Accessing the accelerated approval pathway for rare disease therapeutics

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Improvements must be made to the qualification process for biomarkers as primary endpoints in pivotal clinical studies of treatments for the rarest of diseases.

The accelerated approval pathway was originally promulgated in 1992 by the US Food and Drug Administration (FDA) to help speed access to therapeutics for serious and life-threatening diseases. For diseases like AIDS, data from biomarkers like blood T-cell counts were considered reasonably likely to predict the longer-term clinical benefit of drugs against HIV. These regulations have been instrumental in the development of many HIV drugs, multidrug cocktails (highly active anti-retroviral therapy, or HAART) and numerous cancer drugs.

During the first 16 years of the accelerated approval pathway, a total of 73 new chemical entities (NCEs) were approved by the FDA (64 new drug applications (NDAs) and 9 biologic license applications (BLAs))[1]. Among these approvals, 29 drugs (including four combinations) were approved for HIV and 26 new NCEs were approved for cancer, along with 17 therapies for infections, multiple sclerosis, pulmonary arterial hypertension and other indications. For treating cancer and HIV, accelerated approval has been an enormous success in driving drug innovation, and the FDA and the drug sponsors and companies should be applauded for their efforts in allowing this innovation to move forward and change people's lives.

That said, in the same 16-year period, only one rare genetic disease therapy, Fabrazyme (agalsidase beta), was approved. The evidence supporting accelerated approval for Fabrazyme was based on a biomarker, the resolution of lysosomal storage pathology on renal biopsies. Despite the fact that many rare genetic diseases have relatively distinct biochemical markers directly in the genetic pathway of disease, makers of drugs for rare genetic diseases are not accessing the accelerated approval pathway using novel biomarkers.

In this article, we argue that clearer, more practical qualification criteria are needed to foster the development of therapies for rare genetic diseases. Our arguments are based on a white paper[2] produced by a working group of foundation, industry and academic representatives assembled by the EveryLife Foundation for Rare Diseases (Novato, CA, USA) in 2014.

A poorly defined biomarker qualification process for rare diseases

The qualification process for novel biomarker endpoints as likely predictive of clinical benefit has been too difficult in rare genetic diseases, leading to some treatments for ultra-rare or challenging diseases not being successfully developed or studied[3]. Although FDA issued new guidances for expedited programs, including accelerated approval[4] and the Qualification Process for Drug Development Tools[4], the qualification process for novel biomarkers as primary endpoints in the accelerated approval pathway remains insufficiently defined. Progress is needed in establishing a more predictable pathway, including a set of reasonable scientific criteria to provide greater access to accelerated approval for rare genetic disease treatments with novel biomarker endpoints. Flexibility by the FDA has been an important part of the approval pathway in rare diseases[5] and is critical for approval of needed therapies. However, flexibility alone is not enough—we need clear and practical qualification criteria to foster the development of therapies for untreated ultra-rare and difficult-to-treat genetic diseases.

In response to criticism regarding accelerated approval accessibility for rare diseases, some experts have noted that rare disease treatments have been approved at times through the standard approval pathway using biomarker endpoints. To evaluate whether any novel biomarkers have been used in any orphan drug approvals recently, whether by accelerated approval or not, we analyzed all FDA orphan drug approvals from 2009 to 2014 (refs. 1,6 and **Supplementary Table 1**). Of the 91 new molecular entities approved as orphan drugs in that period, none included a novel biomarker primary endpoint. **Figure 1** shows

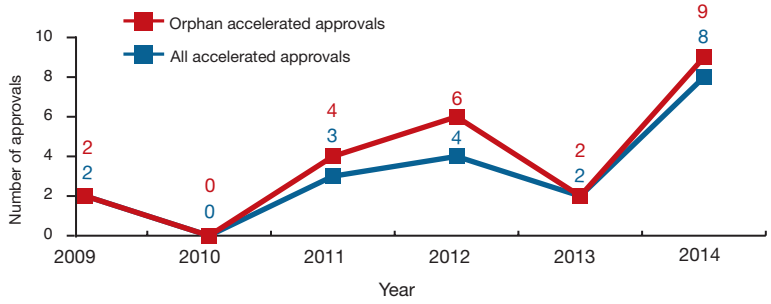

Figure 1 Number of US NDA and BLA orphan and total accelerated approvals.

