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Dismantling Barriers in Patient-Led Research: *Utilizing an AI-Enhanced Access-Centered Research Model to Evaluate the Integration of Patient-Reported Outcomes in FDA Orphan Drug Approvals*

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Background

Policy structures intended to elevate the patient voice have expanded, the open question is whether visible PRO inclusion has followed.

Patient-Focused Policy Context

The FDA's PFDD initiative and the COA Compendium emphasize integration of PROs into regulatory decision-making.

Evidence Gap

Despite these policy initiatives, empirical evaluation of PRO inclusion in FDA labeling for ODTs remains limited.

U.S. Health Policy and Orphan Drug Development

Timeline of regulatory milestones shaping patient-centered measurement

1983 — Orphan Drug Act

Introduced tax credits, user fee waivers, and market exclusivity to stimulate rare-disease drug development.

2012–2016 — PFDD & 21st Century Cures Act

Formalized patient experience data collection and expanded FDA use of RWE.

2018–2022 — PFDD Guidance & COA Compendium

Four methodological PFDD guidance documents matured alongside the COA Compendium, operationalizing fit-for-purpose measurement.

The Orphan Drug Act incentivized rare-disease drug development while enabling, but not requiring, the integration of patient perspectives.

Methods

Study design & eligibility

Design: Retrospective review of FDA ODTs from 2018 – 2024.

Eligibility: Therapies were included if they held an active orphan designation at approval and had accessible FDA labeling and regulatory documentation.

Variables Extracted: PRO terminology, PROM instrument names, endpoint hierarchy, disease classification, regulatory attributes (NME, BLA, BTD, RMAT).

Primary Outcome of Interest: Presence of PRO or PROM content in FDA-approved labeling for ODTs.

Analytical Approach: Descriptive analyses evaluated patterns of PRO and PROM inclusion across regulatory classifications and disease categories.

Data sources & AI-enabled extraction

Data Sources: FDA Orphan Drug Designation database, FDA product labeling (Drugs@FDA), pivotal Phase III clinical trial records (ClinicalTrials.gov), COA Compendium.

AI-Enabled Extraction: Regulatory documents and FDA labeling were structured using Tabular by Reliant AI, enabling extraction from unstructured regulatory and clinical trial sources.

Hybrid Human–AI Workflow: Tabular was integrated with human expertise to facilitate large-scale extraction. The tool's value was evaluated through its ability to support a patient-investigator–led team in completing an evidence review typically requiring 9–12 months.

Objectives

1. Evaluate the frequency of PRO and PROM inclusion in FDA ODTs approved between 2018 and 2024.

2. Examine whether PRO/PROM inclusion varied across regulatory and development attributes — NME status, BLA status, and expedited designations such as BDT and RMT.

3. Demonstrate how a human-in-the-loop AI workflow within an access-centered hybrid research model enabled a patient-investigator–led team to conduct a large-scale regulatory evidence review within a compressed timeline.

> ***"They [patients] are best suited to indicate which therapeutic effects they want most from a therapy, which can then be used to develop outcome measures to test clinical benefit in clinical trials." — Aartsma-Rus, 2022***

Results

PRO inclusion in FDA orphan drug approvals

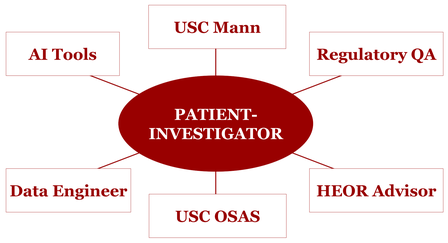
3,046 *drugs analyzed*

150 *ODT approvals*

25 *PRO-positive labels*

Access-centered Team Hybrid Model

Patient-investigator at the center, supported by 6 cross-functional pillars decreased timelines from 9 to 3 months.



