Testimony Submitted by:

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Committee on Health, Education, Labor, and Pensions
Washington, DC 20510

Full Committee Hearing - Treating Rare and Neglected Pediatric Diseases:
Promoting the Development of New Treatments and Cures
The Honorable Tom Harkin, Chairman
The Honorable Mike Enzi, Ranking Member
The Honorable Sherrod Brown

Chairman Harkin, Ranking Member Enzi and Senator Brown:

Thank you for this opportunity to address the Committee and for your leadership in working to improve the treatment of children affected by rare diseases.

I am the Founder and President of the Kakkis EveryLife Foundation, a 501(c)(3) public charity established to improve the development of treatments for patients with rare disorders. I am board certified in both Pediatrics and Medical Genetics and spent the first years of my career working at a county hospital caring for indigent patients in Los Angeles. I have also spent the last 18 years focused on developing treatments for rare diseases working both as an Assistant
Professor at Harbor-UCLA, and as Chief Medical Officer at BioMarin Pharmaceutical Inc. At BioMarin, I developed three approved products for rare genetic disorders and started development on seven other disease treatments. Despite this success, I saw many problems and challenges in development that prevent many rare diseases from ever being treated. To resolve these problems, I founded the Kakkis EveryLife Foundation to improve the regulatory process by proposing efficient and effective science-based changes that would improve the predictability and accessibility to treatment development for many complicated rare diseases. I provide the vast majority of the funds to support our Foundation’s efforts and we do not accept financial support from industry for our initiatives.

Mr. Chairman, the Food and Drug Administration (FDA) has approved a number of treatments for ultra-rare biochemical genetic disorders and have shown significant flexibility at times. What is critical to understand is the current process is unpredictable and often driven by precedent, and for many rare diseases with new science or new treatment strategies, this challenging process does not encourage investment. This leaves many diseases with no chance for any treatment even though a rational basis for treatment exists. Based on these needs, our Foundation continues to advocate for creation of a more specialized drug review office focused on the rare biochemical and genetic disorders within the Center for Drug Evaluation Research, Office of New Drugs that would create and implement new guidances and policies to improve the regulatory process for these rarest and most difficult diseases. My testimony will provide the rational basis for this request and the greater context of how this first critical step will move rare disease treatments forward to patients.

The new rare disease review office is part of our CURETHEPROCESS campaign goals (EXHIBIT A). The campaign is now formally endorsed by 132 unique patient organizations and physician societies. We are currently working to:

1. Establish a new specialized Division/Office of Drug Evaluation for Genetic and Biochemical Diseases
2. Improve the accessibility of the Accelerated Approval process by developing new criteria for surrogate and biomarker endpoints used to evaluate treatments for rare disorders
3. Create efficient clinical study design and analysis paradigms for rare disease clinical studies

By making these three cost-effective and practical changes, we can quickly and dramatically improve the current regulatory process for rare diseases without having to reinvent an entirely new process or a new approval pathway.

Why do we need change? Despite the successes in the first 25 years of the Orphan Drug Act, (1,892 orphan designations and 326 treatments approved¹), 95% of rare disorders remain without a specific treatment approved by the FDA. Treatments for many of these diseases may never be developed because the complexities of the regulatory environment make it difficult to attract investment for some very rare or difficult diseases, even though the science may be available.

EXHIBIT B demonstrates that orphan designations are increasing while approvals are flat over time. The approvals for ultra rare disorders (arbitrarily defined as those affecting less than 6,000 patients) show that only two or three are approved each year despite the fact that more than 80% of all rare diseases are in this ultra rare category². Although there is an expected lag between when a drug gets Orphan designation, and when it gets approved, the expected time gap is approximately five years and thus cannot explain the current slow rate of approvals.

To understand how current science is only generating two or three ultra-rare disease approvals each year, we evaluated the science to look for where the block to development might exist. Our analyses of the scientific literature found approximately 25 rare diseases for which good science exists for a treatment but for which efforts to translate this science to patients is either slow or nonexistent. Some of these diseases are very rare, or they may have more difficult biology such as bone or brain disease, but they could be treated. A commissioned research report on ultra-rare diseases recently showed that although many companies get Orphan


² BioMedical Insights report, “Ultra-Rare Disease Drug Development Trends”, June 10, 2010, commissioned by the Kakkis EveryLife Foundation; Data based on information contained in the Orphanet database and other sources.
designations, those that achieve approval for ultra-rare disease treatments have a median of $500 million in cash, and more than $1 billion in asset value. These data show that only very well capitalized companies can traverse the regulatory process and for rare diseases, and that is a small list of companies. We must do more with the science we already have and turn the billions of dollars of promising research into life saving treatments. To do this, the process needs to be tractable and approachable by small biotechnology and researchers with great ideas.

