Recommendations for the Development of Rare Disease Drugs using the Accelerated Approval Pathway and for Qualifying Biomarkers as Primary Endpoints in Pivotal Clinical Studies

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I. INTRODUCTION

According to the National Institutes of Health, there are thousands of rare diseases which together affect as many as 30 million Americans.[1] These are often serious or life-threatening diseases and yet only there are only about 400 drugs currently approved for rare diseases.[2] Developing drugs for rare disease can be challenging due to specific disease characteristics such as small heterogeneous patient populations, long time-frames for disease progression, a poor understanding of disease natural history, and a lack of prior clinical studies. Recent advances in medical science have enhanced our understanding of these disorders at the biochemical and pathophysiologic level and have created more opportunities to address unmet needs[3] by developing specific therapeutic options for rare disease patients. Improving the development process for these diseases is now an important part of assuring that many of the rarest and most difficult-to-treat rare diseases have specific drugs developed.

In the United States, the regulatory approval of any new drug is based on its benefit-risk ratio, which is assessed in part through the conduct of adequate and well-controlled clinical trials in the relevant patient population. "Benefit" refers to a demonstrated improvement in clinical function as measured using a clinical endpoint, which is defined broadly as the way a patient feels, functions, or survives; "risk" refers to the safety profile of the drug. The requirement for clinical endpoints defined by the "feels, functions or survives" paradigm can be challenging as some promising investigational treatments for serious or life-threatening diseases may not be practically assessed for a demonstrated improvement on clinical endpoints for many reasons. The challenge with clinical endpoints can occur in studies of the extremely small or heterogeneous patient populations or in diseases characterized by long periods with subclinical or slow progression and or substantial irreversible damage at the time of diagnosis.

To assist in the difficult challenge of transforming scientific discoveries into new drug treatment for patients with serious or life-threatening disorders, the U.S. Food and Drug Administration (FDA), Congress, and the public have all endorsed the need for flexibility in the regulatory review process for rare disease drugs. This regulatory flexibility has been designed to speed access to new drugs, while preserving standards for safety and efficacy. Perhaps the best expression of this flexibility is the creation of the Accelerated Approval (AA) pathway in regulations promulgated by the FDA in 1992.[4] Initially, these regulations created by the FDA were a response to the AIDS crisis, and the growing public pressure to accelerate access to medications. Congress codified the AA pathway in 1997, with the passage of the FDA Modernization Act (FDAMA).

The AA regulations specify when evaluating drugs for serious and life-threatening diseases with substantial unmet medical need, the FDA may approve a treatment based on an efficacy evaluation using a surrogate endpoint or a clinical endpoint earlier than survival or irreversible morbidity that is "reasonably likely to predict clinical benefit." Drugs granted AA are approved with the stipulation that confirmatory studies to verify the clinical benefit may be required as a condition of continuing marketing authorization.[5] The regulatory flexibility offered under the AA pathway incorporates our belief that when a patient has a lethal or devastating disease, the benefit-risk assessment must account for the severity of the disorder and the degree of unmet medical need, i.e., the availability (or not) of effective alternative treatment options. It is important to emphasize, however, that AA is valuable specifically for those situations in which timely standard approval via a clinical endpoint is unlikely or

impossible due to practical, scientific, or ethical reasons.

The use of biomarkers in the AA pathway is not intended to substitute for clinical endpoint-based studies in diseases with sufficient patients and readily measured clinical endpoints that may change in reasonable timeframes. Studies based on clinical endpoints are preferable in the development process when feasible. In rare diseases, often the population size and heterogeneity, the nature of the disease and the limited historical clinical data can make traditional studies with clinical endpoints, difficult or impossible to conduct.

Although the AA regulations have been used to great advantage for diseases such as AIDS and cancer, there has been more limited success in applying this pathway to treatments for non-oncology rare diseases.[6,7] Despite substantial scientific insights into the pathogenesis and pathophysiology of many rare disorders, the translation of scientific discoveries into effective medicines for these disorders has been notably more challenging and at times impossible under the current regulatory framework, even when the understanding of the science underlying the disease is far superior to that for many multi-genic common diseases.

Rare disease treatments are sometimes approved via the standard pathway using unvalidated biomarker endpoints due in part to flexibility in the drug review process. [8] In most cases, this flexibility is based on either regulatory precedent for the endpoint, or the existence of substantial clinical data with a prior treatment. For example, the regulatory precedent for the use of ammonia levels in urea cycle drug development is based on prior approvals for phenylbutyrate and other urea cycle drugs, and allowed ammonia levels to be used in the recent approval of glycerol phenylbutyrate. One recent example in which substantial prior clinical outcome data was important was the approval of sapropterin based on the use of blood phenylalanine levels in phenylketonuria (PKU). Blood phenylalanine levels were considered predictive based on published studies of intellectual outcomes in PKU during dietary therapy and were used in the management of PKU. However, if there are no regulatory precedents for use of the relevant specific biomarker, and if there is no substantial prior clinical data to support the predictive value of the biomarker as a surrogate, then qualification of a new biomarker for use as a primary surrogate endpoint in a pivotal study can be difficult or impossible. [9]

Although the AA pathway is rarely used to approve non-oncology rare disease treatments, many rare diseases pose similar levels of severity, lethality, and unmet medical need as diseases treated by drugs that currently do access the AA pathway, such as AIDS and cancer. This is largely because the current benefit-risk assessment framework as applied to rare diseases has not adequately addressed uncertainty about the level of evidence necessary to rely on a novel biomarker endpoint.[4, 10] The expectation for demonstrated clinical outcome data has made the use of the pathway challenging for rare diseases, despite the often excellent science that exists regarding the underlying disease, drug and biomarker. A re-evaluation of the type and quality of data required for biomarker qualification is needed to create a more relevant AA pathway for rare diseases when the other science is strongly supportive of the biomarker but when clinical outcome data is limited or non-existent.

The 2012 passage of the Food and Drug Administration Safety and Innovation Act (FDASIA)[11] amended the AA provisions to reflect recent advances in science and to enhance the application of the AA pathway to drugs for rare disorders, with the intention of expediting the development and approval

of new treatments. FDASIA extends FDA's authority to take into account other available endpoints to qualify for AA and requires the development of more relevant guidance on the types of evidence that may be acceptable in support of using a novel surrogate endpoint. In addition, the law also contains provisions to incorporate the patients' benefit-risk preferences into a structured evaluation process. Together, these provisions create a significant and valuable opportunity to advance the translation of promising scientific discoveries into new treatments for rare disorders.

This paper provides recommendations for an effective and detailed scientific framework to improve the relevance of the AA pathway for rare diseases with unmet medical need where sufficiently strong science exists. It outlines the types and levels of information that increase the predictive value of biomarker endpoints, as well as the scientific bases sufficient to merit utilization of AA for rare diseases using novel biomarker endpoints. The scientific framework cannot substitute for good judgment or accommodate all the complexities of the science behind so many rare diseases, but the framework does provide a more predictable structure for development and review of potential biomarker endpoints. Specifically, the goals of this paper are to:

- Establish the key considerations for rare disease factors that should impact qualification for Fast Track and the use of the AA pathway
- Provide for the use of a disease survey early in development to help characterize the factors considered important for qualification of the disease for AA and in drug development
- Provide a reasonable scientific framework for considerations regarding the disease, drug, biomarker and other data that can support adequate qualification of a biomarker as a surrogate primary endpoint that is "reasonably likely to predict clinical benefit"
- Define a regulatory process for assessing biomarkers in rare diseases earlier in the development process to encourage investment in new treatments: the Biomarker Qualification Request

Ultimately, the adoption and incorporation of these recommendations for a scientific qualification framework into the regulatory process will create an opportunity to increase the number of available treatments for rare diseases when there is adequate science to support development while maintaining safety and effectiveness standards.