Subgroup findings within the 150-approval cohort

24 of **116** rare-disease orphan drug approvals included PRO content ***(20.7%)***

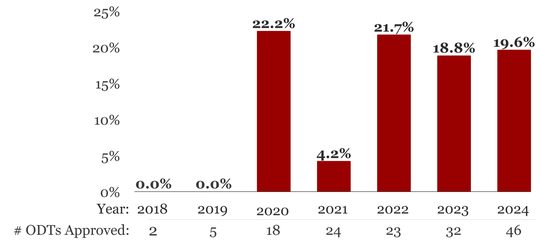
1 of **34** non-rare orphan drug approvals included PRO content ***(2.9%)***

14 of **96** BTD-designated approvals included PRO content ***(14.6%)***

0 of **150** approvals received RMAT designation during the study period ***(0%)***

PRO inclusion by year, 2018–2024

PRO inclusion in orphan drug approvals by year (2018–2024).



Sponsors with repeated PRO/PROM inclusion

6 of 15 PRO-positive sponsors (40%) included PRO across multiple years

Sponsor	Years with PRO	Frequency
Loxo Oncology (Eli Lilly)	2020 · 2022 · 2024	3 years
AstraZeneca Pharmaceuticals	2020 · 2024	2 years
Flamel Ireland / Avadel	2023 · 2024	2 years
Pfizer Inc.	2022 · 2023	2 years
Rhythm Pharmaceuticals	2022 · 2024	2 years
Sarepta Therapeutics	2023 · 2024	2 years

Discussion

Reporting transparency remains inconsistent

Despite PFDD guidance, transparency and methodological rigor of PRO documentation remain uneven across submissions — substantial gaps persist in reporting how patient perspectives informed development.

Validated outcome measures are lacking

Validated outcome measures are lacking in many rare diseases, sponsors may lack ready-to-use, validated tools, and few late-phase programs demonstrate sufficient validation for the target population.

Orphan designation extends beyond rare diseases

23% of orphan-designated approvals were for non-rare conditions, and only 2.9% included a PRO claim — a broader utilization of the policy's incentives than originally intended, potentially diluting PFDD relevance for sponsors.

Three Guiding Principles for Inclusive Research

Intentional design ensures that disability is never a barrier to high-level scientific contribution.

1. **Shift the paradigm:** Move from *"providing accommodations"* to *"designing for capable patient-investigators."*
2. **Leverage tech:** Human-in-the-loop AI and assistive tools open access to complex datasets and streamline analytics for everyone.
3. **Include diverse perspectives:** Investigators with lived experience contribute unique perspectives that drive life-sciences innovation.

Conclusion

PRO and PROM inclusion and reporting is limited

Since the introduction of PFDD-guidance, PRO inclusion has increased, but adoption is still not widespread.

8.3% → **16.7%**

Hong et al. (2019) baseline — 2002–2017 · ODT approvals

Current study — 2018–2024 · ODT approvals

Expedited programs showed no clear relationship with PRO evidence

BTD submissions rarely describe patient engagement, few RMAT programs detail mechanisms for integrating patient contributors

AI-enabled access-centered research expands participation

Hybrid human–AI workflows (USC × Tabular by Reliant AI) reduced manual barriers and enabled a principal investigator with a disability to lead a complex multi-source regulatory analysis — modeling accessible research operations for academic and industry settings.

Inclusive infrastructures, rigorous evidence methods, and patient insights can collectively shape the next era of rare-disease innovation and healthcare decision analysis.

Abbreviations: AI – Artificial Intelligence, BLA – Biologics License Application, BTD – Breakthrough Therapy Designation, COA – Clinical Outcome Assessment, FDA – Food and Drug Administration, NME – New Molecular Entity, ODT – Orphan-Drug Therapeutic, OSAS – Office of Student Accessibility Services, PFDD - Patient-Focused Drug Development, PRO – Patient Reported Outcome, PROM – Patient Reported Outcome, RMAT – Regenerative Medicine Advanced Therapy, RWE – Real world evidence, U.S. – United States, USC – University of Southern California

References: Hong DS, *et al.* Orphanet Journal of Rare Diseases. 2019;14(1):38. DOI: 10.1016/j.jval.2019.03.010; Aartsma-Rus A, *et al.* Nucleic Acid Ther. 2022 Apr;32(2):118-122. doi: 10.1089/nat.2021.0048.

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