

NASEM meeting kicks off study on FDA and EMA processes for rare disease drugs

This week, the National Academies hosted a two-day meeting to initiate a study requested by Congress to assess FDA and EMA practices for evaluating products to treat rare diseases. Presenters provided insight into current FDA policies for rare diseases, patient perspectives on these policies, and comparisons to policies of other regulatory authorities.

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NASEM's latest project: Processes to Evaluate the Safety and Efficacy of Drugs for Rare Diseases or Conditions in the U.S. and the E.U.

- **A new ad hoc committee** of the National Academies of Science, Engineering, and Medicine (NASEM) has been tasked with conducting a study on the processes for evaluation of drugs to treat rare diseases or conditions in the U.S. and the E.U. The FDA was required to contract with NASEM on the completion of this study per [Section 3202](#) of the Food and Drug Omnibus Reform Act (FDORA). This requirement is a component of the Helping Experts Accelerate Rare Treatments (or HEART) Act, which was added as a provision to the Consolidated Appropriations Act of 2023.
- **As incorporated in Section 3202 of FDORA, the HEART Act of 2022 requested that FDA perform several tasks related to rare diseases.** First, the bill required FDA to complete a detailed report on the operations and output of the agency's orphan drug program. This report must be provided to Congress before the end of FY 2026. The FDA must also convene at least one public meeting "to solicit input from stakeholders regarding rare disease patient burdens, treatment options, side effects of treatments, etc." The FDA must release a report on the proceedings of the public meeting and any recommendations within 180 days. Finally, the agency must complete a study via a contract with NASEM, focusing on the "processes for evaluating the safety and efficacy of drugs for rare diseases or conditions in the United States and the European Union." [\[Read Agency IQ's analysis of all the FDA requirements listed in FDORA here.\]](#)
- **The new NASEM committee is comprised of twelve members that represent perspectives from academia, industry, patient advocates, and regulators.** The Chair, JEFFREY KAHN, is Director of the Johns Hopkins Berman Institute of Bioethics. There are three other academic experts included on the committee: Jonathan Watanabe of University of California-Irvine, Anaeze Offodile of Memorial Sloan Kettering and Shein-Chung Chow of

Duke University. The industry perspective will be provided by GAVIN HUNTLEY-FENNER, who provides consultative guidance to sponsors and law firms. And the regulatory perspective will be provided by HANS-GEORG EICHLER, a prior senior medical officer at the European Medicines Agency (EMA); ANNE PARISER, who brings decades of experience in rare diseases from both the NIH and FDA; and STEVEN GALSON, a prior acting surgeon general and director of FDA's Center for Drug Evaluation and Research (CDER).

- **One-quarter of the committee is comprised of patient advocates who also bring a wealth of additional expertise.** PAT FURLONG is the president of Parent Project Muscular Dystrophy (PPMD) and a member of the Duchenne Community Advisory Board in Europe, with a prior career as a nurse practitioner involved in patient preference research. RONALD BARTEK, the current president of Friedreich's Ataxia Research Alliance, was previously a long-time federal employee working on defense, foreign policy, and intelligence issues. And Terry Jo Bichell, who serves as the CEO of COMBINEDBrain, has more than 20 years of experience as a public health nurse and an advanced degree in neuroscience.
- **AgencyIQ notes that *just one* member of the committee has direct experience working with the EMA** and *one* of the committee members (Pariser) currently works in the biopharmaceutical industry.
- **This week, the committee held its first meeting.** [The two-day meeting](#) (November 6-7) featured a series of presentations and Q&A sessions that were open to the public, along with intermittent closed-door sessions for committee members to confer amongst themselves.

What we heard at the meeting: FDA's perspective

- **The meeting was front-loaded with presentations from five FDA staff members on the agency's current processes and initiatives related to rare disease drug development.** Sandra Retzky, director of the Office of Orphan Product Development, kicked things off by clarifying the statutory basis for granting orphan drug designations in the U.S. Per 21 USC 360bb(a)(2)), orphan drugs are "drugs or biological products used for prevention, diagnosis, or treatment of a rare disease or condition, generally defined as affecting < 200,000 individuals in the United States." She noted that several incentives exist for stimulating orphan drug development, including tax credits, exemption from user fees, and seven years of market exclusivity awarded at the time of approval. She also spoke to FDA's priority review voucher (PRV) programs and the process for sponsors to be considered.
- **The FDA also provided an overview of trends in orphan drug product approvals since 2010.** The proportion of total CDER approvals that are orphan drugs has increased nearly two-fold between 2010 (29%) and 2022 (54%). Like CDER, the proportion of novel products approved by the Center for Biologics Evaluation and Research (CBER) has increased between 2010-2022. However, CBER has seen a much more dramatic increase in orphan drug approvals—in 2010, *not one* novel biologic was granted orphan drug status, whereas by 2022, 63% of novel biologics approved by CBER were orphan drugs.
- **A review of FDA expedited programs.** CDER's manager of Expedited Programs, Miranda Raggio, outlined the programs sponsors can leverage to prompt the quicker review of products to treat rare diseases. These include FDA's priority review of applications, Fast Track Designation, Breakthrough Therapy Designation, and the Accelerated Approval

Pathway. She also mentioned FDA's Regenerative Medicine Advanced Therapy (or RMAT) designation which, like the other expedited programs, speeds application review but can only be used for cell and gene therapy products.

