RECOMMENDATION 2: ADVANCE INNOVATION FOR RARE DISEASE

Key takeaways:

- Rare diseases affect an estimated 30 million Americans and impose substantial burdens, but only about 5% of those diseases have FDA-approved treatments.
- Developing rare disease therapies is uniquely challenging due to factors such as the small patient populations and often limited understanding of the diseases.
- Products for rare diseases must meet the same approval standards as other products, but FDA has taken a pragmatic approach to determining what evidence is needed. While this more flexible approach has enabled innovative approaches, developers lack predictability as to how FDA will apply its requirements.
- FDA should provide greater specificity, consistency and predictability by finalizing draft guidance, promoting greater coordination through the Rare Disease Innovation Hub and working with Congress to codify certain approaches.
- FDA should support scalable approaches to developing products for extremely rare and "n of 1" diseases, including by expanding the Platform Technology Designation Program for Drug Development to specifically address rare diseases.
- FDA should enable greater use of external controls in studying rare diseases.
- FDA should address the impact of the IRA on rare disease therapy development.

As FDA works to facilitate modern approaches to evidence generation, it should give particular focus to advancing the frameworks for developing treatments and cures for rare diseases. There are as many as 10,000 identified rare diseases (defined as any disease or condition that affects fewer than 200,000 people in the United States) that affect an estimated 30 million Americans, but only about 5% of those diseases have FDA-approved treatments.[74] Many of these diseases involve severe or life-threatening conditions that worsen over time and impose substantial and tragic burdens on American families, including many progressive conditions that impair children's development and cut short their lives.[74,75] Rare diseases also impose substantial economic burdens: One recent study found that the 2019 U.S. costs associated with 379 rare diseases were $997 billion.[76]

Unfortunately, developing drugs and biologics for rare diseases involves distinctive scientific, clinical, and ethical challenges. Small and often heterogenous patient populations can make traditional, randomized clinical trials infeasible, and the severity of many rare diseases can make the ethics of placebos especially challenging. In addition, there is often limited information on what course the disease takes absent treatment (often referred to as its "natural history"), which can make it difficult to generalize from anecdotal reports or know what outcomes to measure when studying a treatment. And many rare diseases progress slowly, meaning that it can take years to tell what effect, if any, an investigational treatment may have. For a patient who is not receiving that treatment as part of a study, waiting years for a trial to be completed could have severe or fatal consequences.[74,77,78]

FDA has launched a variety of programs to help address these challenges, including programs to advance scientific knowledge and provide early support for rare disease development programs.[79–81] In late 2024, it established a Rare Disease Innovation Hub to coordinate activities across the agency's drugs and biologics centers.[82] In addition, while products for rare disease must meet the same approval standards as other products, FDA has taken a pragmatic approach to determining what evidence is needed to meet these standards. This approach has included flexibility on the design, size and number of clinical trials needed to demonstrate substantial evidence of effectiveness; using surrogate endpoints (early markers of a product's effect that are predictive of its eventual clinical benefit) when possible to reduce the time needed to study a product before approval; using the accelerated approval pathway to enable more timely patient access based on a likelihood of clinical benefit; and accepting greater uncertainty about a product's effectiveness when it would address a significant unmet need and developing more robust evidence is not feasible.[83]

These steps mark important progress in addressing the regulatory challenges of developing rare disease products, but much more can and should be done. FDA should prioritize actions to further advance innovative product development to address the serious unmet needs in this space.

Recommendation 2.1: FDA should provide greater specificity, consistency and predictability as to how it will assess the evidence for rare disease products

As FDA continues to develop and refine its policies for regulatory pragmatism in rare disease product development, it should prioritize actions to ensure that its policies and approaches are consistently and predictably applied across centers and review divisions. Reducing regulatory uncertainty is important in any context, but particularly so when addressing rare disease, because (1) the challenges of development using conventional methods often leads developers to rely on innovative methods for which there may be limited precedent; (2) small patient populations may limit opportunities for financial return on investment, thereby making regulatory

certainty all the more important; and (3) developers targeting a particular rare disease area may have product candidates that fall into multiple product classifications (e.g., drugs, biologics and medical devices), such that consistency in regulatory feedback is critical.

