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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061, (HFA-305)
Rockville, MD, 20852

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RE: DRAFT GUIDANCE COMMENTS FOR DOCKET NO. FDA-2013-D-0575

Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics

The EveryLife Foundation for Rare Diseases is an organization dedicated to improving the science and predictability of the development of rare disease therapeutics. We have assembled a working group of patient foundations and industry to develop a consensus statement around the implementation of the Accelerated Approval (AA) provisions contained within FDASIA. One intent of FDASIA is to modify and improve the existing AA regulations for rare diseases to allow the greater accessibility of the pathway. The modifications included the use of rarity or prevalence as factors in assessing the need for AA. FDASIA also allows for a broader array of scientific information in the assessment of the predictive value of novel biomarkers and better accommodates the type of information available for biomarkers (pathophysiologic and pharmacologic data) in some rare disorders. This working group has developed a White Paper on this topic which will be published shortly (“Recommendations for the Development of Rare Disease Drugs using the Accelerated Approval Pathway and for Qualifying Biomarkers as Primary Endpoints in Pivotal Clinical Studies”). The White Paper represents the consensus of many rare disease groups and the key companies specifically working to develop orphan drugs. The comments below are primarily a focused set of responses to the proposed guidance by FDA on the most critical parts of the guidance related to Accelerated Approval on pages 14-21 of the proposed guidance.

Comments from the Rare Disease Working Group:

Overview of the response

The FDA is to be commended for assembling a useful guidance that summarizes the various expedited pathways that exist, and allows the more precise comparison of the various regulations and how they can be used in development. We are pleased that they have sought to include details regarding the basis of Fast Track designation, the new Breakthrough Therapy designation, Accelerated Approval (AA) pathway, and the Priority Review designation. This overview will be useful in clarifying what the opportunities and criteria are for these pathways both for industry but also for patient groups, foundations and academia that are increasingly

involved in the drug development process. In this regard, we consider the guidance is useful and successful.

With regard to the Accelerated Approval Section VII of the guidance, it is noted in the Federal Register announcement that FDA intends this section to fulfill fully Section 901 of FDASIA:

“Section 901(c)(1) of FDASIA requires FDA to issue draft guidance to implement amendments to the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (Enhancement of Accelerated Approval Access to New Medical Treatments) within 1 year of the date of enactment. The fast track designation, accelerated approval, and other relevant provisions of this draft guidance are intended to fulfill this requirement.”

While the guidance in this section does begin to address the details contained with FDASIA, we do not believe it adequately addresses the full extent of the law and its express intent with regard to rare diseases. We are disappointed that the Agency is reinforcing the notion in this guidance that all cases will be reviewed on a case by case basis (line 609), and that there is no scientific framework that can be developed based on the specified types of data to include in the guidance. This leaves the development pathway and the judgement of biomarkers to be unpredictable and often overweighted to types of data such as clinical outcome data, which is almost never available in rare diseases. The current situation demonstrates that this case by case process is not sufficiently clear to allow rare disease treatments to access the pathway, as demonstrated by the single approval of a specific rare disease treatment using a novel surrogate in the first 16 years of AA. FDASIA’s intent is to change this specific problem to allow all of the scientific data to contribute to the decision. The current guidance does not support this aspect of FDASIA, and would leave the current practice at FDA regarding accelerated approval in rare diseases essentially unchanged and the pathway unavailable. The sense of Congress and the intent of FDASIA section 901, is to change and improve the AA process for rare diseases, and this goal needs to be evident in the guidance.

We believe some changes would improve the guidance and are suggesting three issues for consideration:

First Issue: FDASIA asks that rarity or prevalence be considered as a factor in the Accelerated Approval pathway, but the current guidance does not address this issue

FDASIA clearly states that rare diseases must be specifically accounted for in the guidance and regulations and other than a direct quote in the beginning of the AA section on page 14, the guidance is silent on rare diseases. Specific language addressing rare disease needs to be included to be compliant with FDASIA

As correctly quoted on page 14 of the guidance, the process shall take into account in assessing the predictive value of the surrogate the “...rarity or prevalence...” of a condition as well as the lack of available therapies. Considerably more should be included on this topic, given the section below in FDASIA:

“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.”

The guidance makes no mention of rare diseases other than in the quote, nor the particular challenges in qualifying biomarker endpoints that is critical to FDASIA’s implementation.

