Real World Evidence (RWE) Remains Essential for Rare and Ultra Rare Disease Drug Development

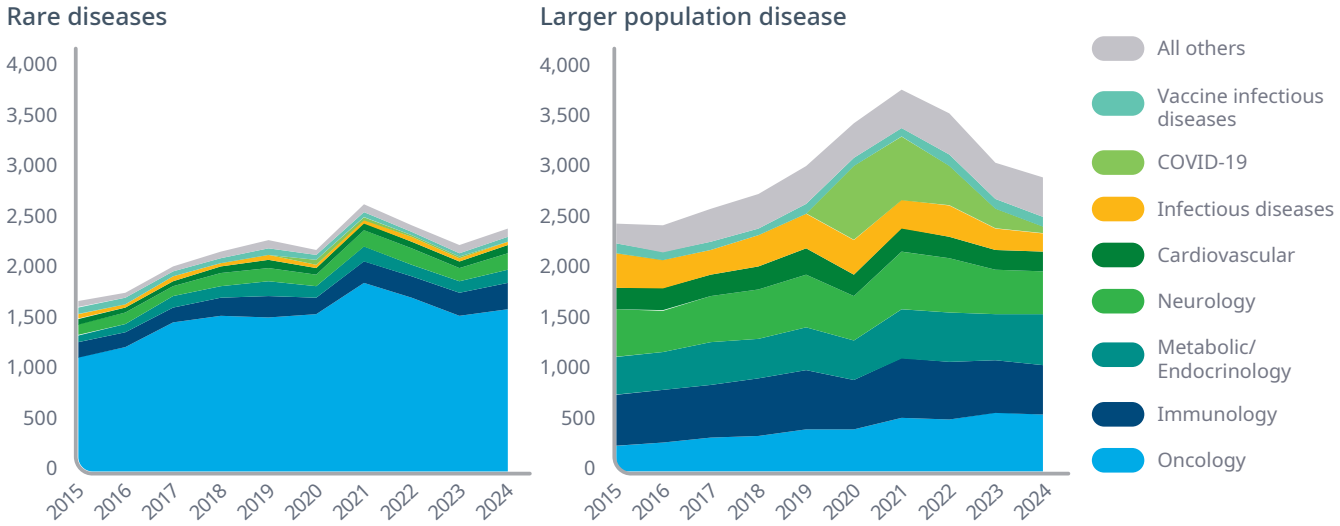
Introduction

Rare diseases have different definitions regarding their prevalence: around <1/1650 affected individuals in the U.S. (<200,000 people in the U.S.), and in the EU, no more than 1 in 2,000 people.[1-2] In total, there are an estimated 7,000-8,000 rare diseases, meaning tens of millions of lives are affected by rare disorders and many of these have no available therapies. Extremely rare diseases, or "ultra-rare" disorders do not have a strict definition but references often use a prevalence of <1/50,000.[3-5]

Specific (or "separate" or "special") regulatory pathways for accelerated and orphan drug development to treat rare and ultra-rare diseases have been ongoing for decades, and the rare disease product pipeline remains robust, with many rare oncology trials in addition to other therapeutic area targets such as immunology, neurology, and metabolic conditions (Figure 1).

Rare oncology accounted for most rare disease trial starts, while trials in larger population diseases were more varied

Figure 1: Industry sponsored interventional trials by start date, Phase I to III, 2015–2024



Ultra-rare disorders in recent news, and RWE has been contributing to the rare disease drug development pathway for decades

On April 18th 2025 during an interview on the *Megyn Kelly Show*, FDA Commissioner Marty Makary announced plans in support of accelerating the approval pathway for ultra-rare disorders, including "plausible mechanism" pathways as an alternative to traditional randomized controlled trials, which are often impractical or infeasible for ultra-rare disease patient populations.[6] While these plans are yet to be detailed, there are a number of existing examples of new products approved under alternate study designs, including a number of products whose approval package has included Real-World Evidence (RWE) for rare diseases that can inform the new planned approach.

Particularly in cases (especially rare disease cases) where progression may be slow, clinical endpoints are limited or insufficient for clinical efficacy evaluation given the relatively short time frame of a clinical trial. Using surrogate endpoints, like biomarkers, can provide strong predictive value of clinical efficacy. Notably, there have been well over a dozen rare disease treatments approved largely using disease-cause biomarkers, including some Urea Cycle disorders (Ammonia levels), Phenylketonuria (Phenylalanine levels), Wilson disease (Copper levels), Gaucher disease (Spleen size/Hemoglobin levels), and Fabry disease (Renal substrate storage).

Unfortunately, given underdiagnosis and diagnostic delay often inversely correlated with disease prevalence, many patients are identified only after irreversible clinical damage has already occurred, Clinical benefit may then be harder to demonstrate, but establishing plausible efficacy through disease-cause biomarkers can lead to accelerated approval, providing a necessary impetus for adoption of newborn screening to identify pre-symptomatic at-risk individuals where greatest efficacy can be achieved through earlier intervention.