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Table 1 Rare genetic disease approvals using biomarker primary endpoints for 2009–2014

Proprietary name	Established name	Disease	Primary endpoint for approval	Biomarker endpoint	Previously approved biomarker endpoint	Approval type	Approval date	Application number
Vpriv	Velaglucerase alfa	Gaucher disease type 1	Hemoglobin concentration change	Yes	Yes Agalsidase beta 1992	Standard	2/26/2010	NDA 022575
Carbaglu	Carglumic acid	Acute hyperammonemia of NAGS deficiency	Plasma ammonia levels	Yes	Yes Phenylbutyrate 1996	Standard	3/18/2010	NDA 022562
Krystexxa	Pegloticase	Chronic gout	Plasma uric acid level	Yes	Yes Allopurinol 1966, 1980 + others	Standard	9/14/2010	L 125293/0.0
Ferriprox	Deferiprone	Thalassemia syndromes	Serum ferritin levels	Yes	Yes Deferoxamine 1968	Accelerated approval	10/14/2011	NDA 021825
Elelyso	Taliglucerase alfa	Gaucher disease type 1	Spleen volume	Yes	Yes Agalsidase beta 1992	Standard	5/1/2012	NDA 022458
Juxtapid	Lomatapide	Homozygous familial hypercholesterolemia (HoFH)	Percent change in LDL-C	Yes	Yes Multiple statins	Standard	12/21/2012	NDA 203858
Kynamro	Mipomersen sodium	Homozygous familial hypercholesterolemia (HoFH)	Percent change in LDL-C	Yes	Yes Multiple statins	Standard	1/29/2013	NDA 203568
Ravicti	Glycerol phenylbutyrate	Urea cycle defects	Plasma ammonia levels	Yes	Yes Phenylbutyrate 1996	Standard	2/1/2013	NDA 203284
Procysbi	Cysteamine bitartrate	Cystinosis	Cystine in WBC	Yes	Yes Cysteamine 1994	Standard	4/30/2013	NDA 203389
Myalept	Metreleptin	Leptin deficiency complications	Reductions in HbA1c, fasting glucose and triglycerides	Yes	Yes Diabetes drugs	Standard	2/24/2014	BLA 125390

NAGS, *N*-acetylglutamate synthase; WBC, white blood cells.

the total number of accelerated approvals over the same period along with new molecular entities filed as NDAs or BLAs that were granted an orphan designation.

When focusing on the subset of the 22 approvals for rare genetic diseases (**Supplementary Table 2**), only one of 11 applications using biomarker primary endpoints was approved using the accelerated approval provisions. This approval was for an iron-binding product, a well-worn pathway for treatments of diseases requiring frequent transfusions (**Table 1**). The remaining ten standard approvals all relied on biomarker endpoints used in approvals in the 1990s (**Table 1**). For example, the approvals for carglumic acid in 2010 and glycerol phenylbutyrate in 2013 were based on plasma ammonia levels. Plasma ammonia levels were used in multiple prior approvals for phenylbutyrate (1996) and other urea cycle drugs. Similarly, in 2013 for Procysbi (cysteamine bitartrate) in cystinosis, white blood cell cysteine level was used as the biomarker endpoint after previously being used for the approval of the original form of cysteamine (1994). The only example of a standard approval using a novel biomarker endpoint known to the authors was outside this five-year interval; this was an approval in 2007 for Kuvan (sapropterin) to treat phenylketonuria using serum phenylalanine levels as the primary endpoint. In this isolated case, the support for the phenylalanine endpoint came from extensive prior clinical experience with another therapy (dietary restriction), which was evaluated in a meta-analysis of previously published clinical study data[7]. The quantity of clinical study data available on an existing treatment would rarely if ever be available for most ultra-rare diseases for which there are no other treatments and no history of prior clinical studies.

