# OPINIONS

# Drugs Against Rare Diseases: Are The Regulatory Standards Higher?

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**The US Food and Drug Administration (FDA) recently issued a draft Guidance for Industry for Rare Diseases: Common Issues in Drug Development (referred to as "Rare Diseases Guidance"). In our opinion, the FDA should consider: (a) explicitly acknowledging the standards are higher for rare diseases for the reasons presented in this article; and (b) illustrating innovative development pathways that may be acceptable for rare diseases, including case studies.**

### The efficacy bar is higher for rare diseases

The US Food and Drug Administration (FDA) Rare Disease Guidance states "The statutory requirement for marketing approval is 'substantial evidence' that the drug will have its claimed effect. This requirement is the same for common and rare diseases.[1] Substantial evidence is based on the results of adequate and well-controlled investigations." Conventionally, substantial evidence of effectiveness banks on two statistically significant trials (barring mortality/morbidity indications) at a type I error rate of 5%. There is very little provision in the regulations for interpreting the clinical significance. The statistical significance depends on magnitude of the effect, variability, and sample size. Small sample sizes and heterogeneous populations muddle the inferences drawn from statistical analysis techniques that drive efficacy assessment. Consider patients with major depressive disorder, Viibryd reduced the symptoms (measured by Montgomery-Asberg Depression Rating Scale) by 2.5 units on an average compared to placebo (-10.8 units). This difference was shown to be statistically significant with a sample size of 463.

What if major depressive disorder were a rare disease? Contrast the estimated 15.7 million adults that had at least one major depressive episode in the last year in the United States alone, to diseases that afflict only hundreds or thousands globally. If depression was a rare disease and only 50 patients could be recruited, then the effect has to be at least a 7.5 unit reduction (compared to the 2.5 units for Viibryd). Furthermore, several major depressive disorder programs repeat trials until two positive trials are achieved. Rare diseases do not have the luxury of such patient recruitment opportunities. Is not then the bar higher for demonstrating efficacy for rare diseases? In fact, the European Medicines Agency Guidance specifically discussed the challenge of achieving statistical significance and its interpretation for rare diseases.[2] It is important for the FDA to more comprehensively acknowledge this fact in the Rare Diseases Guidance to reassure sponsors and patients that the FDA is willing to be flexible.

### Acceptable pathways for registration of drugs against rare diseases

We do not believe the Guidance accurately reflects the regulatory practices leaving a notion (wrongly so) that the FDA may be rigid in its view toward rare diseases. The FDA is indeed flexible. In fact, the FDA is the one of the most advanced regulatory agencies of the world! According to its website, "Customized, flexible trial designs are used in 80% of rare disease approvals. Almost two-thirds of orphan drugs are approved on the basis of a single clinical trial, rather than the traditional standard of two randomized, controlled trials. Some of these trials use historical information about untreated patients as a 'control' group, rather than a concurrent control group receiving a placebo or an 'active control' treatment if there is one."[3] Consider the approval of Xuriden for the treatment of hereditary orotic aciduria based on data from four patients. No inferential statistical testing can be deemed acceptable for analyzing data from an open label trial in four patients without a suitable control. In fact, the product label states that only two of the four patients met the prespecified criteria. Yet the FDA approved the product. The National Organization for Rare Diseases catalogued the flexibility exhibited by the FDA in approving drugs against rare disease.[4] We applaud the FDA for weighing the clinical significance and not being subservient to statistical methodology. Would the draft rare disease Guidance suggest to sponsors that the FDA is open to such development paths? We believe not. To be fair, the draft Guidance does call for early interactions with sponsors to discuss development plans to be determined on a case-by-case basis. However, relying on