A recent report by the U.S. Government Accountability Office found that product sponsors are concerned about the consistency with which FDA applies its review standards to rare disease development programs. In one example, a sponsor reported an experience in which one FDA product center was reluctant to accept a surrogate endpoint for a disease even though another center had already accepted the same endpoint for the same disease.[83] When regulatory standards are applied inconsistently, it creates uncertainty as to what approaches are likely to pass muster. By applying its authorities more predictably, FDA can reduce this uncertainty and facilitate more product development that is likely to align with regulatory expectations.

FDA can take several concrete steps to advance this goal:

First, it should prioritize revising and finalizing the draft guidance documents it has already issued. In 2021, an FDA-commissioned analysis of decision-making on "borderline" applications found that the agency "has no mechanism to find or tradition to cite similar cases when weighing evidence for approval, resulting in stand-alone, bespoke decisions."[84] Even if agency staff are willing to think flexibly about what evidence of effectiveness is required for each rare disease, it is difficult for product sponsors to invest in development programs when it is unclear how reviewers will apply the agency's evidentiary requirements in any given case. Written guidance documents can help.

Although FDA guidance documents generally are not legally binding, they represent the agency's "current thinking," and FDA staff cannot depart from them without "appropriate justification and supervisory concurrence."[85] They provide a common touchpoint for reviewers and product sponsors alike and, as such, can introduce additional predictability and stability into the process. FDA can improve its guidance on rare disease in two key respects:

- *Provide more specific examples:* FDA should update its guidance to provide more case studies, hypothetical or real, that can guide reviewers and help align individual product decisions toward a more consistent agency policy.
- *Finalize draft guidance:* Unlike final guidance, draft guidance documents are issued for comment purposes only and are not meant for agency-wide implementation.[85] Although FDA has finalized some of its guidance on developing treatments for rare diseases,[86] much of the guidance describing approaches in this area is still in draft form, including guidance on early drug development,[87] natural history studies[88] and demonstrating substantial evidence of effectiveness.[83] Finalizing this guidance would enable the agency to formally implement the policies and better educate its reviewers to ensure consistent practices.

Second, FDA should empower the new Rare Disease Innovation Hub to promote consistent practices. The Hub was established with the explicit goal of "enhanc[ing] intercenter collaboration," including by addressing "cross-disciplinary approaches related to product review" and promoting "consistency across offices and Centers."[82] FDA should ensure that the Hub has the delegated authority and resources necessary to effectively meet these goals and practice, and that it does not simply become an added layer of bureaucracy.[89] To this end, the agency should report regularly on the specific work the Hub is doing to advance these goals, including its progress on efforts described in its strategic agenda,[90] the authorities and resources it is being given to do so, and the progress it is making to build a library of precedents that will enhance predictability for drug developers. If the Hub is successful, it would not only benefit the rare disease community, but it could serve as a model for other non-rare disease products to promote regulatory alignment across therapeutic areas regardless of the product modality.

Third, FDA should work with Congress to develop legislation that codifies many of the pragmatic approaches already being utilized. Such legislation would promote clarity and predictability by providing reviewers and developers alike with direct statutory language. This legislation should include specific direction on the use of quantitative patient preference information to guide FDA on the acceptability of varying uncertainty levels in its regulatory decisions, including with respect to clinical trial design and the ultimate benefit/risk approval assessment.[56,91]

To be clear, the approaches FDA has been using are fully consistent with existing statutory authorities; although the same approval standards apply to all drugs and biologics without regard to the prevalence of the underlying disease or condition,[92,93] FDA has considerable flexibility in how it applies those standards to weigh the benefits and risks presented by individual products.[94] However, the lack of statutory language addressing certain concepts—such as FDA's ability to accept a higher degree of uncertainty in appropriate contexts—can make it more challenging to ensure that those concepts are utilized appropriately across the board.

In advancing such legislation, it will be important not to inadvertently diminish existing authorities or approaches already being used in the rare disease context or otherwise. For this reason, any legislation should include language clarifying that (1) codifying the availability of particular approaches does not imply that the flexibility of using that approach is not available in other circumstances, and (2) FDA retains the flexibility to use approaches that are not specifically identified in the legislation.

Recommendation 2.2: Modernize pathways for extremely rare and "n of 1" diseases

The challenges associated with rare disease product development are particularly acute for extremely rare and "n of 1" diseases, in which the population (n) of people with the disease may be as small as just one or a few individuals.