II. BACKGROUND

Section 901 of FDASIA, entitled "Enhancement of Accelerated Patient Access to New Medical Treatments," amended the AA provisions found in Section 506 of the U.S. Public Health Service Act. [12] These changes are intended to take advantage of the significant advances in science over the last several decades to increase the application of AA to drugs for serious, life-threatening, and rare disorders. New assay techniques and methodologies, including advances in genomics, molecular biology, and bioinformatics, have allowed us to better understand the pathophysiology of disease and to develop new therapies. Per FDASIA, Title IX, Section 901 (1) C:

> "As a result of these remarkable scientific and medical advances, the FDA should be encouraged to implement more broadly effective processes for the expedited development and review of

> innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate. This may result in fewer, smaller or shorter clinical trials for the intended patient population or targeted subpopulation without compromising or altering the high standards of the FDA for approval of drugs."

FDASIA also underscores the importance of taking the context of the specific disease state targeted by the drug into account when conducting benefit-risk determinations. In particular, the section addressing AA was amended to note the FDA should consider the "severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments" when reviewing a product which demonstrates an effect on a surrogate endpoint.

The legislation also expands the list of potential information to consider when assessing the predictive value of a surrogate endpoint. Specifically, it states the evidence "may include epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools." These changes are significant, as they increase breadth of data that may be used to provide reasonable inferences into the predictability of benefit.

FDASIA requires the development of guidance to clarify the considerations unique to the application of the AA pathway to review drugs for rare disorders. Such guidance will address issues that may arise under the AA and Fast Track processes outlined in Section 506 of the Federal Food Drug and Cosmetic Act for drugs designated for a rare disease or condition under section 526 of the Act (21 U.S.C. 360bb). This supports the earlier inclusion of rarity as a factor for AA and provides support for the principle that rarity alone leads to significant development issues that this guidance should address and help to resolve: "In developing such guidance, the Secretary … *shall also consider any unique issues associated with very rare diseases* [emphasis added]*."*

FDASIA further directs the FDA to consider how the rarity of a disease alters the type of data that might be available to ascertain the suitability of a surrogate endpoint, indicating that, in some cases, limited data regarding the pathophysiology of disease or the pharmacology of the drug might be sufficient:

> "The Secretary shall consider how to incorporate novel approaches to the review of surrogate endpoints based on 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."[13]

FDASIA emphasizes that the AA pathway should be accessible to severe and very rare diseases. Additionally, it calls for a broader-based approach to the application of scientific data when assessing the viability of a biomarker as a primary surrogate endpoint for AA. For example, in situations where long-term clinical outcome data do not exist due to the severity and/or rarity of the disease (e.g., lack of qualified trial participants, time constraints, etc.), other scientific criteria may be used if they are believed to sufficiently meet the "reasonably likely" standard.

To ensure the changes outlined in FDASIA are implemented effectively, a working group was formed (the authors) to develop recommendations to better address the qualification of surrogate endpoints as

"reasonably likely to predict clinical benefit" for rare disease using a scientific framework. The scientific framework is intended to include a broader array of considerations regarding the disease, drug, biomarker and experimental data that help improve the biologic understanding of the biomarker in the context of the disease and drug. The fundamental assumption of this proposal is that the more known about the scientific basis of a disease, the drug, and the biomarker endpoint, the better the ability to assess predictive power of the biomarker.

The AA pathway is critically important for the development of treatments for rare disorders that are more challenging to study using routine clinical study than many fast-track-eligible common disorders.[14] However, the Food and Drug Modernization Act (FDAMA) did not specifically delineate considerations unique to the review of treatments for rare diseases under AA. Subsequently, FDASIA does now call for the consideration of additional factors specific to rare and very rare disorders when considering regulatory flexibility under the AA pathway. Not all of these rare disease considerations need to be met in order to qualify for review under the AA pathway; rather, they should be seen as a list of specific factors that warrant consideration when assessing the need for regulatory flexibility in accessing the AA pathway and for the qualification of a biomarker as a primary surrogate endpoint in a pivotal clinical study.

III. THE QUALIFICATION PROCESS SHOULD TAKE INTO ACCOUNT THE SPECIFIC CONTEXT OF THE DISEASE, ITS RARITY AND OTHER FACTORS WHEN EVALUATING A BIOMARKER FOR THE ACCELERATED APPROVAL PATHWAY.

The regulations outlining AA did not specifically delineate considerations unique to the review of treatments for rare diseases under AA. In contrast, FDASIA does call for the consideration of additional factors specific to rare and very rare disorders when considering regulatory flexibility under the AA pathway. A number of aspects that merit particular deliberation are outlined in the section that follows.

The proposed list of considerations during the qualification process:

1. Extremely high unmet medical need
2. Extreme rarity of the disorder
3. Lack of any prior clinical studies or clinical data
4. Slowly progressive diseases or low event rate
5. Diseases with delays between irreversible pathologic damage and clinical diagnosis
6. Lack of readily measurable, recognized clinical endpoints due to unusual clinical disease biology

The assessment should be specific to the disease targeted for treatment, including an assessment of whether and to what degree the targeted disorder can be characterized as serious, life-threatening, and rare or very rare. This assessment should include a disease survey designed in consultation with the FDA and key stakeholders such as patient groups and physicians with relevant expertise. The disease survey results should be discussed and examined with the FDA as part of the review and evaluation process, validated by patients and patient groups as reflective of their collective view, and verified by experienced physicians in the specialty as consistent with their experience. This survey should consider whether and to what extent characteristics of the disorder targeted by the treatment meet the criteria of

serious, life-threatening or rare or very rare, thus meriting flexibility for qualification of the biomarker under the AA pathway.

A. The key considerations for the disease assessment:

- **Extremely high unmet medical need**

  Diseases with devastating and severe outcomes and no approved treatments deserve particular consideration with regard to utility of AA. The unmet medical need in these diseases greatly impacts the benefit-risk calculations made by physicians, patients, and caregivers, and these preferences should be weighed as part of the regulatory review process.

- **Extreme rarity**

  Rare disorders affecting very small populations or genetic subpopulations present especially difficult challenges that have a negative synergistic effect on drug development, such as:

  1) The lack of available patients to be enrolled in clinical trials which incorporate clinical endpoints, negatively impacting a study's ability to reach a reasonable level of power to detect a statistically significant change.

  2) The need to include a significant fraction of the total available population of patients in clinical studies, leading to the need to accept heterogeneous populations in terms of age, severity and presence of specific clinical disease symptoms, as well as stage of disease progression

  3) The limited market potential for the drug, resulting in small or non-existent financial incentives to invest in the development of treatments for extremely rare disorders, particularly without some degree of confidence that AA is available early in the program's life before significant work has begun

- **Lack of any prior clinical studies or formally collected clinical data**

  Very rare diseases with no existing treatments have often never been studied in clinical trials. As a result, surrounding medical literature may be limited to case reports and small sets of patients. Frequently, rare disease patients are evaluated only in terms of disease management, and not for clinical endpoint assessments. The lack of regulatory precedents for endpoints relevant to a rare disease often makes the determination of how to evaluate a disease or treatment effect difficult or intractable.

- **Slow disease progression with significant irreversible symptoms or rare severe events**

  Many rare diseases have long and/or unpredictable timeframes for progression, making it difficult or impossible to conduct clinical studies within a reasonable timeframe (i.e., less than 1 year), which creates a compelling need for the use of alternative biomarker endpoints. In some cases, this may be because the event rate is low, even if these events are very severe. Additionally, if the clinical manifestations of the disease are irreversible and the goal of the therapy is stabilization, achieving sufficient power to detect the difference between placebo and treated patients is far more difficult. In this situation, biomarkers that are directly in the line of the pathophysiologic process could provide a valuable assessment of treatment effect that can reasonably predict clinical benefit.

- **Significant delay between the onset of irreversible pathologic damage and clinical diagnosis**

  Untreated rare diseases often have challenging biology in which the disease process initiates and progresses without clear clinical expression or diagnosis. By the time disease progression has allowed the patient to be clinically diagnosed, severe late-stage and irreversible damage has already occurred. This problem is particularly common in neurological disorders, for example, in which the plasticity and compensatory powers of the brain continuously adapt to the declining brain condition to maintain function. As a result, the appearance of normality is maintained despite substantial disease progression until the adaptation can no longer compensate, at which point the patient rapidly declines. Studying the treatment of a disease during this type of early prodromal period is difficult or impossible with clinical endpoints. The slow and inconsistent clinical change, if any, will be undetectable, and waiting until the patient declines may make the treatment less effective. In some cases, treatment should begin years before disease manifestations are evident, but earlier asymptomatic diagnosis may not be advocated if no treatment is available.