- **Insight into the agency's other initiatives related to rare disease drug development.** Next, KERRY LEE, CDER's associated director for Rare Diseases, and JULIENNE VAILLANCOURT, policy advisor and rare disease liaison for CBER, touched on multiple other agency initiatives to encourage rare disease drug development. One such initiative is CDER's Accelerating Rare Disease Cures (ARC) Program, an umbrella effort to undertake several discrete tasks related to rare disease drug development, patient engagement, and product approval. Another is the joint CBER-CDER Rare Disease Endpoint Advancement (RDEA) pilot program, which offers a limited number of sponsors the ability to bring forward proposals on novel efficacy endpoints for rare diseases for consideration and feedback. There is also the Complex Innovative Trial Design (CID) Meeting Program, a component of the most recent reauthorization of the prescription drug user fee amendment (PDUFA) VII. This program isn't limited to rare disease products but likely has applicability given the utility of novel trial designs to enable product assessment in small patient populations.
- **Finally, the agency reviewed existing collaboration efforts between FDA and EMA on overarching regulatory issues.** Katherine Tyner, FDA's liaison to the EMA, spoke to existing formal collaborations. First, she stated that FDA and EMA offer fellowships, which are short exchange programs that allow agency staff to visit and learn about a specific topic from the other regulator over the course of two weeks. Next she discussed EMA-FDA cluster meetings, which were initially set up in the early 2000s as an avenue to facilitate discussion on pressing regulatory topics of shared interest. Today there are 31 clusters across numerous therapeutic areas and other topics of interest, including one that is specific to orphan drug products. While these meetings were originally just between FDA and EMA, other regulators now participate, and the topics discussed range from high-level policy issues to specific applications under review by multiple agencies.
- **Parallel Scientific Advice (PSA): An opportunity for collaboration between the sponsor, the FDA, and the EMA.** These exchanges are initiated when sponsors formally request a meeting between the two agencies for an application that has been submitted to both. PSAs enable regulators to discuss any potential issues with the application and are intended to result in less duplication of work for sponsors in situations where both regulators determine additional information or studies might be required. It also offers sponsors insight into the discussion of the application which usually occurs behind closed doors. In theory, this should provide the sponsor with a clearer understanding of how certain regulatory decisions are made and/or how the issues raised by regulators should be addressed.

What we heard at the meeting: The rare disease perspective

- **One particularly insightful session described the series of events which culminated in the NASEM study.** This background information was shared by SAIRA SULTAN, a policy consultant at the Haystack Project, who led the charge on getting the HEART Act passed last year. Started in 2016, [the Haystack Project](#) is a nonprofit coalition of 140+ ultra-rare disease patient organizations working together to advance patient access to novel treatments, specialists, and diagnostics for extremely rare conditions.
- **According to Sultan, it all started with a patient group outside of Haystack that had been shopping the legislation around the Hill.** The group was encouraged by

Congressional staff to move forward with the bill; however, the group recognized that they needed partners to gain traction. As Sultan described, the group pitched it directly to the 100+ organizations which belong to Haystack and was met with “resounding interest.” The groups are hopeful that this study will shed light on the root cause of these issues, and how they can be addressed moving forward.