While these data may define the statistics that describe the breadth and depth of the problem, the pain and tragedy of the problem is better captured by my personal experiences with rare disease. Nearly every week for the last few years, I have received calls and counseled families struck by genetic lightning, their small child affected by a devastating, unpronounceable biochemical or genetic disease. These parents are seeking hope and inspiration that somehow their newly established foundation can manage to navigate the inner workings of drug development in order to save their kids, because no one else seems to be investing in those treatments. I do my best to help and support their efforts, but I hope that Congress can do much more to change their tragedy into opportunity for all Americans affected by rare diseases.

To understand the challenges facing rare disease drug development, I would like to review the case of the enzyme replacement treatment Aldurazyme® (laronidase) used to treat the ultra-rare disorder mucopolysaccharidosis type-1 (MPS I) which affects 1 patient per 100,000 births or about 200 or so patients in the U.S. MPS I is caused by the body's inability to produce a specific enzyme required for the breakdown of specific sugar-like compounds. The deficiency causes the accumulation of these sugar-like materials in virtually every cell of the body. As a result, cells and tissues do not function properly and progressive damage accumulates throughout the body, including the heart, bones, joints, respiratory system and central nervous system. The disease is usually fatal by the first or second decade. From the development experiences of Aldurazyme, I will extract some of the key lessons that apply to many rare disease treatments and why these experiences form the basis for the CURE THE PROCESS campaign.

The Aldurazyme project began in 1991 when I started my work in a World War II-era research bungalow at Harbor-UCLA with minimal funding to develop an enzyme replacement therapy.
My work received critical financial support from the Ryan Foundation, formed by Mark and Jeanne Dant for their son Ryan, who has MPS 1\(^3\). I completed development of the treatment at a startup biotech company, BioMarin. Our work was ultimately successful, leading to the approval of the enzyme treatment called Aldurazyme and I am proud to report that Ryan is now a healthy 22-year-old young adult working for the Texas Rangers and going to college part-time. He has been on Aldurazyme for 13 years. The challenges encountered during this program are instructive.

**EXHIBIT C** outlines the major challenges that affected this program, and almost every development program for a rare disease.

First, we were unable to use a reasonable biomarker based on the best science available to measure the improvement in our patients because there was no other independent clinical data to support its use. (Biomarkers or surrogate endpoints can be a test of a person’s blood or urine like a cholesterol level that measures an effect of the disease on body chemistry or function but not a clinical outcome like a heart attack. Subpart H created the Accelerated Approval process for life threatening diseases to allow the approval of treatments based on a biomarker test of the disease that is “reasonably likely to predict clinical benefit.”) For rare diseases that have never been studied before, there is almost never prior clinical data to help prove the usefulness of the biomarker. Since there is no defined policy, guideline or qualification criteria for biomarkers, anyone attempting to develop a drug that requires a blood or urine test for an ultra-rare disease, would have an uncertain path ahead of them. Without some prior independent clinical data, it is highly unlikely to get a product approved on a new biomarker. When the basic science of the biomarker or surrogate is reasonable, we should be able to use this measure to seek approval via the Accelerated Approval pathway when independent clinical data are lacking. A written set of reasonable qualification criteria for what it means to “reasonably predict clinical benefit” would help drive better science ahead of the clinical work, and then would also create real access to the Accelerated Approval pathway for rare diseases without prior clinical experience.

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\(^3\) Recounted by Margery Stein, “Saving Ryan”, Reader’s Digest, May 2001, p75
Today, there is no guidance on what can be qualified as a reasonable surrogate endpoint to meet Accelerated Approval requirements meaning that no rare disease treatments can reasonably expect to be approved via this pathway.

Second, we ran into problems with our statistical analyses because we were not allowed to use the more powerful methods that would help rare disease studies overcome the variable nature of the patients. The slight miss on one endpoint with the weaker statistical method, led to a requirement to collect additional clinical data, again delaying the program. For rare diseases, some understanding and agreement is needed to allow the very best and most powerful approaches to be used to help compensate for the small study sizes and variable patients. If these most efficient and powerful approaches are not allowed to control variation and extract the most information from the data, many rare disease studies will fail to achieve significance, even when the drugs are effective.

Currently, there is no guidance on the acceptable or optimal design and analyses for rare diseases.