Recommendations:

- 1) In opening Section VII: a paragraph on the particular issues for rare diseases needs to be included, that verifies the particular challenges and in general how the Agency will improve the consideration of rare diseases in accessing this pathway.
- 2) Under Section VII, A. Qualifying Criteria for Accelerated Approval, the Agency should include an additional Section 3, after Section 1, Serious Condition and Section 2, Meaningful Advantage Over Available Therapy, to address rare disease issues, and the impact of the prevalence of the disorder, the limited prior experience in clinical development, and the many particular needs regarding the nature of these diseases. Rare diseases and the prevalence of the disorder should be expressly considered per FDASIA. The following rare disease issues could be included in a section 3 in that section:
 - **Extremely high unmet medical need**
 - **Extreme rarity**
 - **Absence of prior clinical studies or formally collected clinical data**
 - **Slow disease progression with significant irreversible symptoms**
 - **Significant delay between the onset of irreversible disease and clinical diagnosis**
 - **Lack of readily measurable, recognized clinical endpoints due to unusual clinical disease manifestations**

Additional detail on these considerations is contained within the White Paper.

- 3) The basis for meeting the serious or life threatening standard, and the lack of available treatments, could be assessed more effectively and systematically by a disease survey of patients, patient groups, and expert physicians as a more systematic way to provide this information to the Agency. Our White paper proposes that a formal option exist to employ a benefit-risk survey as a useful tool in this determination and also used in the determination regarding the qualification of a biomarker endpoint. The survey may have other important impact in development. We believe this is a more practical and

effective way to get relevant patient input on benefit-risk than the 20 public meetings planned over a 5 year period. See the attached White Paper by the working group for more details.

Second Consideration: FDASIA requires that novel approaches and other types of scientific data be involved for rare diseases and currently this is not considered anywhere in the guidance

FDASIA clearly indicates that the variety of scientific data to qualify a biomarker and the approach taken in the case of rare disease should be modified. The Guidance does not address this topic adequately in Section VII, B, Accelerated Approval Endpoints.

Specifically the law reads:

“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.”

In this section there is no description how novel approaches might be used or how pathophysiologic and pharmacologic data can be used in the case of rare diseases in which other types of data cannot be practically obtained. This is a critical part of FDASIA, that derives from the Faster Access to Specialized Therapies (FAST) Act that was incorporated into FDASIA.

The section VII, C, 1, (a) and (b) on pages 17-20, do begin to outline the areas of science that can speak to the predictive value of a biomarker and does reflect the structure of recommendations contained within the White Paper. Specifically, C, 1 (a), understanding the disease process, and 1(b), understanding the relationship between the disease process and the drug's effects, are useful. However, in Section C, 1, the guidance specifically excludes the use pharmacologic criteria alone and cites the Final Rule (reference 21 therein) from 1992. The opportunity to meet the specific items of FDASIA are missed in this section with respect to the use of data and novel approaches to available data is missing.

The section also fails to describe the full breadth of data which could be useful to industry as guidance for what kind of information should be included, as well as agreement internally as to what type of data is sufficient to support qualification of a biomarker as a primary endpoint in rare disease situations as described by FDASIA. We believe this is necessary to make the guidance compliant with FDASIA.

Finally, we would like to commend FDA for taking on the issue of intermediate clinical endpoints and for appreciating their potential value in the drug evaluation process, despite the acknowledged limited experience to date. There are many clinical physiological tests used to diagnosis and treat disease that might not normally meet the criteria for a clinical endpoint, but for which the relationship to clinical outcomes in common diseases has been established. For example, sleep apnea is a condition predicted to have adverse long-term clinical outcomes demonstrated in large populations (like right heart failure and cognitive problems), but such

ultimate clinical outcomes may be difficult to measure (such as daytime sleepiness or cognition) or assess (right heart failure may take years of study) in small rare disease studies. Reducing oxygen desaturation and apnea at night, is predictive of improved clinical outcomes in major disease states, but these findings will never be proven in many tiny rare disease populations due to the lack of population size and time. Many other types of clinical physiology measurements are routinely conducted to evaluate patients and are used in their clinical management, and so should be considered as relevant measures based on the relationships established with clinical outcomes in larger population disorders, when the mechanisms between rare disease and larger population disease are similar.

We believe that intermediate clinical endpoints should be more readily accepted in accelerated approval as primary endpoints in rare disease studies, and our White Paper describes support for this decision. Similarly, changes on these clinical measures, whose magnitude may be small, but which are directionally a positive change from the normal path of decline, can be evaluated during longer term treatment in confirmatory studies to verify the magnitude of the effect and to establish clinical benefit over time. Use of intermediate clinical physiologic tests as intermediate clinical endpoints is a good step forward for rare and other diseases and we appreciate the FDA's recognition of this important category.