- **The patient groups who were pushing the HEART Act forward last year are eager to see the NASEM study touch on several key issues.** First, they want committee members to carefully inventory the flexibilities, authorities and/or mechanisms available to regulators in the U.S. and the E.U. which could be used in the context of rare diseases. Secondly, the groups are requesting that the NASEM study assess how both regulators consider supplemental data—including data associated with open label extensions studies and expanded access programs specific to rare diseases or conditions—during application review. Interestingly, a third point that did not actually originate from the patient organizations but was instead promoted by the FDA, is an assessment of the “collaborative efforts between U.S. and E.U. regulators on: product development programs under review, policies under development and/or recently issued, and scientific information related to product development /regulations.”
- **Patient groups would like the committee to carefully consider not just *which* flexibilities regulators have, but *if, how and when* they are actually using them.** “I can't tell you how often in the back and forth with FDA and Congress and Haystack Project as we were negotiating the language for each of these provisions, that we were repeatedly told by FDA that they have all the flexibilities and authorities they need, and that this legislation was not needed. This study was not needed,” Sultan said. For this reason, Sultan said it's key that the study not just assess which flexibilities FDA already has but how they are using them, whether they are being used consistently, whether some divisions are using them while others aren't, and more.
- **Sultan also stressed the importance of a comparison between what is being done in the U.S. versus the E.U.,** although she noted that it wasn't included in the committee's current “statement of work.” She referred to an example where a product was approved by the EMA but not by the FDA. In this case, the European regulators were willing to accept additional data that had been gathered after the marketing application was submitted, but prior to the final decision on the application. In contrast, the FDA was unwilling to consider the additional year of data. She remarked, “It doesn't mean that they didn't have the flexibility or authority to do so, but did they use that flexibility or authority? Or did they simply not have it? What they told the patients was that ‘they simply didn't have it,’ and so, the comparison I think is really important.”
- **Patients and patient advocates are also hoping for a review of the remit and composition of FDA advisory committees.** “We were told repeatedly during negotiations on the HEART Act that they [FDA] had the flexibility and did not need help—or did not need legislation—to be able to ask expert clinicians in the actual disease to participate in an advisory committee meeting in a non-voting fashion, for example,” said Sultan. But she said patient groups want to see these experts in actual voting roles. She continued, “And we're often told, ‘Oh yes, we have expertise on the advisory committee’ but when the patient group asks who that is, it's a generic geneticist. That is not the same as a clinician with actual experience treating an extremely rare disease.”
- **Patient groups see many of the current activities performed by FDA as performative exercises that lack meaningful impact, said Sultan.** Putting it bluntly, she described FDA's Patient-Focused Drug Development sessions as “dog and pony shows.” While a few organizations in the Haystack Project have had positive experiences with these meetings, the overwhelming majority have not. “It's not helpful for them to know that the Office of Patient Engagement is attending or that the Office of Orphan Drug Products is attending

because they in no way affect the decision on the actual application,” she reinforced. Furthermore, patient groups don’t know whether any reviewers attend these meetings, and if they do, Sultan said they’re not actively participating or asking questions, “How is it possible that a disease you have never heard of—that affects 500 people in the United States—that you have not a single question or follow-up clarification for them?” Yet preparing for and attending these meetings is burdensome for patient groups, not just in terms of the logistics but also in terms of monetary investment. So, she clarified, it’s frustrating for patients to feel as though the meetings are not actually being used to make decisions on applications.

What we heard at the meeting: Comparisons between the FDA and other regulators

- **The Centre for Innovation in Regulatory Sciences (CIRS) offered input on an important question: What differences in processes or practices between the U.S. and the E.U. could ultimately impact patient access to treatments for rare conditions or diseases?** A small nonprofit located in the U.K., CIRS has been working to bring together industry, policymakers, regulators, payors and academics for more than 35 years. Since 2002, the organization has used a “benchmarking” system developed to enable direct comparisons between health authorities that are operating within different government structures and have different regulatory pathways in place. The data that’s been used to create and continually refine the benchmarking system is collected from the E.U., U.S., Japan, Canada, Switzerland, and Australia; CIRS is currently working to incorporate data from Brazil and China as well.
- **One critical consideration for the committee: Most regulatory authorities employ different definitions for “rare disease.”** In the U.S., sponsors may qualify for an orphan drug designation if the product is intended to treat an indication affecting fewer than 200,000 people within the country. In Europe, products which treat diseases occurring in less than five in 10,000 people qualify for the EMA’s orphan drug designation, although AgencyIQ notes that the E.U. is currently considering a change to this definition as part of proposed revisions to its pharmaceutical legislation. HealthCanada sets the bar for rare diseases at “fewer than one in 2,000 people,” which is technically aligned with the current EMA definition. In China, sponsors can qualify for orphan drug status if the disease affects less than 50,000 people in the country.
- **According to CIRS current data, orphan drug approvals have accounted for an increasing proportion of overall approvals at both EMA and FDA.** In the E.U., orphan drugs accounted for 33% of new product approvals from 2013-2017 and 38% of new product approvals from 2013-2022. Similarly, orphan drugs accounted for 44% of FDA’s new product approvals from 2013-2017, and 55% of new product approvals from 2013-2022. The data also shows that the FDA has had more approvals, orphan or otherwise, when compared to the EMA. However, it does not identify the number of applications submitted to both agencies, so it’s hard to determine whether this higher rate is related to FDA processes or simply a differing rate of applications.
- **The therapeutic categories for approvals differ between the two regulators.** In the U.S., 52% of orphan drugs approved from 2018-2022 were anticancer therapeutics, while just 24% of anticancer treatments were approved as “non-orphan” products. Even across other therapeutic areas, this trend was consistent, showing that some therapeutic areas are much more likely to gain orphan drug designation than others (e.g., blood and blood-forming agents). In contrast, EMA approved a comparable proportion of orphan and non-orphan

products across just about every therapeutic area. While anticancer treatments still accounted for a large proportion of orphan product approvals, about half of anticancer treatments were not granted orphan drug designation.