Developing drugs and biologics in this context uniquely challenges the traditional frameworks for clinical research. For example, when the population is this small and there is limited information about how the disease might progress untreated, it can be difficult to know what effects—positive or negative—should be attributed to the treatment, or what dose and treatment regimen are most appropriate.[95] In addition, when the entire known universe of people suffering from the disease may be already receiving the product as part of a study, practical considerations may lead many researchers to maintain the product in perpetual study rather than pursue a regulatory approval for which there is no clear pathway. Given this reality, it is unsurprising that FDA's guidance on extremely rare and "n of 1" drug development is focused on helping academic researchers navigate the regulatory requirements of FDA's framework for studying investigational new drugs (INDs), not with submitting an application for product approval.[96]

Against this regulatory backdrop, the path to scalable commercial development for these products is highly uncertain. Much of the research is being conducted by academic investigators who do not have the experience or infrastructure to support large-scale development.[97] Nor is such development feasible while the products remain in investigational status under FDA's IND framework, which imposes strict limits on how drugs can be promoted, commercialized or compensated before they receive FDA approval.[98,99] Although there is precedent for some products to remain in investigational status for decades, supported by nonprofit organizations or the government,[95] that model is not designed to facilitate innovation at scale. FDA can be doing more to facilitate such innovation.

First, FDA should support scalable efforts to study products for multiple "n of 1" diseases as subgroups of broader diseases or conditions. As we gain greater understanding of the pathophysiology of various diseases, opportunities increase to categorize many diseases into subgroups, each responding differently to a given treatment, that can be researched in precise ways while leveraging shared infrastructure.[100] FDA should support efforts to research "n of 1" diseases under this model, such as through multiple smaller trials under a single umbrella (or in a single basket) that share common data standards and endpoints. To this end, the Rare Disease Innovation Hub should specifically include such efforts as part of its work to advance methods development including novel endpoints, biomarker development and assays, innovative trial design, real world evidence and statistical methods.[101] It should also look to learnings from efforts and pilot projects in other jurisdictions, such as the Rare Therapies Launchpad in the United Kingdom.[102]

Second, FDA should do more to facilitate greater use of section 506K of the Federal Food, Drug, and Cosmetic Act in the context of extremely rare disease. This provision, which Congress added in late 2023, authorizes FDA to designate certain technologies that can be used across multiple drugs or biologics (e.g., a nucleic acid sequence, molecular structure or vector) as "platform technologies," and then facilitate more streamlined development for products that incorporate these designated technologies.[103] This new authority has the potential to revolutionize development for extremely rare and "n of 1" diseases by enabling multiple products that share a common chemical backbone or other feature to achieve scalable efficiencies.

Unfortunately, FDA's recent draft guidance on the 506K designation program does not mention rare diseases at all.[104] This is a missed opportunity. FDA should revise the guidance to provide clear direction on how programs seeking to develop products for multiple extremely rare or "n of 1" diseases can use 506K designation to achieve efficiencies and scale not possible when developing each extremely rare product on a wholly distinct basis. FDA should also provide further guidance as to how such development programs can navigate the regulatory restrictions on commercializing investigational products[98,99] when building a commercial program around a designated platform technology. These guidance updates should be a priority regardless of whether FDA expects a critical mass of readily deployable platform technologies soon, since greater regulatory certainty can help provide a foothold for novel commercial arrangements.

Recommendation 2.3: Enable greater use of external controls in studying rare disease

Rare disease studies are often the clearest cases that would benefit from using ECAs, given that the patient populations are often too small to support traditional controls, and it can be ethically fraught to withhold potentially effective treatments from patients who have no other treatment options.[50,105,106]

Unfortunately, as discussed under Recommendation 1.1, FDA's existing guidance on ECAs could be read as overly discouraging, given its emphasis on challenges to the exclusion of helping developers identify appropriate use cases. As FDA updates this and other guidance to present examples and considerations for beneficial use cases, it should ensure that it addresses the unique challenges and opportunities associated with using ECAs for rare disease development. In its current form, FDA's draft guidance on ECAs does not address rare disease as distinct from other disease areas.[33] The guidance should be revised to provide specific considerations for rare disease.[107] In doing so, FDA should cross-reference and expand upon its draft guidance on natural history studies for rare disease, which contains a short discussion of using natural history studies as ECAs.[108]

FDA should also facilitate design approaches in which ECAs are used in connection with master protocols. For example, master protocols can be used to collect information for use as an external control in a subsequent trial,[109] or to enable the use of a single ECA to study multiple candidate treatments. However, external controls are carved out of the scope of FDA's draft guidance on master protocols.[53] FDA should update the guidance to include these topics and help guide innovative approaches.