus a single office may not have adequate expertise or resources to evaluate treatments to the fullest extent needed for these rare diseases. Table 1.0 summarizes the most common rare disease challenges, their related regulatory science challenges and proposed ways that a Rare Disease COE can help.

Table 1.0: Challenges and Opportunities for a Rare Disease Center of Excellence

Rare Disease-Challenges	Regulatory Science-Related Challenges	How a Rare Center of Excellence Can Help Address Challenges
Small patient populations	Limited or no natural history data; incomplete or limited understanding of disease progression; phenotypic variability within a disease.	Issue guidance on topics like use of unbalanced drug to placebo randomization, external or simulated controls, use of RWE, use of Bayesian statistical models and other approaches to compensate for limited size; support development of tools to better understand disease progression; build FDA experience and expertise of addressing variability within a population as well as for cross-disease learning and related needs.
Limited clinical experiences	Lack of well-characterized and validated biomarkers or other surrogate endpoints to assess trials in rare populations	Issue guidance for sponsors that combine biomarkers, clinical outcomes assessments, and other composite tools that can help sponsors and regulators improve the capture innovative endpoints for efficacy, safety and related data to better assess benefit/risk in complex disease states.
Delays in receiving a diagnosis	Limited diagnostic tools including companion diagnostics	Issue guidance pertaining to diagnostics including companion diagnostics; support programs to develop rare disease diagnostics.
Inconsistent approaches to review of rare disease applications	Variability among processes and approaches between offices, divisions and centers	Build expertise and capacity on rare disease therapy development to enable robust review capabilities including shared learning and modular application approaches across centers, offices and divisions.

The Proposal

The enactment of the 21st Century Cures Act in December 2016 demonstrated that our nation's policymakers recognized the value of an organizational unit within FDA that would leverage the combined skills of regulatory scientists and reviewers with expertise in drugs, biologics, and medical

devices to help expedite the development of safe and effective products within an area of critical public health importance. Specifically, Section 3073 of this law requires FDA to establish one or more of these organizational units or InterCenter Institutes, which FDA calls Centers of Excellence. Given the unique challenges and, therefore, the unique expertise needed to advance the development and review of products for rare diseases, a Rare Disease COE could provide the necessary infrastructure to allow Centers and Offices across FDA to consistently and efficiently review novel products for these conditions while also advancing regulatory science tools for rare disease therapeutics. While this is a shift from FDA's traditional orientation towards Centers that focus on specific products, it is supported by advances in precision medicine that requires an integrated approach to the clinical evaluation of products for the treatment of rare diseases while at the same time maintaining the current regulatory review structure. This proposal already has the support of many in the rare disease stakeholder community, yet, to proceed, it will require Congressional support, additional funding, and human resources support to establish the organizational units and positions within it. The community recognizes there will be challenges, but stresses that the rewards will be great. This proposal emphasizes that signatory authority for reviews would continue to reside with the existing Centers as delegated to Offices and review divisions and would not change.

Following Precedent: The First Center of Excellence

The first Center of Excellence established by FDA was proposed by *Friends of Cancer Research* to be a pilot in oncology. On June 29, 2016, then-Vice President Biden announced the FDA Oncology Center of Excellence as part of the Cancer Moonshot. On December 13, 2016, the 21st Century Cures Act was enacted, resulting in FDA taking the administrative step to issue a notice in the *Federal Register* in July 2017 to establish a new organizational structure for the Oncology COE.

The [Oncology COE](#) has been a remarkable success story, benefiting FDA, product developers, and patients. In its relatively brief existence, the COE has established procedures for collaboration across the

Centers, including creating disease-specific interest groups so that experts across the various FDA review divisions can talk about cutting-edge science and non-disease-specific tools like diagnostic biomarkers and platform trials. By breaking down silos and focusing on oncology-specific issues, the COE increased communication and collaboration and allowed for the creation of best practices to integrate the reviews of exciting new technologies. This resulted in the approval of dozens of new drug and biologic applications, including the first two cell-based gene therapies and the first site-agnostic therapies. [9] Additionally, the COE has inspired and facilitated the launch of exciting pilots – real-time oncology review, the assessment aid, and international collaboration. Additional successes and accomplishments of the Oncology COE can be found [here](#).