- **Still, the FDA tends to approve products more quickly than the EMA across all product and designation types.** This trend especially stands out for orphan drugs. Per CIRS, there are several underlying issues which could be contributing to these trends. To start, sponsors with greater resource availability and/or with more experience are likely to have fewer application issues, leading their dossiers to be reviewed and acted on more quickly. Another limitation is that it's much more challenging to find data on products that didn't receive approval versus those that did.
- **The FDA also tends to award orphan drug designations more frequently than the EMA.** CIRS created a list of 25 products approved by all five agencies with at least one orphan designation from one of the five regulators (N=25). The E.U., Switzerland, and Australia were generally consistent with one another in granting about 50% of these products orphan drug designations. In contrast, the U.S. and Japan both granted orphan designations to 88% of the products. According to the CIRS presenters, this shows that there is a need for better alignment among health authorities when it comes to recognizing and utilizing flexibilities and authorities to speed access to products intended to treat rare diseases.
- **CIRS has several recommendations for regulatory authorities to improve transparency and predictability.** First, there is concern that regulatory "incentives" have become more like awards (offered and reassessed at the very end of the process) and that agencies could work to build incentives and/or dialogue earlier in development. Secondly, regulators should reach a shared understanding of what data is required from sponsors and how the collection of this information might be streamlined to make it easier for submission across multiple authorities. Finally, following product approval, additional research could focus on market entry across the countries/regions to identify barriers in achieving timely patient access.

What's next?

- **The clock is ticking for NASEM to complete the study and submit a report to the FDA.** According to a Statement of Work (SOW) accompanying FDA's [notice of intent to Sole Source to NASEM](#), the final report is due on or before October 31, 2024. In addition to a draft and final report, NASEM is responsible for providing FDA with documentation of meetings and quarterly progress reports. The report itself is set to provide "recommendations as it relates to improving treatments for rare diseases." [[See AgencyIQ's full analysis of the SOW here.](#)]
- **The provisional committee appointments are open for comment until November 11.** Per [NASEM's website](#), the twelve members appointed to the committee are provisional and may change. The public can provide comment on the current provisional roster at this time, assisting NASEM in determining "whether the committee contains the requisite expertise to address its task and whether the points of views of individual members are adequately balanced such that the committee as a whole can address its charge objectively."
- **The key question for companies interested in rare disease regulatory policy: What changes might this lead Congress and regulators to make?** Congress' intent seems clear: This report is to form the basis of recommendations for future legislative changes, especially with respect to collaborative efforts. As [AgencyIQ has previously noted](#), one potential policy difference that legislators could seek to borrow is the E.U.'s definition of "rare," which uses a set percentage, rather than a specific number of patients, preventing rare diseases from becoming more rare as the population increases.

- **This study is being initiated at a time when Europe is actively debating changes to its provisions for orphan drugs.** Right now, the European Commission is in the midst of considering a major overhaul to its pharmaceutical legislation, which proposes to alter the regulatory protection incentives for medicines and orphan drugs. [\[See AgencyIQ’s analysis of how the original legislation may impact the orphan drug market here.\]](#) However, this legislation is being actively debated, with Parliament's recent proposed position further trimming orphan drug exclusivity. [\[See AgencyIQ's analysis of Parliament's positions on this and other provisions in the proposed pharmaceutical legislation revisions here.\]](#) AgencyIQ will continue to cover this topic as the debates unfold.
- **The Haystack Project is currently advocating for the passage of a new, separate piece of legislation related to rare diseases.** The [Providing Realistic Opportunity To Equal and Comparable Treatment for Rare \(or PROTECT Rare\) Act](#) seeks to ensure that off-label products used to treat rare and ultra-rare diseases are available to patients covered by Medicare or Medicaid. One of the provisions contained in the bill would allow public payers to leverage additional sources such as “peer-reviewed literature” or clinical guidelines to determine whether a treatment meets the criteria of a “medically accepted indication” for a rare disease, specifically. The bill would also require private payers to “create an expedited review pathway for formulary exception, reconsideration, and/or appeal of any denial of coverage for a drug or biological prescribed for a patient with a rare disorder.” The bipartisan House bill is sponsored by Mike Kelly (R-PA), Doris Matsui (D-CA), Neal Dunn (R-FL) and Mike Thompson (D-CA).

Featuring previous research from Alec Gaffney and Amanda Conti.

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Key documents

- [Processes to Evaluate the Safety and Efficacy of Drugs for Rare Diseases or Conditions in the United States and the European Union \(Meeting 1 - Virtual\)](#)