- **Lack of readily measurable, recognized clinical endpoints due to unusual clinical disease manifestations**

  A distinct challenge for some rare diseases is the atypical nature of their clinical outcomes, even when the underlying cause and primary pathophysiology is understood. The disease may not readily fit into existing clinical models and previously identified clinical endpoints may not be applicable. For example, in autosomal recessive dystrophic epidermolysis bullosa, a genetic deficiency causes the epidermal and dermal layers to split and blister. The disease process cannot be readily measured using intermediate clinical endpoints short of major clinical events like hospitalizations for infections which are infrequent and avoided via symptomatic care. In many cases, the non-specific palliative treatments utilized can confound the process of clinical evaluation, as it would of course be unethical to deny such supportive care. In rare diseases, there may be long-term downstream clinical outcomes such as hospitalizations that could be described and appreciated, but conducting the controlled clinical study over the timeframe required will likely be impractical or impossible as their occurrence may be too variable or their frequency insufficient.

B. Summary

An effective application of AA should reflect several important criteria. First, the therapy must be intended to treat a serious or life-threatening disorder where there is unmet medical need. Second, in cases of rare diseases, if the disease itself displays any of the specific criteria outlined above, enhanced flexibility in the qualification of the biomarker endpoint to allow utilization of the AA pathway is merited.

Third, patients, patient groups and physicians with appropriate expertise should evaluate the disease and relevant benefit-risk by formally assessing the unmet need and risk-acceptance of affected patients through direct disease survey or other acceptable means. These considerations are intended as a guide for determining the need for additional regulatory flexibility in the biomarker qualification process to enhance development of and access to innovative treatments. This type of disease survey and analyses

may also provide opportunities to identify and support a possible clinical endpoint for use in clinical studies as well as support the qualification of a biomarker.

IV. ESTABLISH A BIOMARKER QUALIFICATION REQUEST PROCESS FOR INDIVIDUAL DRUGS AND DISEASES

In the evaluation process for choosing products to develop, sponsors consistently will review the potential clinical development pathway and the possible regulatory strategies for approval. The lack of accepted biomarker endpoints for a rare disease with difficult to measure clinical disease manifestations, will mean that the pathway will be considered too difficult to warrant development and investment. The tendency to develop additional drugs for rare diseases for which drugs have already been approved, is in part driven by the certainty of the development pathway and the endpoints. The acceptability of a biomarker endpoint is occurring too late in the process, typically at the End-of-Phase 2 meeting, and is a considerable barrier to the development of many novel drugs for untreated rare diseases. Unfortunately without development pathway predictability, these drugs may never even enter the development process but will rather languish in academia.

If the biomarker qualification determination can be made earlier in the development process, before considerable investment in IND-enabling work, the application of the AA pathway would greatly increase investment in research and development and accelerate the availability of new treatments for the most difficult untreated rare diseases. There is currently no regulatory process for qualifying a surrogate endpoint for a specific disease and drug, until typically at the End-of-Phase 2 meeting, late in the process. Establishment of a **BioMarker Qualification Request** for individual drugs and diseases could allow discussions before an IND is developed and help guide appropriate research before substantial investment has occurred.

The proposed request would be made in parallel or before a pre-IND meeting via a process similar to that for the pre-IND meeting. A briefing book would be prepared along with questions for the FDA, and the data considered. Based on this meeting and discussion, the FDA could agree that for this disease and drug in the specific proposed context, that the biomarker could be used as a primary endpoint with a set of reasonable assumptions, or that it might be qualified if certain specified data were obtained or bolstered in the package, or the FDA might decline to qualify the biomarker under any circumstances due to a specific set of scientific concerns for that biomarker in that specific context of use. The timing for this process need not be restricted to the pre-IND stage, and could occur later in the process if this is convenient. The only key goal is to help provide the option of earlier certainty in development, and the potential then to raise the sufficient funding to develop a rare disease drug when the pathway is clear.

The proposed new request process is different from the currently available biomarker qualification process that is focused on broadly used biomarkers for multiple diseases, as in defining biomarkers for renal injury in drug development for many drugs. The current process operates via the Office of Translational Sciences within the FDA and involves multiple stakeholders, many iterations of evaluation and multiple years. The current process does not accommodate individual drugs and individual biomarkers. Given no specific avenue for this process for a specific drug, it is difficult to engage with review divisions at the pre-IND stage on this topic. The proposed BioMarker Qualification Request would be managed by the appropriate review division, with consultation of the Office of Translational

Sciences, and could occur as early as the pre-IND stage. Managed well, this process could open the door to drug development in some of the most difficult, serious diseases that are not being studied frequently enough today.

V. SUMMARY LIST OF QUALIFICATION CONSIDERATIONS OF A DISEASE/DRUG/BIOMARKER SET FOR ACCELERATED APPROVAL IN RARE DISEASES

At the Biomarker Qualification Request meeting, a briefing book would be prepared that would collect the relevant data to support the qualification based on information set forth in FDASIA. The main principle behind these considerations is that the more that is known about the pathophysiology of the disease, the pharmacology of the drug, the science behind the biomarker, and the data in both animal models and humans with the biomarker, the better the predictive value for reaching the "reasonably likely to predict clinical benefit" standard required by the AA pathway. Currently, the information required to support qualification of a biomarker as a surrogate primary endpoint for use in a pivotal clinical study has not been well described and is developed on a case-by-case basis[16,17]. Unfortunately, a "case-by-case" approach to review without any specified guidance does not provide adequate regulatory predictability and diminishes the potential investment in early development work when the probability of using AA is uncertain. In addition, the emphasis on the availability of prior clinical outcome data to support the use of a biomarker as a primary surrogate endpoint renders AA essentially inaccessible for many rare diseases.

Novel biomarker endpoints should be acceptable under the AA pathway when the novel biomarker can be shown to be "reasonably likely" to predict clinical outcomes. However, achieving this standard has been difficult because of the limited or lack of clinical outcome data. The rest of the data supporting the relevance of a biomarker as a measure of a drug's effect of a disease may have little impact on the qualification process, despite its scientific relevance to reaching the "reasonably likely to predict" standard. To solve this problem, a scientific framework should be developed that establishes a broader set of scientific considerations for qualifying a biomarker as a surrogate endpoint, without requiring prior clinical outcome data. This is particular important when such outcome data are impossible or impractical to collect as noted in FDASIA.[18]

For this reason, FDASIA calls for the consideration of novel approaches to qualifying biomarkers on pathophysiologic and pharmacologic criteria when other types of information are not available. The development of clear qualification considerations will encourage better early development work by assuring a more comprehensive evaluation of a biomarker at a pre-IND stage meeting. The data will support the basic underlying science from disease to drug to biomarker in assessing "reasonably likely to predict clinical benefit."

Listed below are the proposed pathophysiologic and pharmacologic considerations to help drive confidence in a biomarker's predictive value. It should be noted that while these considerations are not absolute requirements, they should be viewed as data points to support the use of a biomarker for AA in that specific context of use. In the subsequent section, these considerations are further described in detail.