Expanding the Concept: Digital Health and Compounding Pharmacies

In December 2019, FDA created its second COE, for compounding quality, with three main areas of focus: education and training; facilitate the exchange of ideas and best practices, and to inform the Agency on key issues faced by industry. [9] The third, and most recently established COE, the Digital Health Center, is embarking on a multi-phased approach to enhance internal and external resources to support development and clearance of digital health tools. Like the Rare Disease concept, the Digital Health Center is focused on building FDA expertise on digital health topics and producing updated guidance and processes to support review and marketing approval of digital health technologies. Also like the rare disease concept, the Digital Health Center is not tasked with product approvals.

The proposed Rare Disease COE will leverage successful elements of the Oncology COE, Compounding Quality COE and the Digital Health Center, while adapting a model that is more appropriate to the unique challenges in rare disease product review and while maintaining signatory authority in the existing Centers. Table 2.0 demonstrates the variability in scope and organization of the existing COEs.

Table 2.0

Comparison of FDA Centers of Excellence

Center	Founded	Review of Applications	Related Advisory Committee	Structure & Focus	Training & Capacity Building – Internal	Training – Extern.	Conferences & Meetings	Build Collaboration between FDA & Others	Information Sharing	Pilot Programs
Oncology	January 2017	Yes, e.g., Medical Oncology Review and Evaluation (MORE) team and other initiatives; product center “makes final application approval determination.”	Yes, Oncologic Drugs Advisory Committee	In-house leadership with center director and multiple deputies and associate directors; multiple product centers work within CoE.	Yes, such as FDA – NCI Clinical Investigator or Program.	Yes, spanning multiple partners and levels of career development	Yes, wide variety including workshops	Yes, including cancer stakeholders and other foreign regulators.	Yes, including issuance of guidance documents.	Yes, multiple programs currently supported.
Compounding Quality	December 2019	No	Yes, Pharmacy Compounding Ad. Comm.	FDA contracts to Deloitte	No	Yes – Focused on outsourcing facilities	Yes	Yes, with a focus on professionals working in the sector.	Yes, through training offerings.	No
Digital Health	September 2020	No		Led by a director who is an FDA employee within CDRH but	Yes	Yes	Yes, including workshops	Yes	Yes, including hub for relevant guidance documents .	Yes, e.g. Pre-cert program .

				mission is FDA-wide. Three-part focus on sharing knowledge, connecting stakeholders and innovating regulatory approaches.						
Proposed Rare Disease center of Excellence		No, the center would support review activities but not review applications directly.	Yes, would envision creation of a complementary rare disease advisory committee.	Envision an in-house operation led by a director and building upon recent OND changes and existing rare disease activities .	Yes, envision a focus on building internal capacity in rare disease regulatory science, innovative trial design, small pop. Studies and other issues.	Yes, envision robust engagement and interaction to build rare disease scientific capacity.	Yes, would envision a range of activities including workshops.	Yes, would envision building upon existing FDA-NIH programs and other initiatives involving stakeholders, including foreign regulatory authorities.	Yes, would envision a role in rare disease guidance development and related efforts.	Yes, would envision targeted pilots to advance rare disease initiatives.

How a Rare Disease COE Complements CDER's Office of New Drugs Reorganization

In 2017, CDER set out to reorganize the Center's Office of New Drugs, [11] the office responsible for new drug review. This multi-phased project was completed in spring 2020. Perhaps of greatest import to rare disease stakeholders, this move established an Office of Rare Diseases, Pediatric, Urologic, and Reproductive Medicine (ORPURM) and a corresponding Division of Rare Diseases and Medical Genetics (DRDMG). However, review of products for other rare disorders affecting specific body systems continue to be reviewed by offices and divisions outside of the DRDMG (e.g., Office of Neuroscience, Office of Immunology and Inflammation, Office of Cardiology, Hematology, Endocrinology and Nephrology) and CBER and CDRH retain significant responsibility for cell and gene therapy and medical devices and diagnostics, respectively.

