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Three misconceptions about the accelerated drug approval pathway

By Emil D. Kakkis *and* Camille BedrosianMay 10, 2023

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On Friday, the Food and Drug Administration's Cellular, Tissue and Gene Therapies Advisory Committee will meet to discuss the Biologics License Application for Sarepta Therapeutics' gene therapy delandistrogene moxeparvovec for the treatment of Duchenne muscular dystrophy[3]. The late decision[4] by the FDA to reverse course and hold an advisory committee to get expert input into the drug's review occurred after concerns were apparently raised that the FDA was leaning toward rejecting the drug. This would have been a devastating blow for the boys living with

Duchenne today, who have only a short window to get optimal benefit. Any further delay would harm their futures.

While holding this advisory committee meeting doesn't ensure a different outcome, it is an important opportunity[5] for the community and experts to speak out on the issues and particularly the need to make the accelerated approval pathway accessible to rare diseases.

The original misconception with applying accelerated approval to rare disease is that it's lowering the scientific bar on drug approvals by using surrogate biomarker data in lieu of clinical outcomes. But the opposite is true: Applying the same criteria and framework used in common diseases afflicting hundreds of thousands of people to an ultrarare condition with prevalence of a few hundred or few thousand people creates a much higher bar and makes it difficult, and often impossible, to achieve accelerated approvals. The truth is that the science behind many of these rare diseases and their treatments is far more compelling and predictive than many larger population diseases — but the evaluation process for rare diseases does not adequately take that into account.

This lack of equity is creating unequal access in health care and is exactly where we need FDA to provide considered guidance in support of new treatments for this minority population. As committed drug researchers who have successfully developed a dozen therapies for rare diseases over the past two decades, we have long advocated for a science-based regulatory pathway that supports rapid development of effective treatments for these rare and ultrarare disease communities that are being left behind by the current regulatory framework. The accelerated approval pathway offers a potential solution, yet it is almost never used in rare disease and has never been applied to an investigational gene therapy.

Here are the major misconceptions about the accelerated approval pathway that are harming the proper regulation of rare disease treatments. The advisory committee should be aware of these fallacies when it meets.

Misconception #1: Biomarkers are a compromise in approving rare disease drugs. The argument is that relying on surrogate biomarkers could lead to the approval of expensive drugs that may not actually improve patient outcomes. The accelerated approval pathway was conceived to shorten time to drug approval in cases where it is impractical to collect sufficient clinical outcome data within a reasonable timeframe. The use of specific types of biomarkers that directly and precisely represent the underlying disease state can rapidly and effectively accelerate the cycle time for drug discovery, clinical study and approval resulting in dramatically improved drugs, or even combinations of drugs that treat the underlying disease optimally.

The HIV field is a striking example, where prevention of progression to AIDS and certain death would not have been possible without primary disease biomarker-based approvals[6]. In HIV, the first drug approvals in 1992 of efficacious drugs used biomarkers rather than slow and difficult clinical outcomes. This approach rapidly led to better and better drugs. After the first HIV drug was approved, rapid development led to approval of 29 drugs (including four drug combinations) in 16 years, making HIV a well-controlled disease rather than a death sentence. These drugs would have been impossible to develop with variable clinical outcomes like infections, hospitalizations and death.

The best analogy to this scientific idea is that of a car with broken brakes that will crash as a result. In this analogy the drug is intended to fix the brakes, as measured by the biomarker, and prevent the crash, which represents the clinical outcome. Whether, when, and how seriously the car

crashes depends not only on the broken brakes, but also on the vehicle, the driver, the road conditions, and other factors of the real world. Measuring car crashes to assess whether the brakes are fixed is very noisy and inefficient. If we measure the brake functionality directly, we can do so with great precision, speed, and accuracy, with confidence that when we fix the brakes, car crashes will decline with enough time of observation. Biomarkers of the underlying primary disease, like deficient dystrophin or accumulating substrate in a biochemical disease, all represent ways we can measure "the brakes" and optimize efficiently. Waiting for and counting the variable car crashes may not be possible and is often not ethical in rare genetic diseases.

Furthermore, primary disease biomarkers have a strong track record for success. All drug approvals in rare genetic diseases (whether via accelerated or standard approval) that used primary disease biomarkers to measure the underlying disease, are demonstrating clinical effectiveness[8] through confirmatory studies or post-marketing requirements, and none have been withdrawn[9].

Biomarkers that represent the underlying disease state are not a compromise. In fact, primary disease biomarkers are superior to clinical endpoints in terms of designing and developing improved treatments by providing accurate and precise ways to measure the disease.