Specific overall biomarker qualification considerations:

A. Disease Considerations

- Cause of disease clearly understood: distinct pathophysiologic cause based on a measurable entity or single gene disorder
- Pathophysiology mechanisms relating to clinical outcome reasonably understood
- There is no known major alternative pathway of disease that is not assessable

B. Drug Considerations

- Drug mechanism of action is direct and known
- Drug pharmacokinetics, pharmacodynamics and metabolism are relevant to the disease process being treated and can be accurately and readily measured
- Drug can be made reproducibly with appropriate quality to provide a consistent treatment effect

C. Biomarker Considerations

- Biomarker has reasonable biologic stability and a direct relationship to an important pathophysiologic pathway
- Sampling compartment for biomarker predicts the important disease compartment/tissue
- Biomarker assay is a valid and reproducible: Sensitive, accurate, precise and specific with a sufficient dynamic range to calibrate biomarker change with pathology
- Accepted clinical physiologic measures may be considered predictive if the measure is associated with major clinical problems in other diseases even if not considered a clinical outcome themselves

D. Preclinical Considerations

- The model should be relevant to the pathophysiologic basis for the disease
- Magnitude and type of treatment effect is relevant and substantial relative to the human disease state
- Preclinical treatment studies show dynamic dose-response relationship of the biomarker on pathophysiology and/or clinical effect
- Preclinical studies show a meaningful clinical or physiologic effect on the disease if the models reflect human disease reasonably accurately
- Measurement of the biomarker compartment should be confirmed to reflect tissue compartments of interest

E. Clinical data considerations for biomarker qualification

- The biomarker predicts clinical severity or progression in a cross-sectional clinical survey, natural history study or in preliminary investigational studies
- The dynamic range of the biomarker is sufficiently broad to assess the full spectrum of severity or the appropriate difference between normal and disease states
- The biomarker shows predictive value for other similar rare diseases with comparable pathophysiology

VI. DETAILED DESCRIPTION OF THE SCIENTIFIC CONSIDERATIONS FOR THE QUALIFICATION OF BIOMARKER ENDPOINTS USING DISEASE, DRUG, BIOMARKER, PRECLINICAL AND CLINICAL INFORMATION

A. Disease considerations regarding the underlying disease pathophysiology that support predictive value

To understand the scientific basis behind how a drug's effects on a biomarker relate to disease outcomes, a clear understanding of the pathophysiologic pathways involved in disease pathogenesis, particularly related to the root cause of disease and their relationship to clinical outcomes are important. The greater the clarity of the underlying scientific basis and the pathophysiologic processes for a disease, the greater the confidence regarding the interpretation of a biomarker for this disease. The utility of animal models such as gene knockout models for diseases of monogenic origin should be considered particularly relevant in this context. Data from the clinical literature, *in vitro* studies, and relevant comparable diseases should be provided as supportive evidence of the current understanding of pathophysiology.

- **The cause of the disease is clear.** The specific and distinct root cause of disease, such as a specific genetic defect, the presence of a particular autoantibody, or similar specific biological change is known or understood based on basic science, preclinical or human data.

- **The pathophysiology of the disease is generally understood.** When there is an understanding of how biochemical or pathological processes result in a disease manifestation or group of manifestations, the predictive value of the biomarker is increased. There may be aspects or secondary pathways that have not been fully understood but at least one of the major pathways of interest should be known.

- **There is no known major alternative pathway of disease pathogenesis that is not assessable.** When there is no evidence of an alternative disease pathway, the predictive value of a biomarker is enhanced. The existence of alternative pathways that are poorly understood can cause uncertainty regarding how a biomarker might impact overall outcome.[19] However, exclusion of all possible pathophysiologic processes is impractical and unnecessary, particularly if the root cause of disease pathogenesis leading to important clinical manifestations has been identified.

B. Drug considerations for pharmacology of the treatment and its relationship to the disease and biomarker

An understanding of the basic structure, delivery and actions of a drug can also enhance a biomarker's predictive value. Drugs with direct and well-understood mechanisms of action provide greater confidence in the plausibility of a relationship between a biomarker effect and a clinical outcome. In addition, information about a compound's distribution at appropriate effective concentrations to sites of action and the basis for this action can further support the likelihood of a cause-effect relationship. Conversely, when the basis for the drug's action is unclear or its distribution to the relevant site of action cannot be established, then the basis for the drug's action and the understanding of the changes in the

biomarker or disease are less certain. The data on the pharmacology of a particular drug, then, can help to provide greater certainty that its action on a specified biomarker comes through a pathophysiologic process associated with a major clinical outcome. What follows is a list of the specific drug considerations that will enhance a biomarker's predictive value.

- **The drug's structure and identity are clear** and its production at developmental scale in the correct active form is reproducible, particularly in the critical aspects relevant to its absorption, distribution, metabolism, and action, so that each study using the agent is relevant.
- **The mechanism of action of the drug is direct and understood**. An understanding of the drug's mechanisms contributes to greater certainty about the interpretability of the relationship of the drug's action to the biomarker and relevant clinical outcomes become more predictable. Such mechanisms could include replacement for a deficiency, enhancement of a deficient activity, induction of a specific protein, or synthetic process by a mechanism demonstrable *in vitro* in cell lines or in highly relevant animal models.
- **The specific pharmacologic action and activity of the drug can be demonstrated** in *in vitro* or *in vivo* systems to provide confidence on the effective concentration, distribution to the site of action, uptake, and action.
- **Studies of the drug in models demonstrate relevant absorption, distribution, metabolism and excretion (ADME).** When the drug's ADME are consistent with delivering the drug to the site of action at a relevant concentration consistent with the plausibility of action on the target tissue or tissues, this increases the likelihood that the effect on a biomarker and disease state are connected to clinical outcome.

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Table 1. Examples of pathophysiologic maps from cause, to pathophysiology to clinical physiology to clinical outcome

Disease	**Cause** (gene or protein level)	**1^{o} Pathophys.** (cell level)	**2^{o} Pathophys.** (tissue level)	**Clinical Physiology** (system/organ)	**Early Clinical** (integrated systems)	**Late Clinical** (final major outcome/events)
Mucopolysaccharidosis type 1 (MPS 1)	IDUA gene mutations Reduce iduronidase enzymatic activity	Accumulation of heparan sulfate and dermatan sulfate GAG in cells and tissues	• GAG infiltration of upper airway tissue • GAG infiltration of lungs, liver, rib and spine development • Synovial storage • Thick heart valve • Abnormal bone formation	• Sleep apnea, ↓O2 • Impaired PFT • Joint ROM defect • Nerve compression • MR on Echo • Dysostosis multiplex	• Sleep deprivation • Pulmonary insufficiency • Difficult hand mobility • Enlarged heart • Joint pain, stiffness, contractures • Reduced growth rate	• Right heart failure • Hospitalization/oxygen • Increased respiratory infections • Unable to do ADL • Carpal tunnel syndrome requiring surgery • Congestive heart failure • Wheelchair bound • Orthopedic interventions • Short stature
Phenylketonuria	Defect in PAH gene that expresses PAH that metabolizes Phe	↓Phe destruction leads to ↑Phenylalanine in blood	• ↑Phenylalanine causes cytotoxic effects • Myelin abnormalities	• White matter abnormalities • Altered neuro function	• Mild cognitive impairment	• Advanced cognitive impairment
Myasthenia gravis	Antibody to the AchR	Inhibition of Ach-based signaling	• Muscle weakness	• Drooping eyelids • Weak legs	• Difficulty keeping eyes open for vision • Difficulty walking	• Wheelchair bound
Duchenne muscular dystrophy	Genetic defect in dystrophin gene	Deficiency of dystrophin protein	• Rupture of myofibrils • Myopathy • Centrilobular nuclei	• Muscle weakness • Heart abnormality • Decreased FVC	• Gower's sign • Difficult walking • Decreased play	• Loss of ambulation • Heart failure • Death
Alpha Dystroglycan related muscular dystrophy	Hypo-glycosylation of alpha dystroglycan	Defective binding to extracellular matrix, sarcolemmal membrane instability	• Stem cell regenerative defect • Muscle cell death • Myopathy, fibrosis	• Impaired PFT • Decreased balance, walking, climbing stairs, rising from chair • Decreased ejection fraction (echo) • Brain abnormalities in a subset of patients	• Respiratory insufficiency • Muscle weakness, impaired mobility • Enlarged heart • Cognitive impairment	• Ventilatory support • Wheelchair bound • Congestive heart failure • Decreased IQ and behavioral abnormalities
Fabry Disease	Mutation α-galactosidase gene	Accumulation GL3 in lysosome	• Multiple cells storage (cardiomyocytes, podocytes etc) • Small vessels storage	• PNS • CNS • Eye • GI tract • Heart • Kidney • Skin	• Acroparesthesia • Heat intolerance • Angiokeratoma • Proteinuria • Arrhythmia	• Renal failure • Cardiac insufficiency • Stroke • Deafness

Table2. Biomarker types organized by biological level and compared via stages with examples