This reorganization will hopefully advance the review capacity for drugs for rare diseases by creating a defined rare disease review division for some rare diseases and encouraging the recruitment of more specially trained reviewers. These reviewers will become more specialized in the diseases they are reviewing and will have more opportunities to keep current on the latest science. It will generally improve review efficiencies in disease areas that cover a significant proportion of rare diseases (e.g., inborn errors of metabolism).

Given the recognition that an organ-based approach to rare disease therapeutic development is no longer adequate in the 21st Century, it is essential that rare disease expertise permeate the entire agency and not be siloed in CDER. Each office and Center within the FDA need the ability to access expertise contained within the COE to support their regulatory reviews.

While this CDER action is most welcomed, it would be unfortunate to declare victory prematurely. Rather, it is imperative to build upon the CDER reorganization by establishing a Rare Disease COE that enhances this reform by providing a mechanism for greater support and knowledge-sharing in the review of drugs, biologics and devices for rare diseases across divisions, offices, and Centers. Given the

increased number of review divisions as a result of the CDER reorganization, there is an even greater need for sharing of best practices and lessons learned by a Rare Disease COE; otherwise, this expanded number of review divisions may result in more inconsistent rare disease expertise and variable regulatory application from one division to another. To facilitate this, the Rare Disease COE could include joint appointments and liaisons from office and review division staff from across CDER, CBER, and CDRH. In addition, the Rare Disease COE should incorporate leadership from the National Center for Toxicological Research (NCTR), which has unrealized potential to contribute to the advancement of ultra-rare and personalized treatments that lack the capital to move out of the early phase toxicology work.

Structure, Function, and Responsibilities of a Rare Disease COE

The proposed Rare Disease COE would be an organizational unit that, like other Centers, reports to the Immediate Office of the Commissioner. There, it would leverage the combined skills of regulatory scientists and reviewers with experience in rare diseases in drugs, biologics, and medical devices (including diagnostics) and create a mechanism for greater visibility and accountability for rare disease programs across the agency. The Rare Disease COE would be tasked with expediting the development of medical products and supporting appropriately flexible approaches in the clinical evaluation of drugs, biologics, and devices for the treatment of rare diseases. The Rare Disease COE would be established and operate in accordance with an Inter-Center Agreement, which would be made responsible for:

- Development of best practices and lessons learned regarding rare disease-specific regulatory approaches, including in the science of small trials and n of 1 or very small population situations;
- Coordination of rare disease-specific regulatory science initiatives and outreach including policy and guidance development and working with stakeholders to inform development of patient organization-initiated draft guidance and related items;

- Identifying gaps and shortfalls in the current regulatory system that impede development of therapies for rare diseases and consideration of new approaches to address these barriers;
- Fund pilot programs and targeted extramural research through Broad Agency Agreements and other mechanisms;
- Implementation of cross-Center rare disease-focused meetings and internal staff education programs;
- Stakeholder engagement to the external community and international regulatory agencies on rare disease product development; and
- Staffing of an advisory committee on rare diseases that would provide the FDA with the external expertise needed to advise on and consider current and emerging issues in the field.

Through these activities, the COE would expeditiously fill knowledge gaps that exist today, reduce regulatory variability across review divisions and reduce overall uncertainty. The result would be an FDA where all divisions or Centers are as responsive as possible to applications for rare disease therapies and able to apply the latest knowledge and approaches to evaluating such applications. **It would mean that a rare disease application filed in one division or office would receive the same treatment as an application in any other, significantly reducing the variability that is commonplace today.**

The Director of the Rare Disease COE would have a key leadership role and would be responsible for the overall functioning and direction of the COE. The Director would have equal status to the other Center and COE Directors and would have a similar upward reporting structure.