Finally, it is very clear to me after 11 years at BioMarin that the FDA is under increasing duress with limited resources for drug reviews, and is unable to provide the optimal level of time and staff required for complicated rare disorders. While the Prescription Drug User Fee Act (PDUFA) has generated revenue for the Agency, these fees now make up 67% of all drug review costs and base Agency funding for drug reviews has been flat for many years. With approximately one-in-three recently approved products having Orphan status, and given that PDUFA fees are waived for rare disease (Orphan) drugs, the review of these products is being conducted on an ever-decreasing budget. Given these financial strains, the Agency has been unable to support the sufficient degree of specialization of their review divisions that would allow them to hire sufficient numbers of specialists trained in the rare disease areas and to allow these specialists to remain dedicated to rare disease specialties. Reviewing drugs is an extraordinarily difficult challenge and the FDA needs to have the resources to be able to hire enough people with the right training and experience to accomplish this difficult task.
Aldurazyme was eventually approved and so this might not seem so important. However, the problems encountered during Aldurazyme development led to the canceling of programs for two other rare diseases, MPS IV A and MPS VII due to financial concerns and the inability to use the Accelerated Approval pathway. These diseases still do not have treatments approved. Currently, most rare biochemical and genetic diseases cannot use the Accelerated Approval pathway because they are so rare that they lack the historical clinical data that is required to qualify surrogate endpoints, even though their scientific basis is strong. To see the breadth of this problem, we summarized the data in the table posted on FDA’s web site regarding Accelerated Approvals since implementation in 1992.

In EXHIBIT D, only one genetic disease has been approved via this pathway in 16 years. (This particular approval did not have FDA agreement on the surrogate until after an Advisory Committee recommended its acceptance after all the studies were done.) While other genetic diseases have been approved on biomarker endpoints such as for urea cycle defects or phenylketonuria, these approvals have been based on the existence of prior approvals from the distant past or the existence of substantial other clinical data. These examples do not eliminate the fact that treatments for diseases from new areas, with no other clinical data or prior approvals in that disease class, cannot readily access the Accelerated Approval pathway. Furthermore, there is no way to predict what work could be done to verify the “reasonable likely to predict” standard established by the law.

Scientists, patients, Congress and regulatory authorities need to come to agreement quickly as to what science should be sufficient to allow access to the Accelerated Approval pathway and it must take into account the effect that rarity has on both the amount of clinical data that exists, as well as on the risk-benefit to society of the use of the surrogate endpoint. To achieve these changes in policy, we believe it is essential that a specialized review office or division be established to lead the way in guidance formation and policy based on the joint work of experienced FDA reviewers and disease experts.

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4 Taken from the FDA web site and collated by disease category. Genetic treatments include only those drugs specifically targeted to an individual genetic disease. For example, iron-binding treatments were not considered genetic disease specific.
A dedicated FDA review division will improve the development path. A new review division for biochemical and genetic diseases will help create a more specialized drug review by experts who understand complex genetic diseases (see EXHIBIT E). The new division/office should be structured to allow the reviewers to focus and gain experience on specific rare disease areas that need increased expertise. Reviewers may also provide assistance, as needed, to other review offices with rare disease issues. By helping to facilitate collaboration with the Office of Orphan Product Development and links with the National Institutes of Health, the division/office will improve the overall academic environment and assure that the reviewers are keeping up with the latest scientific issues and advances. This division/office will also be essential to help implement the policy changes recommended by the Brownback/Brown Amendment\(^5\) committee’s findings and assure that the excellent work of Drs. Timothy Cote, Elizabeth McNeil and other FDA staff will not be lost.

The current FDA Office of New Drugs is already in part organized by specialized offices and divisions. Therefore creating a new division or office (a group of divisions) will not negatively change the structure of the FDA nor create any “silos” preventing organizational learning (as some have inferred). In some cases, the degree of specialization is driven more by caseload rather than science. For example; inborn errors of metabolism are reviewed currently in the Division of Gastroenterology and Inborn Errors of Metabolism, a combination of two disparate disease areas. A separate office with specialized review divisions would allow the reviewers to leverage the experience, and recruit to specific positions required for these rare disorders. These divisions could readily become consultative divisions for other groups at FDA. The current Associate Director of Rare Diseases will be an important advocate in the process; however this position does not have final review or decision-making power over the approval and cannot substitute for improved specialization in the review divisions. In order to fully understand the treatment effects of a product, it is essential that reviewers who are responsible for approving the drugs be allowed to focus on specific rare diseases and leverage experience. This is especially important in those diseases affecting children where pediatric specialists bring more specific and relevant experience and training.

\(^5\) Brownback Brown Amendment for Rare and Neglected Diseases in the FY 2010 FDA Appropriations Budget, H.R. 2997, Section 740
We also recommend that this new review division, working with the new Associate Director of Rare Diseases, be responsible for rapidly creating new guidances for industry that could make the Accelerated Approval pathway available for more rare diseases and improve the clinical trial process. Among many possible recommendations from the FDA committee, we believe that two guidances should be included:

- **New standards for the use of surrogate and biomarker endpoints for rare disorders,** to allow treatments for these diseases to have full access to the Accelerated Approval pathway.
- **New clinical study design and analysis paradigms for rare diseases that properly account for clinical heterogeneity and disease complexity to accurately and efficiently establish treatment effects.** We at the Foundation are working on creating the data to support this guidance this year.