Recommendations:

- 1) The Agency should include an additional item under Section VII, A. for rare diseases relating to the prevalence as a factor in qualifying for accelerated approval consideration to be in compliance with FDASIA.
- 2) Under Section VII, C, 1, the evidentiary criteria for accelerated approval, and whether an endpoint is reasonably likely to predict clinical benefit, the Agency should include:
 - a) A section describing the use of pathophysiologic and pharmacologic criteria to qualify a biomarker in rare diseases in which other types of data cannot practically be collected at the time of the evaluation,
 - b) the Agency should add additional sections relating to the biomarker characterization, the nonclinical supportive data, and the use of clinical data other than drug treatment based outcomes data (which is rarely available) from registries or natural history studies in support of the qualification. These latter information would help assure that industry, foundations and academics, are looking at the value of these additional elements early in development, and that the inclusion of these data when possible can add to the qualification process. The proposed list of considerations from the White Paper are included below:

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

We recognize that not all programs can possibly collect all types of data, or some information may be irrelevant. Therefore the more expanded list is not intended to

restrict the opportunity for accelerated approval. The better the detail provided in the guidance, then the hope is to drive improved standards and approaches to rare disease development, and to capture the scientific value of the diverse sets of information that speak to the question of whether an endpoint is reasonably likely to predict clinical benefit.

Third Consideration: An improved process for earlier evaluation and feedback on biomarkers as endpoints is needed in order to enable clinical development of more rare disease drugs: the BioMarker Qualification Request

The decision on whether to initiate development of a rare disease drug occurs well before an IND is ever filed, and yet those decisions depend on the predictability and precedence around the development of a drug for a specific disease. An early process to qualify a biomarker could help ignite more interest in treating the most rare and difficult diseases with novel therapies that are currently not being developed. The current guidance does not address the issue of “when” in the development process, the qualification of a biomarker should occur. Traditionally, the review of a biomarker as a primary endpoint in a pivotal study has been occurring at the End of Phase 2 meeting. By this point, millions of dollars have been already spend on nonclinical toxicology, GMP manufacturing, and early phase clinical trials. This investment will rarely be made at the beginning in a rare disease program, unless a clear clinical development path exists for the product in that indication. This means that the board of directors and management of sponsoring companies will rarely make the decision to invest in a rare disease treatment that has complex biology or is very small in population, unless some clarity regarding the development path exists. Once a development path exists, multiple parties will often invest in development. The guidance provides no clarity on the timing of the process and we believe this needs to be addressed as one of the current barriers to more effective use of Accelerated Approval in rare diseases. The current biomarker qualification program in the Office of Translational sciences is directed to biomarkers of broad significance for multiple products and is expressly not for specialized biomarkers for rare diseases. Sponsors cannot wait until the end of phase 2 for this determination and still reliably invest in early stage rare disease programs where complex biology exists or a lack of clinical precedent endpoints makes development challenging.

Recommendation:

- 1) In order to open the door to more investment in the development of treatments for the smallest and most complex of the rare diseases, the guidance should include a new process for a specific Biomarker Qualification Request, presented in the form of a separate briefing book, in conjunction with a pre-IND meeting for a specific drug in an indication. This process could include consulting referrals to the Office of Translational Science for the review division considering the pre-IND request. This request at the pre-IND stage could be a critical step in opening the door to more rare disease drug development, especially in the smallest and clinically complex

diseases, that have little opportunity today. We recognize that this process will increase the workload for the Agency, but it is also a process that might streamline development later, and would integrate well with Breakthrough Therapy designation and other expedited processes which the Agency intends to drive forth more life-saving and life-changing therapies for patients.

Thank you for accepting our comments on this guidance. We are happy to entertain questions or comments from the Agency regarding these comments and our proposals. Contact Emil D. Kakkis MD, Ph.D. at ekakkis@everylifefoundation.org, 415.884.0223.

Cosigned by the following organizations:

American Behcet's Disease Association (ABDA), FL
Batten Disease Support & Research Association (BDSRA), FL
Children's Cardiomyopathy Foundation, NJ
Children's PKU Network, CA
CureDuchenne, CA
EveryLife Foundation for Rare Diseases, CA
Gene Spotlight Inc., FL
Gerald Cox, MD - Genzyme, MA
Global Genes | RARE Project, CA
Hannah's Hope Fund, NY
International Rett Syndrome Foundation, (IRSF) OH
Jonah's Just Begun, NY
Kortney Rose Foundation, NJ
Let Them Be Little X2 Foundation, NJ
Little Miss Hannah Foundation, NV
MLD Foundation, OR
Multiple System Atrophy Coalition, NC
National Fragile X, CA
National MPS Society, NC
National Tay-Sachs & Allied Diseases Association (NTSAD), MA
Noah's Hope, IL
Organic Acidemia Association, MI
Parent Project Muscular Dystrophy (PPMD), NJ
Phelan-McDermid Syndrome Foundation, FL
PMD Foundation (Pelizaeus-Merzbacher Disease), NJ
Ryan Foundation for Orphan Disease Research, TX
Sanfilippo Foundation for Children, TX
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Succinic Semialdehyde Dehydrogenase Deficiency (SSADH) Association, TX
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