One of the ways that the proposed Rare Disease COE would be different from the Oncology COE is in its involvement across a broader number of Centers, Offices and review divisions. When the first COE was developed, CDER's Office of Hematology and Oncology Products (OHOP) naturally became a significant part of the Oncology COE. Many of the structures that were in place prior to the creation of the Oncology COE are still in place and were not changed, including many of the leadership positions and

reporting structures. The Rare Disease COE would be similar to the Oncology COE in ways like working within existing structures, yet it will have some unique differences. These include involving a greater variety of disease areas and review divisions.

To leverage the existing in-house rare disease expertise present throughout the Agency, current FDA officials with substantial expertise in rare disease product development and review could serve in joint appointments in their current position and within the COE. This approach would allow for COE staff to bring an understanding of the existing processes and procedures of the various Centers, which would help inform the establishment of COE intra-Agency policies and procedures to implement its responsibilities. This would also allow for FDA staff from areas where rare disease drug development and approval has been particularly well-established, such as inborn errors of metabolism, gene therapy, and neurology, to share their learnings and insights to inform best review practices in rare diseases. The COE would also enable more effective identification and coordination with external expertise in ultra rare disorders where internal disease-specific expertise may be limited, consistent with previous authorities granted in PDUFA V.

Beyond Leadership: Fostering Agency-Wide Policies, Training, Stakeholder Engagement, Informatics, and Collaborations to Support Rare Disease Product Review

Beyond the core functions and responsibility of the Rare Disease COE leadership team, dedicated staff in the COE would be needed to help in identifying, developing, and communicating rare disease policies and programs. These staff would coordinate and provide guidance on the development of rare disease policies and procedures, including rare disease-related guidance. They would have an active role in User Fee Act (e.g., PDUFA, MDUFA) development and negotiations, including internal FDA meetings as well as meetings with stakeholder groups broadly representing the interests and needs for rare disease drug development. These staff would also be involved in regulatory science initiatives at the Agency that

might impact rare disease drug development and review, including CPATH meetings for rare disease products and diseases.

Rare Disease COE staff would coordinate and develop training for rare disease product review within the Agency and deliver training programs to the extended rare disease stakeholder community. This would include training for FDA review staff, both new hires and existing staff.

The Rare Disease COE could help identify potential topics and needs for symposia or conferences related to specific rare disease topics. These could be directed towards regulated industry, patient advocacy groups, academia, or any combination of these. An area of envisioned focus would be a program oriented toward the unique challenges associated with developing and delivering therapies for n of 1 diseases or very small population situations. This would include a variety of issues such as:

- Manufacturing standards for such therapies in non-industry settings
- Trial study designs and metrics to determine efficacy
- Pathways for abbreviated toxicology studies
- Standards for allowing overlapping animal studies and patient dosing
- Identifying potential incentives or other policies needed to spur interest in developing such therapies

Rare Disease regulatory science and informatics would need to be further developed for the collaborative creation of new tools, standards, and approaches to assess safety, efficacy, quality, and performance of rare disease products. The RD COE would liaise with pharmacology, toxicology, clinical pharmacology, biomarkers, and COA review staff at the Agency. They, along with the proposed Rare Disease Advisory Committee described below, would be involved in evaluating FDA readiness for the use of new and emerging technologies related to rare disease drug development, including novel biomarkers and outcomes assessments, and rare disease registries and natural history studies.

Certain scientific areas would require special collaborations between the RD COE staff and other Agency staff. Such a collaboration would be needed for topics like toxicology analysis and statistics due to the

complicated statistical issues related to study design, small patient populations, the need for creative and flexible approaches, and the need for internal training within the agency for statistical evaluation of rare disease clinical trials. The Rare Disease COE would engage with statisticians from other Centers and become a resource within the Agency for rare disease statistical issues. Also, since greater than 50% of rare diseases affect children [14], the Rare Disease COE would need to work closely with the Division of Pediatric and Maternal Health staff and the Office of Pediatric Therapeutics. They additionally would work closely with the Office of Orphan Products Development which oversees orphan designation, rare pediatric disease priority review vouchers and orphan grants.