Biomarker Type	Pathophysiologic Process or Stage	General Examples	Specific Examples	Pros	Cons
Genetic marker	1^o Cause	Presence of a gene mutation	CF mutations	Measure presence of gene	Not a function
RNA/gene expression	1^o pathophysiologic	Expression of aberrant RNA RNA splicing error Presence of new gene expression	Friedrich's ataxia Fragile X	Direct impact on gene expression	Unclear about downstream effect
Enzyme or protein level	1^o pathophysiologic	Enzyme activity in tissue Protein in circulation	Alpha-1-antitrypsin	Direct measure of active compound	Difficult to verify tissue effect
Biochemical	1^o pathophysiologic	Blood level of an accumulating metabolite due to a 1^o block Decrease in level of critical needed biochemical	Phenylalanine in PKU BH4 in BH4 deficiency	Directly toxic compound or active compound	Not a measure of tissue effect
Secondary Biochemical	2^o pathophysiologic	Increase in secondary metabolite that is toxic or part of pathophysiology but not from original defect	Succinyl-lactone in tyrosinemia I Homogentisic acid in alkaptonuria	Directly measure of toxic effector	Cannot always measure downstream toxicity
Biopsy	2^o pathophysiologic	Presence of abnormal cells or marker Pathological change in structure	GL3 granules in Fabry Dystrophin in Duchenne	Direct measure of disease or absence of protein	Variability of biopsies, representative sampling, variable assay methods
***Ex vivo* explant**	2^o pathophysiologic	Evaluate a cell removed from the patient for a phenotype or function	CGD/y-interferon	None	Failed : questionable validity of an ex vivo assessment
X-ray/Imaging	2^o pathophysiologic	Bone structure Presence of abnormal lesions Change in size Visual appearance like fundoscopy	X-ray ricket score	Bone structure is nature of disease	X-ray does not show function exactly
Clinical Physiology tests	1^o clinical effect	Tests used in clinical evaluations of clinical conditions dependent primarily on a single tissue/organ EMG, EKG, NCV, BAER, hand held dynamometry	FVC in CF Muscle strength in DMD or HIBM	Measure of a physical function that is directly relevant	Not strictly a clinical outcome and hard to gauge size of effect with clinical outcome
Clinical function	2^o clinical effect or intermediate clinical measure	Tests that study integrated multiple body systems/organs, Pulmonary function tests, sleep apnea, muscle function	6min walk test Walking speed	Measure of a patient's function	Need to interpret magnitude of change for relevance to patient

C. Biomarker considerations regarding the specific scientific bases of biomarkers or intermediary clinical endpoints that support the likelihood of predictive value

Biomarkers as surrogate primary endpoints have had both successes and failures in their ability to accurately predict clinical benefit.[19] The large variety of biomarkers and disease contexts can make the systematic scientific evaluation process difficult, but there are specific points of supporting information that can enhance the likelihood of real predictive value. While statistical correlations established through large interventional outcomes studies have frequently been used to develop predictive relationships, correlations alone do not provide predictive value for a biomarker that can be evaluated based on its biology. The biological bases of biomarkers and their relationship to the pathophysiology of disease represent a valuable and critical insight into predictive value.

Biomarkers can represent any point along the pathophysiologic process, from primary disease cause to just before clinical outcome, and different considerations exist for different types of surrogates (see Table 1 for examples). A map of the pathophysiologic pathway from primary cause, primary and secondary pathophysiologic processes, primary and secondary clinical effects, early clinical outcomes and final clinical outcomes should be prepared to help establish the basis for the relationship of the biomarker, and to provide a structure for verifying the degrees of evidentiary support that exist for these steps. Understanding the precise process level for the biomarker and the type of biomarker is important in guiding the type of information required about a biomarker and its position within the pathophysiology of the disease and reflecting the drug's mechanism of action (Table 2).

- **The biomarker is directly in line within the pathophysiological map** for at least one of the major pathophysiologic pathways. This is a critically important factor as reviewed by Fleming. [20]

    - An effect on a biomarker close to the primary pathophysiologic cause of the disease is likely to be predictive of a meaningful impact on the disease and is less prone to unknown links or secondary parameters.

    - If the biomarker is part of a secondary pathophysiologic process, the process must be demonstrated to be important and critical to the clinically important pathophysiology, and the links to the primary pathophysiology should be demonstrated in model studies.

    - A combined effect on multiple secondary pathologic biomarkers, particularly in the setting of an effect on a primary pathophysiologic mechanism, should provide greater confidence in predicting a clinically meaningful effect.

    - A biomarker or intermediate clinical biomarker close to a major pathophysiologic clinical outcome should also be considered relevant to and predictive of a specific clinical outcome.

    - A biomarker should be matched with the most appropriate stage of disease and used in that context. A biomarker of early disease pathophysiology may no longer be relevant

once significant, irreversible damage to an organ has occurred (e.g. malformation or failure), and conversely, a biomarker of late disease pathophysiology may not be informative early in the disease course.

- The biomarker should not have other unpredictable parallel pathophysiologic pathways that could confound the interpretation of the biomarker. This could include a pathway for metabolizing the biomarker or creating the marker that is a normal biologically variant factor. Controls for this issue should be considered in study designs.

- **The sampling compartment for the biomarker predicts the disease compartment.** The site of sampling, whether blood, urine, cerebrospinal fluid, an X-ray/image, or a biopsy, must reflect the relevant disease compartment, even if sampling the disease compartment is not possible. For example, if a blood biomarker were being studied for a CNS indication, studies in model systems should show that the blood compartment sufficiently reflects the brain disease state. Confirmation within a clinical cross-sectional survey and within preclinical models is valuable. The disease process could occur in multiple compartments beyond the sampled compartment, but in this case, it should be shown that the sampling compartment is relevant and correlated with other compartments across a variety of therapeutic situations or that it is at least predictive of the important compartment in preclinical models.

- **Changes in the biomarker are sensitive and specific to changes in patient condition with a sufficient dynamic range between normal and abnormal patients.** The assay should be able to distinguish abnormal from normal with sufficient precision and accuracy to be a reliable tool in the clinical setting. To ensure that various gradations of abnormality in specimens are accurately detected, the difference between abnormal and normal should be large relative to the standard deviation or coefficient of variation of the assay in a clinical study setting. When possible, these data should come from untreated patient specimens and be comparable to normal persons of similar age and type. If collected in preclinical models, the ability to detect an abnormal result with sufficient dynamic range should be convincing. The dynamic range must be adequate to assure that biological variation between patients or the assay methodology could not overshadow the relevant changes in the biomarker. Changes in preclinical models with treatment should substantiate the characteristics of dynamic range and responsiveness to change over time.

- **The biomarker should demonstrate reasonable biologic stability.** If the disease state is relatively stable and no change in physiology is occurring, the biomarker's relative level should not dramatically change. Obtaining these data may require testing a group of individuals or preclinical models over a significant timeframe.

- **The assay methodology for measuring the biomarker should be validated** using reasonable and relevant criteria. In order for approval to be based on a biomarker, the assay must reliably measure the biomarker's value in humans. This is of particular importance for tissue biopsy analysis, as well as for other techniques in which complex samples are

analyzed using tools that may be prone to variation from the sampling process, the reagents or signal detection.

- **Accepted clinical physiologic measures may be considered a predictive biomarker if they are directly relevant to major clinical problems in the rare disease**. Many clinical physiological tests are used to assess and treat a specific clinical condition in common and rare diseases. These tests are routinely accepted for use in clinical practice for the diagnosis and management of clinical conditions in other common diseases with similar pathophysiology. For example, measures for joint range of motion, sleep apnea, heart enlargement by echocardiography, and similar tests have been associated with clinical outcomes and are actively used to initiate treatment in common diseases. If the comparability between the pathophysiologic processes, disease characterization, or outcomes can be demonstrated between the rare disease and common diseases, these tests should be considered to have predictive value. The magnitude of the disease present and changes expected should be shown to compare well with clinically significant changes observed in other common diseases where the clinical physiologic measure is used. Although the tests may not have been previously used as primary endpoints, if national standards for the diagnosis and management of the disease condition exist for other diseases, then the comparability of the disease process need only be supported through the use of scientific literature or testing in order to support the use of the test as a biomarker in a rare disorder. Examples of such tests include pulmonary function tests, sleep apnea testing (e.g. apnea-hypopnea index), echocardiography (assessing cardiomegaly or poor ejection fraction), nerve conduction velocity, or similar clinical physiology tests that capture important clinical physiology used for the diagnosis and management of conditions. Included in this category could be physiologic measures normally accepted as clinical endpoints but for which the magnitude of the change might be too small to represent a clinical benefit, thought the direction of the change is positive for the patient.

