Ultra-precision medicine

New initiatives in *N*-of-1 drug development and clinical trial design offer the possibility of therapies for ultra-rare disease patients who have been long neglected by the drug industry.

'Personalized medicine' promised drugs tailored to individuals on the basis of their genetic makeup. Although that never materialized, its scion 'precision medicine' offers drug development for groups of genetically stratified patients sufficiently large to generate a return on investment. For the millions of others who suffer from ultra-rare disease—conditions with a prevalence of <1 case per 50,000 population—most of commercial drug development simply forgot them. Now that situation looks set to change.

A Comment in this issue describes n-Lorem, an ambitious not-for-profit initiative with a mission to discover individualized experimental antisense oligonucleotide (ASO) treatments for patients with ultra-rare conditions arising from a single, often de novo, mutation (for example, an indel, repeat or single point mutation). Since its founding last year, n-Lorem has built a network of public–private partnerships with Ionis Pharmaceuticals, Biogen, Ultragenyx, Charles River Laboratories, Covance, the Korea Institute of Toxicology and the US National Institutes of Health's Undiagnosed Disease Network to discover and develop individualized ASO drugs collaboratively with clinical investigators in academic medical centers. The effort aims not only to register new ASO drugs for ultra-rare conditions, but also to supply these patients with drugs, free of charge for their entire lifetime.

Since drug legislation was introduced for orphan conditions—defined as those affecting <1 in 1,333 people in the United States or 1 in 2,000 people in the European Union—drug development for rare diseases (rather than ultra-rare disease) has become a major focus for the biopharmaceutical industry. Despite the small market size of orphan indications, companies can still build franchises around high pricing, 7 years of market exclusivity, tax credits and exemptions from regulatory fees; indeed, as a share of overall drug approvals, new orphan drug approvals grew from 29% in 2010 to a high of 58% in 2018.

Even so, the process of bringing an orphan drug to market is anything but straightforward.

The small pool of affected individuals often translates into limited knowledge on disease pathophysiology, presentation and progression. Similarly, a lack of relevant animal models stymies understanding of disease mechanism, assessment of drug–target engagement and prediction of drug dosage and biodistribution. In turn, the limited number of physicians with disease expertise means diagnoses can be missed, delayed or inaccurate, with patients and families often enduring years of uncertainty before a definitive diagnosis. As a result, many patients are diagnosed too late in life for therapy to make a difference—if therapy is even available (only ~5% of the >6,000 known rare disorders have any kind of treatment).

For clinical research, disease natural history and disease heterogeneity complicate trial design and endpoint selection. The small and dispersed patient population complicates recruitment, and individuals presenting at different stages of disease may not meet trial enrollment criteria. According to the Tufts Center for the Study of Drug Development, trials for orphan diseases take ~4 years longer than average.

For ultra-rare disease, this convoluted process becomes next to impossible.

With a patient pool of just one person (or at best a handful of individuals) worldwide, not only do the economics not make sense for drug developers, but no unique regulatory pathway exists for individualized therapy.

N-of-1 trials—multicycle, randomized double-blind crossover comparisons of an approved drug and placebo (or other drug) in an individual—have been around for decades. But they have not been used (with a few exceptions) to assess the safety and efficacy of novel drugs untested in humans. It is this regulatory gap that two new draft guidances on ASOs from the US Food and Drug Administration (FDA) seek to address.

ASO drugs are the modality being developed at n-Lorem. Their relatively mature and standardized chemistry, modular designs, specificity against a patient's unique mutation, and ~10–12 month development time to prepare for first-in-human testing make them ideal candidates for individualized therapy. What's more, they are relatively cheap to make; 10 grams of ASO are sufficient to treat many patients for life.

A draft guidance released in January outlines administrative and procedural recommendations for ASO Investigational New Drug (IND) submissions. As well as detailing the required chemistry, manufacturing and controls (CMC) data, it addresses ethical and human subject protection considerations, safety reporting, and annual reporting requirements. It describes a communication plan for FDA interactions, given the likely involvement of academic investigators unfamiliar with agency protocol.

A second document, published in April, recommends specific non-clinical safety studies for an IND, including hybridization-dependent off-target assessments (both in silico and in vitro) and core safety tests. A single three-month, good laboratory practice–compliant toxicity study in a relevant animal model will be required to support first-in-human dosing.

These are the first steps in what will be an ongoing, multiple-year process. A key goal will be to standardize the process of identifying surrogate markers of disease for an *N*-of-1 trial and to create definitive guidance that can lead to an approvable pathway for *N*-of-1 products. Ultimately, the pathway should be applicable beyond ASOs to other individualized treatments: base-editing therapies, personalized mRNA drugs and vaccines, autologous gene and cell therapies, replacement proteins and others. In the more distant future, CMC quality control issues may feed into distributed benchtop manufacturing technology aiming to generate standardized individualized products at point of care.

Similarly, as human genome sequencing efforts progress, mutations initially identified in one or two people may subsequently be found in many more patients, opening up potential new indications that may grow to a sufficient size to become economically viable for commercial development.

Progress has already been rapid. Since opening its doors, n-Lorem has already received 75 applications, accepted 16 and initiated 7 patient programs. That is 16 people who now can dare to hope. ❐

Published online: 04 June 2021
https://doi.org/10.1038/s41587-021-00967-8