Supplementing Internal FDA Expertise: A Rare Disease Advisory Committee

While a Rare Disease COE would build agency expertise and knowledge, there will be occasions in which external expertise is also needed. To provide FDA with such expertise on issues of rare disease medical product development and review, a Rare Disease Advisory Committee should be established. Similar to how the Drug Safety and Risk Management Advisory Committee is called jointly with one of FDA's disease area-specific advisory committees to advise on review of new products with unique risk considerations, the Rare Disease Advisory Committee could be convened jointly together with the appropriate FDA disease-area-specific advising committee for products that are under the jurisdiction of the Rare Disease COE. The committee could also be called to provide guidance on emerging issues of importance to the field of rare disease, such as new approaches to conducting and reviewing small population trials, qualifying biomarkers or establishing new or modified pathways. Members would be selected from among authorities knowledgeable and experienced in rare disease research and development, statisticians with expertise in rare diseases, researchers with expertise in conducting trials for rare diseases (even if the expertise is in a different rare disease than the one under discussion), geneticists with rare disease expertise, and rare disease patient advocates, including caregivers.

Stakeholder Engagement Coordination

Coordinated stakeholder engagement would be another important function to support communication with the rare disease stakeholder community. The COE would complement existing stakeholder engagement efforts involving review divisions and is not intended to detract from such activities or to set up a wall between stakeholders and review staff. The COE staff would actively engage with patients and advocacy groups to help foster research into the measurement of patient experiences and preferences as well as to help generate patient recommendations to help inform regulatory policy decisions.

The Rare Disease COE would need to coordinate and work closely with the Patient Affairs Staff, as well as the Center-level patient engagement groups (e.g., PFDD staff, Science of Patient Input staff), on opportunities to engage with rare disease patients, caregivers, and patient advocates, as well as opportunities to incorporate rare disease patient stakeholder input into rare disease medical product development and review (i.e., patient-focused medical product development). The COE could help coordinate these efforts and could convene representatives from the Office of the Commissioner's Patient Affairs Staff, CDER's Patient-Focused Drug Development staff, CDER's Patient Affairs and Stakeholder Engagement staff, CBER's Science of Patient Input, the CDRH Office of the Center Director, and Oncology COE AD for External Outreach and Engagement as needed to work collaboratively on patient engagement policies, projects, programs, and initiatives that impact rare disease patient stakeholders.

Stakeholders recognize the FDA may face challenges setting up a game-changing Rare Disease COE that truly captures regulatory and scientific expertise that can be deployed effectively across the agency. Many leaders could be concerned with changing the status quo by introducing a new mechanism through which coordination can occur. Hesitation like this should not stop the FDA from ensuring the

most efficient regulatory environment for patients, just as patients hope difficult scientific questions do not deter researchers and innovators.

Advocates also recognize that the success of the Rare Disease COE will rest largely with the staff and leaders ultimately at the helm. To be ultimately as successful as possible, the COE will need to have skilled people in leadership roles that have the visibility and accountability of reporting to the Office of the Commissioner. If fully and properly embraced by FDA leadership and assigned the appropriate resources and expertise, including empowered leaders, the COE could – and will – provide great value to the FDA, innovators, and patients, and complement the work already being done within the individual Centers.

Conclusion

We stand on the threshold of a new era in which scientific advances in many areas (e.g., RNA-targeting small molecule drugs, stem cell and gene therapies) are increasing the possibility of profound new rare disease treatments, sometimes bordering on “cures,” being close at hand. These therapies have the potential to change the way we prevent, diagnose and treat rare diseases. Establishing an FDA Rare Disease COE and a standing Rare Disease Advisory Committee would complement the recently completed OND reorganization and further support the development of transformative therapies and foster greater visibility and enhanced regulatory consistency.

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