Misconception #2: The approval of the first product will inhibit the approval of a better product in the future. The prevalent view[10] is that making a less-than-perfect drug available to the patient community now will preclude them from participating in competitive studies and the field will suffer as a result. The reality is that an approval in Duchenne that requires a full clinical outcomes study will make it nearly impossible to develop competitive products in the future, whereas a first biomarker-

based approval establishes a clear pathway with the efficacy standard to beat.

Requiring approval based on clinical endpoints will have significant consequences for the entire field of Duchenne drug development. In order for a competitor to have the next generation gene therapy (or other modality) drug approved, they will be obligated to run a head-to-head clinical study with Sarepta's gene therapy, which will be incredibly expensive, as the study sponsor will need to buy Sarepta's drug for the trial and then run a large multiyear study to look for differentials in outcomes between the two drugs. Ultimately, this sabotages the entire field. Rather than inviting lower cost entrants into the market, this framework would establish a single high-cost player that is incredibly difficult to unseat.

A first biomarker-based approval provides competitors with a clear, accurate evidence-based standard of comparison that can be achieved in a much shorter timeframe and would not require head-to-head studies. In addition to the HIV example above, in which good drugs were replaced rapidly by better drugs, approval of the first drugs for homozygous familial hypercholesterolemia[11] and urea cycle diseases[12] in the 1990s also led to multiple better drugs[13] developed over the ensuing years. The first approval of enzyme replacement therapies for Gaucher and Fabry, both by biomarkers, led to multiple follow-on products to treat those rare diseases. The allowance of phenylalanine level as a biomarker enabled the first phenylketonuria drug to be developed (sapropterin) and a follow-on product now approved that is more potent (pegvaliase) with yet more in the pipeline.

As a counter example, MPS I and Pompe enzyme replacement treatments were approved with clinical endpoints and not biomarkers, and no follow-

on approvals have occurred over the subsequent 20 years or 17 years, respectively.

The truth is that first biomarker-based approvals enable more investment and approval of new and better drugs, the exact opposite of commonly stated views.

Misconception #3: Some irreversible harm and damage to a placebo control group is OK in the pursuit of clinical drug knowledge. Academic bioethicists often state that placebo control is necessary to answer whether an intervention is effective[14], and that since the drug is not proven to work (we have equipoise) then no harm comes to the patient in the control group that would not have happened anyway. For many diseases like Duchenne, the clinical-endpoint driven trials will require much more time and more progression of disease for comparison with the treated group to adequately power the studies.

Untreated control group patients with diseases like Duchenne would suffer irreversible harm. In fact, there is harm when the possibility of even a 10% chance of benefit is lost to the placebo-assigned patients, and the progress of time during a trial essentially reduces or closes altogether the window for possible benefit from treatment. To conduct a randomized placebo-controlled study design for a disease with irreversible brain or muscle disease should be considered unethical. For Duchenne, requiring a group of children to remain on placebo for long periods of time to demonstrate substantial clinical benefit in the treated group is unconscionable and a sad commentary on our inability to develop and utilize an appropriate, ethical way to measure drug efficacy. We can use longer timeframes and larger numbers in the post-marketing confirmation setting to verify clinical benefit.

All three of these misconceptions are currently animating regulatory policy within the review divisions at FDA, deciding the fate of rare and ultrarare investigational therapies and the communities of children and their families that could benefit from them.

We can confidently say that a first accelerated approval and acceptance of a biomarker that reflects the underlying disease will open the door to more and better therapies for a disease. At Ultragenyx, we make decisions on whether to spend millions of dollars on programs to treat patients with rare diseases, and the existence of an accepted biomarker that represents the underlying disease is an extremely important part of our decision-making process. For the Sarepta Duchenne gene therapy, the first accelerated approval will enable more and better therapies to come, possibly including one we are developing. That said, today's boys need a better treatment right now, even if imperfect, so they do not lose their precious window of time and to pave the way for even better treatments for future generations.

Emil D. Kakkis, M.D., Ph.D., is CEO, president and a director of Ultragenyx. He is also founder of the EveryLife Foundation, where he is a Board member. Camille Bedrosian, M.D., is a full-time strategic advisor at Ultragenyx, where she previously served as chief medical officer. She is on the Board of Crinetics Pharmaceuticals and Rhythm Pharmaceuticals.

About the Authors

Emil D. Kakkis

linkedin.com/in/emil-kakkis/ [17]

Camille Bedrosian

linkedin.com/in/camille-bedrosian-1b74951a0/ [18]

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