We certainly applaud the FDA for granting standard approval based on qualified endpoints and urge the agency to continue this practice. At issue, however, is how many other diseases there are whose development would have been initiated or expedited had biomarker qualification been available; we have previously evaluated 15 diseases in which this was true[3].

Enhancing access to accelerated approval for rare diseases

The relative lack of novel biomarkers being used in NDAs for never-before-treated rare diseases is an indication a more straightforward and predictable approach is needed that uses novel biomarkers in new drug development for rare diseases. Over the first 22 years of the accelerated approval pathway, only one Fabry and one phenylketonuria drug have been approved with novel biomarker endpoints by either accelerated approval or standard approval despite substantial science available for many rare genetic diseases. An improved process to qualify biomarker endpoints is needed to address the difficulty in obtaining agreement on the qualification of biomarker endpoints in rare diseases.

To help improve access to the accelerated approval pathway, the US Congress included language within the FDA's Safety and Innovation Act (FDASIA) in 2012, updating the pathway for new drug development[8]. The purpose was to "expedite the development and access to novel treatments for patients with serious and life-threatening diseases and conditions." Furthermore, FDASIA mandated that the FDA create a guidance that considers "any unique issues associated with very rare diseases" and that the FDA "shall consider how to incorporate novel approaches into the review of surrogate endpoints involved in the pathophysiologic and pharmacologic evidence in such guidance, especially in instances where the low prevalence of a disease renders the existence or collection of other types of data unlikely or impractical." Language in the most recently issued FDA guidance on expedited pathways (May 2014)[4] does not provide a specific scientific framework to help make accelerated approval more accessible, stating

that use of biomarkers as surrogate endpoints are not generalizable. The agency has applied some flexibility on a case-by-case basis, but this flexibility is insufficient to support treatment development for a large number of rare and ultra-rare diseases.

In August 2015, the FDA released a new draft guidance[9] that makes several references to the use of biomarkers in rare disease drug development and recommends that sponsors explore the use of novel or existing biomarkers. However, the guidance does not provide a comprehensive framework or evidentiary standards needed to qualify a biomarker. Instead, it correctly points out that for a biomarker to be effectively used in a drug development program, there must be an assay available that can reliably and sufficiently measure the biomarker.

The FDA's Drug Development Tool (DDT) Qualification Program, as part of the Center for Drug Evaluation and Research, is considered a possible approach to qualify biomarker endpoints, but the program is designed for common endpoints intended for use with multiple different drugs and not for use in a specific drug development program. Over the many years of its operation, the program has achieved approvals for 4 of 79 biomarker applications, and all have been focused on major market diseases or toxicity[5]. Therefore, the current version of the DDT process is not likely to benefit any rare disease drug development program. The challenge remains to find a way to qualify novel, individual biomarker endpoints quickly and efficiently when relevant to a single ultra-rare drug development program.

Putting biomarkers to the fore

Given the sheer number of rare diseases, the rarity of the indications in some cases and the biological challenges that exist for some diseases like slowly progressive neurological diseases, biomarker endpoints should play a necessary, central role in the process of approving drugs for rare diseases by the accelerated approval pathway, particularly when the clinical endpoints are not practical or possible. For ultra-rare diseases with tiny disease populations, it is impossible or impractical to conduct an adequately sized clinical study with a consistent group of evaluable patients. Neurologic diseases with long presymptomatic disease progression or other irreversible complex diseases, in which clinical disease is too difficult to quantify, might only be approachable by biomarker endpoints. In many cases, the biomarker is not a compromise and in fact the biomarker endpoint can be a far more precise and accurate measure of disease activity that provides more accurate and immediate information about treatment efficacy than many clinical endpoints. Phenylalanine level, for example, is associated with IQ loss, but phenylalanine level can be measured each day accurately with known levels associated with adverse effects. In contrast, the use of IQ itself as an endpoint can take years to study, can have extreme population variations, is difficult to precisely measure, and is highly dependent on both prior patient exposure history and the developmental age of the patient at the time of study. Without the biomarker endpoint, phenylketonuria treatments based on IQ changes could not be developed.

