

Proposal for Building an FDA Rare Disease Center of Excellence

Authored by: Frank J. Sasinowski, MS, MPH, JD*† & James E. Valentine, JD, MHS†
*Vice Chair, Board of Directors, EveryLife Foundation; †Hyman, Phelps & McNamara, P.C.

Background

Since enactment of the Orphan Drug Act (ODA) in 1983, there has been increased investment in the research and development of medical products to prevent and treat rare diseases. Regulatory oversight and review of these products presents many unique challenges (many acknowledged by FDA in its *Draft Guidance of Industry, Rare Diseases: Common Issues in Drug Development*, August 2015). Periodic consideration of opportunities to reform and refine the approach to rare disease medical product regulation is warranted as we celebrate the 35th anniversary of the ODA – similar to the review that occurred 10 years ago, which resulted in the establishment of the CDER Rare Diseases Program and first FDA public hearing on orphan drugs in June 2010.

The 21st Century Cures Act provided legislative authority for FDA Centers of Excellence (COE). This was a departure from FDA's traditional orientation towards centers that focus on specific products; instead supporting an integrated approach to the clinical evaluation of products. The first COE (Oncology) was established in 2017. The Oncology COE has been viewed as a success, resulting in the approval of dozens of new drug and biologic applications, including the first two cell-based gene therapies.

Structure, Function, and Regulatory Responsibilities of a Rare Disease COE

The proposed Center of Excellence for Rare Diseases (Rare Disease COE) would involve a combination of three overarching organizational changes at FDA:

(1) It could be structured and function in a manner consistent with the existing Oncology COE. The Center of Excellence would **be an organizational unit within the Office of Medical Products and Tobacco** within the 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). The COE would be tasked with helping expedite the development of medical products and support an integrated approach in clinical evaluation of drugs, biologics, and devices for the treatment of rare diseases. The COE would work with the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH), as well as other offices across FDA (e.g., Office of Pediatric Therapeutics, Office of Orphan Products Development).

The Rare Disease COE would be established and operate in accordance with an Inter-Center Agreement, which could delegate the responsibility for sign off on the clinical portion of novel medical applications for rare diseases. Even without signatory authority, it would provide leadership to the Centers on issues of rare disease product development and review. As such, the COE would be made responsible for:

- Harmonization of rare disease-specific regulatory approaches;
- Coordination of rare disease-specific regulatory science initiatives and outreach;
- Implementation of cross-Center rare disease-focused meetings; and
- Stakeholder engagement to the external community and international regulatory agencies on rare disease product development.

This proposed structure would allow for the appointment/recruitment of COE leadership and staff that would complement existing CDER, CBER, and CDRH staff. If signatory authority was provided, primary clinical reviews would be performed within the existing office/review division, however for novel products (i.e., New Chemical

Entities and novel new biologics, as well as companion medical devices) the supervisory review and signoff would be the responsibility of the COE. This approach allows for minimal disruption to day-to-day review functions, with review staff receiving specialized support and oversight from the COE. Other review disciplines (e.g., toxicology, chemistry) would remain independent from the COE. While the Oncology COE houses signatory authority for all oncology products at the COE level, that is not a prerequisite for this proposed COE, which could consider two other alternatives: (1) only signatory authority for New Molecular Entities and novel biologics, or (2) no delegation from existing signatory authority.

Initially, current FDA officials with substantial expertise in the rare disease development and review could serve in joint appointments in their current position and within the COE. This approach would allow for all COE staff to understand the existing processes and procedures of the various centers, which would help inform the establishment of COE intra-Agency policies and procedures to implement the COE responsibilities. This would also allow for FDA staff from areas where rare disease drug development and approval has been particularly well-established (e.g., inborn errors of metabolism, gene therapy, Cystic Fibrosis) to share their learnings and insights to inform best review practices in rare diseases.

(2) In order to build rare disease expertise across the offices/review divisions conducting primary clinical reviews, **each office/review division could have a deputy or associate director for rare diseases**. This would allow for a dedicated staff person to manage the day-to-day oversight and review of rare disease applications in that office/review division, as well as coordinate with the Rare Disease COE staff early in products' development. This is similar to the model employed by CDER review divisions where a Deputy Director for Safety, in conjunction with reviewers dedicated to safety issues, reviews safety-related activities for new drugs in coordination with the CDER Office of Surveillance and Epidemiology. Similarly, each division has an Associate Director for Labeling that each coordinate with the Director the OND-wide Labeling Development Team for consistency across divisions. Additional FTEs would allow for additional review capacity, as well as create greater opportunities for advancement into leadership positions by review staff.

(3) In order to provide FDA with access to external advisors to advise on issues of rare disease medical product development and review, **a Rare Disease Advisory Committee could 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. Members would be selected from among authorities knowledgeable and experienced in rare disease research and development, and this Rare Disease Advisory Committee would complement the specialized medical expertise of the FDA disease-area specific advisory committee.

Conclusion

We stand on the threshold of a new era in which scientific advances in many areas (e.g., RNA-targeting drugs, stem cell and gene therapies, companion diagnostics) are opening up the possibility of profound improvements, sometimes bordering on "cures," being close at hand. Harvesting these transformative therapies and bringing them to the benefit of patients may be encouraged by fostering greater visibility and enhanced regulatory consistency by considering establishment of a Rare Disease COE, a standing Rare Disease Advisory Committee and Office/Division leadership specifically dedicated to addressing the challenges inherent in the regulation of novel therapies for rare diseases. Most of all, initiating a dialogue about such possibilities may jumpstart brainstorming that may result in other related developments beyond just increased visibility for rare diseases therapies and Congressional appropriations and actions (e.g., a practical way to enhance and augment the prominence of surrogates and Accelerated Approval).