D. Preclinical Evidence to support use of a disease/drug/biomarker set for accelerated approval

For rare diseases, model disease treatment data are often essential to demonstrating an important effect of a treatment on a disease. The proper conduct of preclinical studies can be important to establish a platform of data and a framework for understanding how the disease and drug interact, as well as how the biomarker's behavior is predictive. Certain critical sets of data should be obtained to support the biomarker in *in vitro* and preclinical model experiments. The more appropriate and comparable the model is to human disease, the better it may predict human disease. In the absence of strongly predictive clinical models, a model that demonstrates the treatment and biomarker effects at the level of pathophysiology and pharmacology is sufficient, as preclinical models often do not express every aspect of clinical disease or progression in the same manner as in humans. Clearly, data derived only in animal models of less certain relationship to a disease, must be supported by other types of data in order to allow qualification. Exclusive reliance animal models is not optimal as this can lead to a failure in the predictive value of the biomarker when the model does not fully reflect the human disease state.

The best possible data setting, whether *in vitro* or preclinical, should be sought to support the considerations provided below. However, for some diseases there is no opportunity to make a preclinical model and only *in vitro* models may be available or valid. When measuring the clinical effects in the models is impractical or irrelevant, the data on the preclinical models can be based on the pharmacologic or pathophysiological changes in the model.

Key preclinical data to support the predictive value:

- **The model should be relevant to the pathophysiologic basis for the disease.** This should be accomplished through a comparison of pathophysiology/genetics and using microscopic, biochemical and (if present) clinical disease assessments. Clinical disease varies in models and may not be the same in every respect due to the differences in species and effects of changes, but applicability of the model can still be demonstrated if relevant pathophysiologic changes can be assessed.

- **There should be a broad and dynamic dose-response relationship** over the wide range of disease and treatment effects demonstrating how changes in the biomarker reflect changes in the model disease level. When possible, it is critically important to establish the level of biomarker improvement associated with a potentially clinically meaningful change in disease level (Figure 1). The dose-response relationship should also be established for suboptimal therapeutic dose levels to demonstrate the biomarker's sensitivity in evaluating drug effects that are low and not likely to predict benefit. The impact of any adverse responses (e.g., an immune response to the therapeutic agent) should be evaluated for its impact on the biomarker and treatment effect to show how the biomarker predicts the treatment effect at the biochemical or pathologic level when altered by this condition. For example, if antibodies to a drug interfere with efficacy, the biomarker should reflect this decrease. If there is no clear relationship between the amount of model disease reduction and clinical outcome, then a relative comparison toward the degree of normalization of the pathophysiology should be used as the best estimate of a meaningful treatment effect.

- **Measurement of the biomarker compartment should be confirmed to reflect tissue compartments relevant to the disease state.** A comparison of the dose-response relationship should establish the relationship between the sampled compartment levels and the pathology in tissues associated with adverse clinical outcomes. For example, a blood test should correlate with muscle pathology for a muscle disease treatment. A spinal fluid measurement should be shown to reflect the brain pathology, in a brain disease treatment. In particular, suboptimal levels of treatment should be used to determine whether the biomarker reasonably reflects the pathologic outcome for tissues relevant to disease outcomes.

- **Biomarker changes predict clinical changes in existing relevant models.** Although many preclinical models do not show comparable clinical disease to humans, demonstration of the predictive value of the biomarker on treatment outcome in clinical measures can still help provide support for greater predictive value.

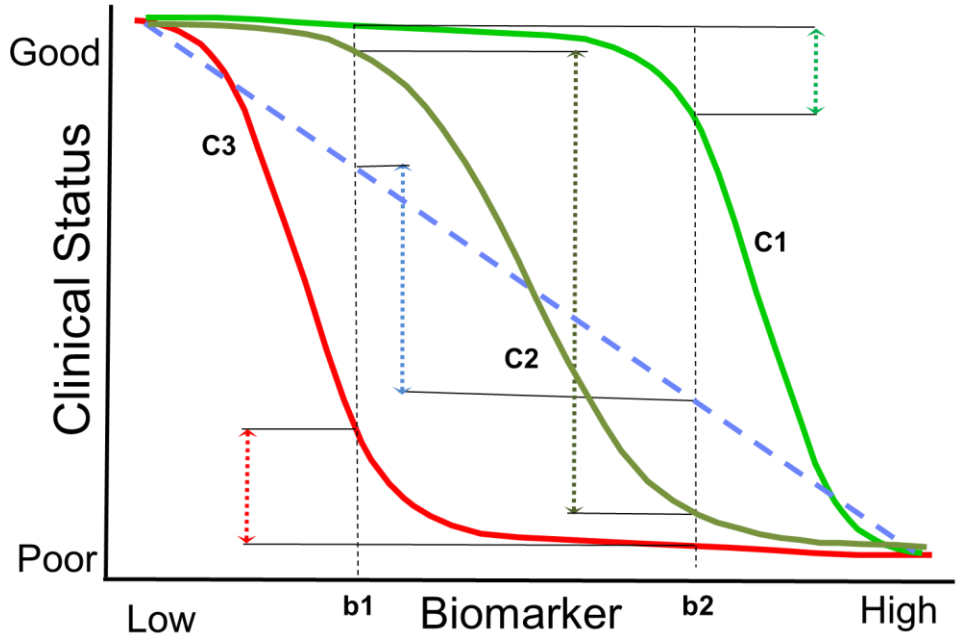

Figure 1. Possible dose response relationships between a biomarker and clinical status Understanding the biomarker-disease relationship is important and can be established to some degree in preclinical studies, with support from cross-sectional or natural history studies. The graph shows how different shapes of the curve can provide very different interpretations of the change in clinical status (C1, C2 and C3) for a similar change in the biomarker (b1, b2). Establishing this relationship is an important part of interpreting the change in a biomarker in a clinical study setting and having this data is therefore important in the qualification process.

E. Available clinical evidence to support use of a disease/drug/biomarker set for accelerated approval

The collection of clinical data has been an especially difficult barrier to access to the AA pathway for rare diseases, due to lack of historical data, insufficient patient numbers, and time to establish firm relationships between a biomarker and clinical outcomes. Optimally, clinical data with an effective treatment are required to develop a predictive relationship for clinical outcomes. When clinical outcome data does exist for the predictive value of a biomarker in a rare disease, these data are important to the assessment in the qualification of a biomarker endpoint for use as a surrogate primary endpoint. In most cases, however, longitudinal treatment studies with other agents have never been conducted, and there is limited useful clinical outcome information available from natural history studies. In these cases, other types of data must be sought when practical to support the qualification of a surrogate.

In the absence of clinical outcome data, significant information can be obtained from cross-sectional survey studies of patients using a biomarker and known clinical condition and assessment measures. These studies can be conducted prior to the investment in manufacturing a drug, or before clinical development has begun, to assist in the determination of the predictive value of the biomarker when reasonable and practical. Ideally, the studies should include patients of different ages, severity and stages of disease. This cross-sectional survey data can often be larger in patient number and broader in scope than the type of data provided by a natural history study, especially if

the long-term retrospective data can be also collected during the cross-sectional evaluation.

Natural history data can be enormously helpful in assessing a disease and planning a development program both in supporting a biomarker and in understanding the disease. However, such studies are costly, take a long time to complete, and can be prone to selection bias, making it exceedingly difficult to collect the kind and quality of data required for assessment of biomarkers in a time frame that allows for a real impact on rare disease programs. Nonetheless, both natural history and cross-sectional data can be very useful in supporting the clinical relevance of a biomarker endpoint.