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closed door case-by-case interactions undermines the need for a Guidance. Most sponsors do not have experience developing drugs against rare diseases and hence may not be equipped to decide what might be acceptable by the FDA. Let us consider approved products for common and rare cancers. In most cases, products approved for rare diseases show similar development programs to their common cancer counterparts – including evidence of effectiveness demonstrated solely through clinical endpoints, such as overall survival or progression-free survival. The drug effect (expressed as hazard ratio for overall survival) for Cabometyx is 0.66 (i.e., 34% reduction in the hazard compared to control) for the treatment of renal cell carcinoma, which was shown to be statistically significant with 658 patients. Zydelig demonstrated an effect (hazard ratio for progression-free survival) of 0.18 (82% reduction in the hazard compared to control) in treating patients with chronic lymphocytic leukemia with 220 patients. Although such a breakthrough therapy as Zydelig can afford to pass the conventional "standard," are we leaving a trail of promising compounds with development programs shelved after attempting to follow the status quo? Unlike other regulatory Guidances, we believe the Rare Disease Guidance should teach sponsors the possible innovative drug development paths for registration and reassure that the FDA is open for unorthodox development paradigms. Case studies ought to be included in this Guidance.

### Innovative approaches to overcome the higher bar

There are a number of opportunities to combat the challenges present to rare disease development programs through judicious use of biomarker-based endpoints, innovative trial design and analysis methodology, and progressive licensing. The notion of evidence of effectiveness for rare diseases needs to be discussed in more depth. Given the breadth of the rare diseases, it is difficult to address the idiosyncrasies of each disease in a Guidance. Despite the idiosyncrasies, the general roles of the mechanism of action, changes in relevant biomarkers, clinical endpoints, innovative trial designs, and powerful analysis approaches in forming the evidence of effectiveness warrants further elaboration. In fact, we argue that this is the single-most important aspect that sponsors need help with.

Alternatives to the "gold standard" of randomized, parallel, placebo-controlled design should be discussed in the Guidance. Trial designs such as n-of-1, early escape, and adaptive randomization designs, have been applied to development programs for diseases, such as Huntington disease, Duchenne muscular dystrophy, polyarticular onset juvenile idiopathic arthritis, fibromyalgia, and many others.[5] The idea behind n-of-1 trials is to periodically switch between active treatment(s) and placebo. As each patient serves as a reference to oneself, n-of-1 designs reconcile the notion that interventions rarely work in everyone, and provide a methodology to address the challenges of sample size and heterogeneity of responses in an objective way while simultaneously offering an opportunity to make informed decisions about the best way to treat each patient. For example, in the case of n-of-1 trials, serial correlation from adjacent measurements, carryover effects from prior interventions, treatment randomization, and blinding protocol nuances must be taken into account. The Guidance is completely silent on these approaches. Even from an internal FDA point of view, inclusion of such innovative approaches might mitigate potential differences among the different Divisions' advice to sponsor. A more proactive Guidance makes the expectations transparent for sponsors to propose innovative solutions.

Progressive licensing would allow the clinical-development program to be restructured to allow for early approval for a population of higher-risk patients. Approval would be revisited at additional checkpoints along the development pathway as additional data from the approved population(s), as well as new data from broadened candidate populations, is assessed. A progressive licensing pathway would shift the focus from premarket assessment to one of continual learning. The challenges to implement such a system are nontrivial and the evolution of science and technology would require buy-in across industry, regulatory, payer, and all other parties involved. Progressive licensing should differ from the Subpart H provision in the accrual of safety and efficacy data not only for the first treatment for a rare disease but also the subsequent ones. We believe a Congressional mandate is required before the FDA can pursue progressive licensing. Perhaps the patient advocacy groups should present this issue.

## CONCLUSION

All in all, we believe that the FDA is indeed more open and flexible with regard to evidence of effectiveness for drugs against rare diseases. Unfortunately, the Rare Disease Guidance does not give that impression. We urge the FDA to explicitly state that the conventional body of evidence of effectiveness may not be applicable to rare diseases; and discuss few innovative approaches that may be more readily acceptable for rare diseases. These changes will render Guidance synchronous with the FDA actions.



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