IQVIA has significant experience in ultra-rare disorders, with 50 trials addressing ultra-rare (~<1:50,000) indications covering years 2013-2023. In the past 10 years, IQVIA has conducted over 500 trials in rare disease.

Novel uses of RWE such as external comparators (e.g., historical controls) are recognized as a way to contextualize the results of a single-arm trials for rare diseases and other special circumstances (Burcu et al, 2020).[7] Often in very rare conditions, historical information on patients, or fully retrospective cases are needed to support comparisons to a treatment arm for clinical development (Ugoji et al, 2024).[8] The approach has been used in the approval process for drugs such as Brineura™ and Zolgensma®, and the FDA has approved several drugs using this method.

Case study: Accelerated product approval based on a single-arm trial with benchmark based on real-world data

DRUG A

- **Conditionally approved** by the EMA, US and Japan for an ultra-rare cancer based on tumor response
- The trial was an **open label**, **single arm**, multi-center study
- **Real-world benchmark** established in the Europe as supportive data through a **de-novo registry collaboration**

	Clinical Trial N = 88	Real-World Benchmark EU Registry N = 29
Overall Response Rate	33%	10%
# of Responding Patients	29 / 88	3 / 29
Median Duration of Response (Months)	86% > 6 45% > 12	1.9

An external comparator **establishes context** for understanding the results of a single-arm study

In 2023, the FDA published final guidance entitled 'Rare Diseases: Considerations for the Development of Drugs and Biological Products Guidance for Industry,' supporting efficiencies and acknowledging the design constraints posed by drug developers associated with patient population limitations.[9] Flexibility in design for rare conditions with no approved treatments and high unmet need continues to be emphasized by the Agency and encouragement for sponsors to engage early with the FDA to discuss their program(s). In more adapted or innovative programs, it is best to prepare to 'co-create' with the FDA, especially as regulations or guidelines evolve.

Conclusion

Rare and ultra-rare disease clinical research will continue to identify and test new therapies to close the gap on such high unmet need. The successful use of innovative trial designs to generate sufficient evidence will still require a high level of scientific rigor for regulatory decision-making.

Real-World Data (RWD) and RWE provides an opportunity for life sciences and patient advocacy partners to support rare disease patients and accelerate the approval of impactful treatments. In addition, these strategies will likely adopt new tools and technologies such as Artificial Intelligence (AI) to identify, predict, or evaluate patient outcomes more efficiently and effectively.

For more information about rare disease research experience and expertise at IQVIA

- **Rare Disease Research (R&D through Post-Approval)**
- **Patient Advocacy experience, leadership and participation**
- **IQVIA White Paper: Natural History Studies of Rare Diseases**
- **IQVIA Blog: A New FDA: Preparing for an Uncertain Landscape with a Refined Regulatory Approach**

References

1. Rare Diseases at FDA. Available from: https://www.fda.gov/patients/rare-diseases-fda#:~:text=on%20rare%20diseases?-,What%20is%20a%20rare%20disease?,drugs%20to%20treat%20rare%20diseases
2. European Commission: Research and Innovation. Available from: https://research-and-innovation.ec.europa.eu/research-area/health/rare-diseases_en
3. National Institute for Health and Clinical Excellence. NICE Citizens Council Report Ultra Orphan Drugs. London, NICE, 2004. [PubMed] [Google Scholar]
4. Huges DA, Tunnage B, Yeo ST. Drugs for exceptionally rare diseases: do they deserve special status for funding? Q J Med 2005; 98: 829–836. doi: 10.1093/qjmed/hci128 [DOI] [PubMed] [Google Scholar]
5. National Institute for Health and Clinical Excellence. Appraising Orphan Drugs. London, NICE, 2008. [Google Scholar]
6. Youtube interview Available from: https://www.youtube.com/watch?v=R4mojSYOTnQ&t=4s
7. Burcu M, Dreyer NA, Franklin JM, Blum MD, Critchlow CW, Perfetto EM, Zhou W. Real-world evidence to support regulatory decision-making for medicines: Considerations for external control arms. Pharmacoepidemiol Drug Saf. 2020 Oct;29(10):1228-1235. doi: 10.1002/pds.4975. Epub 2020 Mar 11. PMID: 32162381; PMCID: PMC7687199. https://pmc.ncbi.nlm.nih.gov/articles/PMC7687199/
8. Ugoji C, Hedit J, Largent J, Bratton E, Hester L, Keshavarzi S, Turner S, Mack C. Important tool in our rare disease toolbox: hybrid retrospective-prospective natural history studies serve well as external comparators for rare disease studies Front. Drug Saf. Regul., 17 December 2024. Sec. Advanced Methods in Pharmacovigilance and Pharmacoepidemiology Volume 4 - 2024 https://doi.org/10.3389/fdsfr.2024.1418050
9. FDA Guidance: Rare Diseases: Considerations for the Development of Drugs and Biological Products Guidance for Industry. 2023. Available from: https://www.fda.gov/media/119757/download