The clinical data to support a biomarker should focus on the following important considerations:

- **The biomarker predicts clinical severity or progression as assessed using other clinical measures of disease.** A cross-sectional clinical survey study or retrospective medical chart survey or natural history study can yield data to support a relationship between the magnitude and change over time of the biomarker measures and severity/progression/disease level by other clinical measures. The survey can provide multiple types of data to establish a reasonable relationship and dynamic range for the biomarker and a clinical parameter. This can be done early in a program before a drug exists or before an IND is submitted.
- **The sensitivity and dynamic range of the biomarker is sufficiently broad** to elucidate the important part of the spectrum of severity of the disease using the biomarker. Patients with mild disease or severe disease can be distinguished from each other and from normal patients.
- **The biomarker shows predictive value for other similar diseases**. Clinical data with approved drugs from similar diseases, for which studies have been completed, show a reasonable relationship between changes in the biomarker and changes in clinical endpoints. This may rarely occur, but if adequate and reasonable parallels for another rare disease with similar mechanisms exist, these data may be useful. This is not to suggest that the use or failure of biomarkers in complex multi-genic common diseases should necessarily be applicable to results in diseases with far more specific and clear underlying pathophysiology. One example of is the use of plasma ammonia level to approve several drugs that reduce ammonia in patients affected by defects in the urea cycle.

VII. CLINICAL TRIAL DESIGN CONSIDERATIONS

In many rare diseases, traditional randomized concurrent controlled studies may be difficult to conduct, both because of the rarity of the disease and the ethical issues associated with the study of some devastating rare diseases. Alternative study designs may be deemed acceptable, but the sponsor will need to provide sufficient information on safety and efficacy to provide reasonable assurance that the criteria for AA have been satisfied.

Some key considerations for the study design and analysis are as follows:

A. Pivotal Study Trial Design: Concepts for studies using a primary surrogate marker endpoint

- **Randomized, concurrent controlled studies are preferred when feasible and appropriate.** The use of placebo control groups is the gold standard for quantitating the magnitude of the treatment effect when no other treatment exists, and should be implemented except in exceptional circumstances. In some situations, blinding a treatment is impossible or it may be unethical either due to the type intervention itself, or the withholding of potential other care with irreversible devastating consequences cannot be justified. When placebo control groups are not feasible or ethical, historical control data can be considered with a single-arm treatment study (e.g. Myozyme for Pompe) or an unblinded parallel control group when blinding is difficult. These study design alternatives have been used in oncology more frequently, but there are situations in which good objective data can be obtained to support the assessment of efficacy. In this open-label setting, the appropriate blinding of the analysis of the biomarker as the surrogate primary endpoint may be appropriate to assure an objective assessment of efficacy can be made.

- **An adequate assessment of safety is still required.** Given the extraordinarily small patient populations for some disorders, it is important to assure the best possible safety assessment by understanding potential adverse safety pathophysiologies that may be operative based on the drug's mechanism of action and the underlying disease state. AA via a biomarker may allow for smaller clinical studies, but the study size of the exposed safety population should also be considered in the context of the expected population exposure and not just in terms of a study size sufficient to demonstrate efficacy. When the number of existing patients is small, limiting the safety dataset in a study, a longer period of observation can provide some additional support for safety. Therefore, it is advisable to continue treatment of early treated subjects in extension studies to provide this additional safety information.

- **Off-target adverse activities need to be evaluated for the drug.** Studies using *in vitro*, toxicologic, or model pharmacologic studies that suggest the existence of any significant alternative pathways or adverse physiologies not reflected in response to the drug or in the specific biomarker proposed for use as a surrogate, needs to be evaluated in the studies. It is important to assess whether these independent adverse effects via another mechanism on the patient which might lead to harm that outweighs the expected benefit. A drug that might be predictive of clinical benefit through one pathway could still have a negative benefit-risk ratio if an alternative unmeasured adverse action occurs that has a greater impact on risk than the primary benefit. If the alternative adverse pathway can be measured and followed in clinical studies, then the confounding effect on benefit may be quantified during the clinical program and included in the benefit-risk analysis.

- **AA does not require internal validation of the biomarker.** The concept of AA is the acceptance of a biomarker as a primary surrogate endpoint without the requirement for positive clinical outcome data within the same study. It is still advisable to measure

clinical endpoints in these studies to begin the assessment of the surrogate and to provide supportive information about treatment and safety. Observations of trends in clinical endpoint data can be supportive, but for some diseases that have prolonged courses, there can be no expectations of supporting clinical endpoint data. In addition to the primary surrogate endpoint, other biomarker and clinical physiology endpoints can help substantiate that the expected biology is occurring.

- **Alternative study designs are potentially acceptable, but require careful planning.**
    - **Open-label studies** using no parallel control groups or conducting within-patient comparisons, have substantial limitations on the interpretation of efficacy and safety. If used, the design and conduct should consider sufficient safeguards and assessments in place to ensure that a reasonable assessment of drug-related safety effects can be made and efficacy assessments are objective. The interpretative value can be improved by conducting blinded readings of data when possible in this setting.
    - **Alternative designs including placebo-run in periods, randomized withdrawal or other alternative within patient controlled designs.** Studies based on alternative controlled designs or the N of 1 concepts of within-patient evaluations under conditions of treatment or placebo or treatment withdrawal can be powerful in assessing efficacy and safety, despite a small cohort of patients.
    - **Historically controlled studies** can be difficult to interpret and require extensive planning and rigorous execution to be accepted. Crucial aspects include controlling for severity or ascertainment of the subjects in the control versus the treated group, differences in ancillary medical care, and the differences that may occur simply as a result of participating in a study. To be successful, the natural history control group data must be robust with adequate assessment of the disease to verify comparability with the treated patient group. This assessment could, to extent possible, include genotypes, phenotypes, age of onset, degree of medical care utilization, physiologic assessments of disease severity and carefully recorded data on ancillary treatments applied. Matched control groups or other designs as close as possible to the contemporaneous population would be preferred in order to minimize the effect of changes in medical care or attitudes about treatment that might have an effect on outcomes.
- **Sufficient long-term data on safety and efficacy is required.** Given the smaller populations of patients affected by rare diseases, longer-term data is critical in verifying the durable effect on a particular biomarker, the safety of repeated treatments, and the potential evolution of adverse responses or other physiologies to have occurred and their effects fully realized. For acute diseases, this is not a relevant consideration.

B. Post-marketing confirmatory studies in rare disease indications

The approval of a therapeutic via AA requires that additional data be collected in the post-marketing setting to support the efficacy and safety of the drug. In rare diseases, post-marketing studies can be difficult to conduct, especially if the confirmatory study is expected to be placebo-controlled. Important clinical outcomes may require a long period of observation, making placebo-controlled studies impractical. Careful planning and effective designs to support the clinical meaningfulness of the data are required.

Recommended steps and considerations for post-marketing confirmatory studies for rare disease indications include:

- **A confirmatory study plan should be discussed early in the development when the AA pathway is being considered.** To assess the complete development pathway regarding the provision of adequate safety and efficacy information, the context for post-marketing studies and the type of data to support efficacy and safety should be carefully considered.

- **Placebo versus non-placebo controlled confirmatory studies.** While placebo-controlled studies provide the greatest assurance of efficacy, they may not be appropriate, ethical, or feasible given the long timeframes for disease progression, the frequency of events in some diseases, or the ability to recruit patients with severe and life-threatening diseases. If placebo-controlled studies are possible, they should be conducted early in the launch of the program and could include periods of placebo treatment for patients prior to being converted to the marketed product. This would allow for the collection of more clinical data on shorter-term outcomes. If placebo-controlled studies are impractical due to the timeframe or nature of the clinical benefit, an effective plan on how to obtain objective data, or sufficiently robust long-term data to support efficacy on hard clinical endpoints, is important to the AA pathway. For diseases with long-term neurologic progression, adequate untreated control subject data with appropriate data on patient comparability and phenotype/genotype are important.

