2022

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

Authors and Acknowledgements

The EveryLife Foundation for Rare Diseases thanks the member organizations and representatives who contributed to the formation of the ideas reflected in this paper. We thank the speakers and attendees of the 10th EveryLife Foundation Scientific Workshop, Conceptualizing a Rare Disease Center of Excellence. We also thank Liesl Broadbridge, ScM, CGC - EveryLife Foundation and Rutgers University, Sarah Lloyd Stevenson – Faegre Drinker Consulting at time of drafting and Steven Silvestri – EveryLife Foundation at time of drafting, for their support and comments on this paper.

Primary Authors

1. Christopher Austin, MD, CEO-Partner, Flagship Pioneering
2. Larry J. Bauer, MA, Senior Regulatory Drug Expert, Hyman, Phelps & McNamara, PC
3. Pam Crowley Andrews, Co-founder and Executive Director, The Firefly Fund
4. Ryan Fischer, Chief Advocacy Officer, Parent Project Muscular Dystrophy
5. Tim Franson, MD, Principal, Faegre Drinker Consulting
6. Annie Kennedy, Chief of Policy, Advocacy & Patient Engagement, EveryLife Foundation for Rare Diseases
7. Nicholas P. Manetto, Principal, Faegre Drinker Consulting
8. Cara O'Neill, MD, FAAP, Chief Science Officer, Cure Sanfilippo Foundation
9. Frank Sasinowski, MS, MPH, JD, Director, Hyman, Phelps & McNamara, PC
10. Dylan Simon, Director of Policy, EveryLife Foundation for Rare Diseases
11. Jamie Sullivan, MPH, Senior Director of Policy, EveryLife Foundation for Rare Diseases
12. James Wilson, MD, PhD, Professor of Medicine and Pediatrics, Director of Orphan Disease Center, Perelman School of Medicine, University of Pennsylvania

Contents

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 trails. 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 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 workshop.s	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.

References

[1] U.S. Food and Drug Administration. Search Orphan Drug Designations and Approvals. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm" (accessed 3 Feb 2022).

[2] Conceptualizing an FDA rare disease Center of excellence. 2018. https://everylifefoundation.org/events-schedule/scientific-workshop/ (Accessed 17 Dec 2019).

[3] Gottlieb S. Taking New Steps to Meet the Challenges of Rare Diseases – FDA Marks the 11th Rare Disease Day. FDA Voice. 2018. https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/taking-new-steps-meet-challenges-rare-diseases-fda-marks-11th-rare-disease-day (Accessed 17 Dec 2019).

[4] Kempf L, Goldsmith J, Temple R. Challenges of Developing and Conducting Clinical Trials in Rare Disorders. American Journal of Medical Genetics, Part A 2018; 176(4) 773. https://doi.org/10.1002/ajmg.a.38413

[5] U.S. Food and Drug Administration. Rare Diseases: Common Issues in Drug Development. 2019. https://www.fda.gov/media/119757/download (Accessed 17 Dec 2019).

[6] Sasinowski F, Panico E, Valentine J. Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs. 2012. Sage J. 46(2) 238. https://www.ncbi.nlm.nih.gov/pubmed/30227043

[7] Sasinowski F, Panico E, Valentine J. Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs (Update July 2010 to June 2014). 2015. Sage J. 49(5) 680. https://doi.org.10.1177/2168479015580383

[8] Tambuyzer E, Vandendriessche B, Austin CP, Brooks PJ, Larsson K, Miller Needleman KI, Valentine J, Davies K, Groft SC, Preti R, Oprea TI, Prunotto M. Therapies for rare diseases: therapeutic modalities, progress, and challenges ahead. 2019. Nature Reviews Drug Discovery. 2020; 19(2) 93-111. https://doi.org/10.1038/s41573-019-0049-9

[9] Goldberg KB, Blumenthal GM, McKee AE, Pazdur R. The FDA oncology Center of excellence and precision medicine. Experimental Biology and Medicine. 2018; 243(3) 308-12. https://doi.org/10.1177/1535370217740861

[10] U.S. Food and Drug Administration. FDA takes efforts to improve quality compounded drugs from outsourcing facilities through collaboration and education as part of new Center of Excellence. https://www.fda.gov/news-events/press-announcements/fda-takes-efforts-improve-quality-compounded-drugs-outsourcing-facilities-through-collaboration-and (Accessed 19 Dec 2019).

[11] U.S. Food and Drug Administration. Modernizing FDA's New Drugs Regulatory Program. https://www.fda.gov/drugs/regulatory-science-research-and-education/modernizing-fdas-new-drugs-regulatory-program (Accessed 17 Dec 2019).

[12] U.S. Food and Drug Administration. Reorganization of the Office of New Drugs with Corresponding Changes to the Office of Translational Sciences and the Office of Pharmaceutical Quality. https://www.fda.gov/drugs/regulatory-science-research-and-education/reorganization-office-new-drugs-corresponding-changes-office-translational-sciences-and-office (Accessed 17 Dec 2019).

[13] Usdin S. Getting Flatter: How FDA Proposes to Reorganize OND to Streamline Drug Reviews. 2018. BioCentury, 2 Jun 2018. https://www.biocentury.com/article/295877/how-fda-proposes-to-reorganize-ond-to-streamline-drug-reviews (Accessed 17 Dec 2019).

[14] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6441966/