There are many other situations where biomarkers are becoming an essential part of development in order for science to progress. Choosing between a good and an excellent treatment effect using IQ or many similar clinical endpoints is essentially impossible, and so the development of improved treatments is also hampered without an efficient measure of efficacy. Biomarker endpoints have also been essential to the development of multidrug regimens in HIV, as noted above, because clinical endpoints cannot precisely quantify the benefit of drug combinations in a plausibly sized clinical study. In addition to the difficulty with clinical endpoints, it also can be difficult, if not impossible, to assemble enough patients or run studies long enough to provide statistically robust conventional clinical data without using biomarker endpoints.

Although the failures of biomarker endpoints to predict clinical benefit are infamous and often cited[10], there is a substantial difference in the clarity of the science and the tractability of clinical endpoints between major market products for which failures have been important and for rare and ultra-rare genetic diseases. The scientific pathophysiological pathways for many genetic-based diseases have become more clearly established and, as a result, increasingly relevant to disease pathophysiology. Translating our scientific knowledge into lifesaving treatments may require the use of accelerated approval as the only plausible way forward in some cases.

To help develop a sound scientific framework for qualifying biomarker endpoints for use in accelerated approval, a working group of foundation, industry and academic representatives was assembled by the EveryLife Foundation for Rare Diseases. The group's white paper[2] provides a detailed, science-based set of considerations for the disease, the drug, the biomarker, the nonclinical data and the clinical data that are believed to help increase the probability of positive predictive value and reduce the probability of failure.

Table 2 lists a set of high-level considerations that will assist in achieving higher quality organized scientific work early in a development program to support or refute the use of a given biomarker as a relevant measure. The data package proposed includes studies that can be done before an investigational

Table 2 Considerations in establishing the scientific framework for qualifying biomarkers as surrogate primary endpoints

Type of consideration	Criteria for establishing the scientific framework for qualifying biomarkers
Disease	• Clear disease cause • Disease pathophysiology pathway • No known alternative disease pathogenesis pathway
Drug	• Clear structure and identity • Direct and understood mechanism of action • Specific pharmacological action demonstrated • Absorption, distribution, metabolism and excretion demonstrated in models to site of action
Biomarker	• Directly related to early pathophysiologic pathway • Changes are sensitive and specific to changes in clinical disease pathophysiology • Relative biological stability • Validated or qualified assay methodology for biomarker measurement • Clinical intermediate endpoints (clinical physiological measures) relevant to major clinical problem
Preclinical	• Treats models relevant to disease pathophysiology • Dynamic dose-response pharmacology relationship • Sampling compartment (e.g., blood or urine) reflects location of disease-affected tissue compartment • Changes in biomarker predict clinical changes in models
Clinical data	• Predict clinical severity or disease progression rate • Sufficient breadth in detecting disease and its range in severity in untreated cross-sectional patient survey • Show predictive value for other, similar diseases

new drug (IND) filing early in the development program combined with some data from nontreatment clinical studies to help support the value of the biomarker. The specific details under these considerations include items that are particularly focused on reducing the risk of failure associated with some biomarker endpoints in the past. The white paper also proposes a novel 'Biomarker Qualification Request' process for use of biomarker endpoints in individual drug programs that can be conducted in the pre-IND setting with a relevant FDA review division and their consultants to help establish the regulatory pathway early, before large development investment has occurred. This process and framework enables the incorporation of improved scientific reasoning earlier in drug development programs that could lead to greater investment in many of the thousands of rare diseases that are currently awaiting the development of novel therapies.

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COMPETING FINANCIAL INTERESTS
The authors declare competing financial interests: details are available in the online version of the paper (doi:10.1038/nbt.3530).

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