- **The size, length, and scope of the confirmatory program should be sufficient to compensate for the limitations of the patient population.** For small patient populations, the post-marketing program should be designed to allow for the participation of enough patients to verify the clinical outcome. For rare diseases, this may require longer-term observation to help support the magnitude of the clinical impact. In studies without parallel control groups, the magnitude or nature of the clinical benefit might need to be sufficient to overcome the potential for bias in assessments. When patient numbers are extremely limited, the inclusion of a large fraction of the patients may be required and can be balanced with a design that allows the major clinical assessments to be collected at intervals during efficient clinical disease surveys of treated patients. This can eliminate the need for all of the patients to participate in an ongoing clinical study, which may be impractical or impossible to conduct. The collection of high quality outcome data from previously untreated patients may be a critical element in supporting the determination of

efficacy in long, open-label post-marketing programs, and this possibility should be discussed with the FDA as part of the AA discussion.

VIII. EXAMPLES OF SUCCESSFUL USE OF BIOMARKER ENDPOINTS DURING DEVELOPMENT OF RARE DISEASE DRUGS

A number of drugs have been approved for the treatment of rare diseases using biomarker-based primary endpoints. In most cases, the standard approval pathway was used and involved some degree of FDA flexibility. [8] AA was used in some cases. While these examples provide support for the types of information that has been successful in achieving approval, they may not necessarily reflect the full range of information needed to successfully develop a rare disease therapeutic.

A. Ammonia in urea cycle defects: glycerol phenylbutyrate

The urea cycle defects cause a block in the process that disposes of ammonia as urea, and results in elevation of toxic ammonia levels. The defect is directly in the pathophysiologic process that creates the biomarker ammonia, and ammonia is intrinsically toxic in excess. A series of drugs that divert ammonia via glycine or glutamine depletion have been approved using ammonia levels as the primary indicator. The most recent example is glycerol phenylbutyrate for urea cycle disorders that was approved with a randomized double cross-over clinical study comparing it with the approved original phenylbutyrate. The control over ammonia over a 24-hour period was compared with the active control treatment. Given the history of approvals for drugs intended for urea cycle defects using ammonia control, and the use of ammonia control in other diseases such as liver diseases, there has been a precedent for ammonia control as a biomarker endpoint.

B. Phenylalanine for phenylketonuria (PKU): Sapropterin dihydrochloride

Phenylalanine is increased in large excess in patients due to defects in the phenylalanine hydroxylase enzyme. This enzyme is primarily responsible for initiating the oxidative degradation of phenylalanine, and without it the phenylalanine level rises many-fold above normal. Phenylalanine has been shown to be directly toxic to neurons and has been shown to predict IQ outcome in multiple clinical studies of another therapy, dietary restriction of phenylalanine. The use of phenylalanine blood level was accepted as a primary endpoint in an 89-patient randomized, placebo-controlled clinical study in the sapropterin dihydrochloride development program for the PKU program. Although the mechanism of action of sapropterin was different from the compared diet therapy used to qualify the biomarker endpoint, its mechanism was demonstrated by labeling studies to involve the restoration of the normal oxidative metabolic pathway.

C. GL3 storage granules in the vascular endothelial cells for Fabry disease: Agalsidase beta

Fabry disease is a lysosomal storage disorder caused by a defect in the alpha-galactosidase gene and results in storage in many cell types. The disease has a pronounced vascular phenotype with disease most commonly in the kidney, heart and brain. Storage within the endothelium is directly responsible for these vascular problems. In the development of an enzyme replacement therapy for Fabry, it was shown that the enzyme can clear the storage and return the endothelial cells to near-

normal if not normal status in terms of GL3 granules using renal biopsies and a scoring system. This pathologic endpoint was used in the approval of the enzyme therapy agalsidase beta in a 58-patient randomized placebo-controlled study. The challenge was that biopsy data can be quite variable in sampling and the scoring can be subjective, so extensive work on multiple biopsies and scoring systems and adjudication of results was needed to develop and gain agreement on the biopsy and the analysis of the pathology. The confirmatory study for this approval had some complications and though the result is debated, agalsidase beta did appear to reduce the major event rate of Fabry disease as expected.

D. Hemoglobin and platelet count for Gaucher disease: Alglucerase

Patients with Gaucher have lysosomal storage in the macrophages which leads to a large spleen and sequestration of red cells and platelets. Anemia and thrombocytopenia can be severe and be associated with bleeding problems. Alglucerase was studied in a 12-patient single-arm, open-label study and shown to improve hemoglobin and platelet counts, as well as reduce spleen and liver size. Although the magnitude of the changes had not been shown to be clinically meaningful specifically in these disease patients, it was assumed based on general medical experience that low hemoglobin and low platelets are problems and that magnitude of the resolution of these problems observed should be beneficial the patient.

E. Alpha-1-antitrypsin level for Alpha-1-antitrypsin deficiency disease

Patients with alpha-1-antitrypsin deficiency disease have excessive protease action that results in pulmonary disease like emphysema over many years, and can also be associated with liver disease. Blood-derived replacement therapy was successfully approved by demonstrating the reasonable restoration of blood levels of the protease inhibitor, although no direct proof of inhibiting proteases at the tissue level was demonstrated. An open-label study of one form alpha-1- proteinase inhibitor (Prolastin) was studied in 19 patients over 24 weeks and shown to achieve a serum level exceeding 80 mg/dl and bronchoalveolar lavage demonstrated that the level in the plasma compartment was reaching the alveolar space.

F. Deferasirox for reduction in iron overload in beta-thalassemia

Deferasirox was approved using a liver biopsy measure of iron as a primary biomarker endpoint for the reduction in iron overload derived from transfusion therapy in the red cell disease, beta-thalassemia. In this program, a randomized, open-label study comparing standard therapy with deferoxamine compared the iron content in a liver biopsy at 12 months to baseline content. Liver iron content is a measure of total iron load and the drug's action is the direct removal of iron via the urine. The biomarker is in the liver, which is an important target organ and therefore an appropriate tissue compartment for measurement. The precision of biopsy methods can be challenging in general, and this study randomized a total of 586 patients to achieve their demonstration of efficacy over 4 dose levels.

IX. CONCLUSIONS AND RECOMMENDATIONS

The effective utilization of the AA pathway for rare diseases will require development and use of a scientifically sound framework of data for qualifying biomarker endpoints allowing the practical use of biomarkers as a measure of efficacy. A scientific framework with defined sets of supporting data should allow the beginning of a more structured approach to qualifying biomarkers for use in pivotal studies of rare disease treatments and ensure a wider array of important considerations are included in this process. The proposed data that help qualify a biomarker will cover the disease, the drug, the biomarker, preclinical data, and clinical survey or natural history data. It is extremely important to recognize that clinical outcome data for a novel biomarker is rarely available or plausible and therefore a systematic process that builds support for the predictive value of a surrogate using data that is available will allow more investment innovative treatments for rare diseases.

This proposed scientific framework is a first step and will need further evolution and development going forward with experience. Regardless, the judgment and insight of experts is needed to assess the scientific support for a biomarker, to weight the importance of the various results and make a structured decision regarding qualification. The evaluation process should also consider the benefit-risk assessment for that disease as a critical factor to managing the qualification process. With a better defined process, there should be more opportunities to advance therapies into development.

A disease survey early in development can establish the factors that make AA more critical to the development of a disease and provides insight on the endpoints and benefit-risk assessment for a disease. This information can be helpful in understanding the degree of flexibility appropriate for a rare disease and the relative impact of the disease relative to potential treatment. Qualification of a biomarker for accelerated approval should include the considerations from the severity and rarity of the disease being studied.

To make the qualification of a biomarker most useful and to enable early investment in the development of treatment, a Biomarker Qualification Request process should be available at the pre-IND stage for a treatment intended to treat a rare disease. For this pre-IND Biomarker Qualification Request, the sponsor should provide a briefing book containing a disease survey, the analyses of a disease/drug/biomarker set by the proposed criteria and verified using preclinical models, as well as any clinical survey/natural history data on the biomarker. The review and approval of a potential biomarker endpoint at the pre-IND stage of development before the investment in drug manufacturing and clinical studies will help support the early investment in the most rare and difficult diseases. If this can be achieved, then greater investment in developing treatments in rare diseases, especially with small populations and complex disease manifestations, will occur and new treatments will finally be developed for so many more untreated rare diseases using the AA pathway.

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