Doctors for America Comment on Fit-for-Purpose Rare Disease Framework Initiative

Re: Docket No. FDA-2026-N-12214, Fit-for-Purpose Rare Disease Framework Initiative; Public Meeting; Request for Information and Comments

Doctors for America (DFA) is a national organization of more than 40,000 physicians and medical students in all 50 states and every specialty. Its FDA Task Force advocates for patient safety, transparency, and accountability at the agency. We welcome FDA's stated aim to provide greater clarity, consistency, and predictability in rare disease regulatory decision-making. We comment today on two of the four areas in the notice: (1) consistency and predictability of FDA's drug development and review requirements, and (2) engagement with outside experts, specifically the role of public advisory committees.

Our central point: for patients and their physicians, predictability means a stable, transparent evidentiary standard that is applied the same way across products, divisions, and leadership changes. Flexibility in *how* evidence is generated is appropriate for rare diseases. Flexibility in *whether* a drug must be shown to work is not.

Rare disease drugs are held to the same statutory standard of substantial evidence of effectiveness as all other drugs; what varies is how that standard is met. FDA has long exercised this discretion: analyses in *Therapeutic Innovation & Regulatory Science* found that for roughly two-thirds of non-cancer orphan drugs approved through mid-2014, FDA did not require the conventional quantum of effectiveness evidence [1,2]. That flexibility has cost. In a *JAMA* study, pivotal trials for orphan cancer drugs enrolled far fewer patients than non-orphan trials (median 96 vs 290) and were less often double-blind (4% vs 33%) [3].

The problem today is less the level of the bar than its movement. Since 2025, FDA has issued at least 23 complete response letters for rare disease therapies, and Senate testimony in February 2026 described review processes as inconsistent with the agency's public commitments to flexibility [4]. Examples cut both ways. In January 2026, FDA reportedly told one sponsor that a single-arm study it had previously accepted was no longer adequate and required a new trial [5]. In other cases, FDA reversed prior demands for additional studies [6]. Meanwhile, DFA's FDA Task Force has objected to approvals granted on insufficient evidence, such as leucovorin for autism, and called for release of the full approval package [7]. Major policy shifts have also been announced through journal articles rather than guidance, which academic commenters have noted conflicts with FDA's Good Guidance Practices regulation (21 CFR 10.115) [8].

Unpredictability in either direction harms patients. A shifting bar wastes scarce trial participants, delays effective therapies, and invites approvals that are later questioned, eroding physicians' confidence in the FDA label. Patients with rare diseases deserve therapies that work and are held to the highest standard for safety and efficacy.

Recommendations to Improve Trust and Transparency in the FDA

1. **Keep one standard, explained in writing.** State in final guidance that the substantial-evidence standard does not change for rare diseases and specify which forms of confirmatory evidence (natural history, biomarkers, mechanistic data) can satisfy it and how they will be weighed.
2. **Make agreements durable.** When FDA departs from a documented prior agreement on trial design or endpoints, it should explain the new scientific basis in writing, publicly, and in time for the sponsor to respond.
3. **Set policy through notice and comment.** Issue rare disease policies as draft guidance or rules with public dockets, not by press release or journal article [8].
4. **Publish the record.** Continue releasing complete response letters and post full review packages for every rare disease approval, including reviewer disagreements [7].
5. **Report on consistency.** The Rare Disease Innovation Hub should publish an annual summary of rare disease actions by center and division, with the evidence relied on, so that variation is visible and correctable.
6. **Fund the reviewers.** Consistent review depends on experienced staff. DFA has repeatedly warned that workforce cuts undermine rigorous review [9].

Advisory committees matter most where evidence is thinnest, which describes much of rare disease drug development. Single trials, external controls, and surrogate endpoints call for exactly the independent scrutiny an advisory committee provides. Outside experts test FDA's and the sponsor's analyses in public, minority views enter the record, and patients and clinicians are heard before a decision rather than after it. A public, reasoned recommendation is itself a source of predictability for sponsors and patients.

DFA has consistently called for public advisory committees on contested decisions, including traditional approval of lecanemab and the leucovorin approval [7,14], and has urged Congress to strengthen committees and keep them free of conflicts of interest [16].

Committees must also be run well. In 2024, an advisory committee voted 10–6 for elamipretide in Barth syndrome despite FDA reviewers' conclusion that multiple studies failed to show effectiveness, with some members citing anecdotal evidence [16]. The lesson is not to avoid committees but to focus them on the evidence.

Recommendations to Strengthen Advisory Committees

1. **Presume a meeting for high-uncertainty rare disease applications.** Convene a committee for first-in-class rare disease approvals that rest on a single trial, an external or natural-history control, or an unvalidated surrogate endpoint, and before FDA reverses a prior position on a program. When FDA declines, it should publish its reasons.
2. **Explain departures.** When FDA acts contrary to a committee's recommendation, publish the scientific rationale at the time of action.
3. **Ask evidence questions.** Frame voting and discussion questions around the adequacy of the data against the statutory standard, and present FDA's own analysis at every meeting.

4. **Seat the right experts.** Include rare disease clinicians, statisticians experienced in small-population designs, and patient representatives, with rigorous conflict-of-interest screening and public waivers. Make fuller use of specialized panels such as the Genetic Metabolic Diseases Advisory Committee.
5. **Use committees to set standards, not only judge products.** Convene them to advise on cross-cutting questions, such as when a traditional prospective trial is truly infeasible [8].

Patients with rare diseases need therapies that work, and their physicians need to trust that an FDA approval means a drug has been shown to work. A consistent, publicly explained evidentiary standard, together with routine use of well-run public advisory committees, serves sponsors, patients, and clinicians alike. DFA's FDA Task Force would welcome the opportunity to discuss these recommendations.

Respectfully submitted,

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