**Conclusion:**

**An improved development path for rare diseases is good for patients and the economy.**

- **New treatments.** A streamlined development path will shorten timelines and reduce the financial risk associated with development of rare disease therapeutics. The result should be a surge in development activity for even the rarest disorders. Certain treatments for rare biochemical or genetic disorders that are now unaddressed because of the difficulty in assessing the clinical outcome, will now be targets of drug development as appropriate surrogate markers are identified. More patients with rare biochemical and genetic disorders will get earlier access to specific, effective treatments.

- **Improved FDA.** A new division or office with experts trained and knowledgeable in the disease area will allow for an improved and more specialized FDA review. Allowing the reviewers to stay focused and gain experience, will allow them to become more expert in the details and nuances of science and medicine of their specialized areas that is required for excellent regulation.

- **New jobs.** Improved FDA regulation will drive more U.S. biotechnology job creation. The creation of the new division will provide a strong signal to the biotechnology
industry and investors that the FDA is working to improve the regulatory path for thousands of rare disorders. This new review division, combined with new policy, will drive more investment in early stage biotechnology companies focused on rare diseases while at the same time producing a positive impact in local communities by creating new, high-paid, U.S.-based biotechnology jobs. Our estimate is that each new rare disease product will likely create 300-600 direct new jobs\textsuperscript{6} in biotechnology and about five times that many in the greater economy.

**Small regulatory changes can make a huge impact.** In the early 1990’s the FDA was uncertain about blood markers predictive value for HIV/AIDS treatments. The need for clinical endpoints would require substantially more time and cost for clinical studies, which would have impaired investment and innovation, and lead to many deaths. Activists spurred the FDA to create “Subpart H-Accelerated Approval of New Drugs for Serious or Life-Threatening Diseases” in 1992. This allowed the FDA to accept a surrogate endpoint for a measurement of the treatment effect if the surrogate was “reasonably likely to predict clinical benefit”. At the time T-Cell counts were qualified as surrogate endpoints based on sound scientific data that the T-Cell count directly correlated to how sick the patient was. Over time, better science improved the marker choice for HIV infection to *viral load*, but the explosion in innovation was remarkable.

As you can see in **EXHIBIT F**, over the following 16 years, 29 new drugs were approved that used six different mechanism of action, devised by multiple startup companies generating approximately 78,500 new jobs\textsuperscript{7}. Four of those drugs were complex multi-drug combinations that would never be developed without an efficient marker endpoint like *viral load*. There was great uncertainty as to whether these markers were “right”, but without taking that reasonable chance, HIV would not have become a chronic managed disease for many patients rather than the death sentence it was in 1992.

\textsuperscript{6} BioMedical Insights report “Ultra-rare Therapeutic Employment Analysis” commissioned by Kakks EveryLife Foundation, June 15, 2010

\textsuperscript{7}
The changes we are proposing can do the same thing for rare diseases as Accelerated Approval did for HIV. By our Foundation’s analyses of relevant clinical development costs, access to the Accelerated Approval process could potentially treat three to four fold more diseases for the same investment. We estimate that a billion dollars spent on clinical development costs using the current pathway would cover only 10-12 products; with access to Accelerated Approval you could develop nearly 40 products for the same investment.

Mr. Chairman, thank you for your time. I commend your efforts to convene this hearing and your leadership to improve the development process for rare pediatric disease treatments. Given the considerable impact an improved regulatory process would have on the economy and the millions of patients without treatment, we hope that you will join the 132 patient and physician organizations and support our request to establish a new Division/Office of Drug Evaluation for Genetic and Biochemical Diseases.
**EXHIBIT A**

**IMPROVING THE REGULATORY PATHWAY:**

**THE CURE THE PROCESS CAMPAIGN**

1. **E**stablish a **N**ew **D**ivision/Office of **D**rug **E**valuation **F**or **G**enetic & **B**iochemical **D**iseases

2. **I**mprove the **A**ccessibility of the **A**ccelerated **A**pproval **P**athway (SUBPART H)

3. **D**evise **N**ew **C**linical **S**tudy **D**esign & **A**nalysis **P**aradigms for **R**are **D**iseases

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**EXHIBIT B**

**Approvals rate flat relative to designations**

Both for drugs treating all Orphan and ultra-rare diseases

![Graphs showing Orphan Designations and Approvals vs. Ultra-Rare Designations and Approvals](image)
**EXHIBIT C**

**CHALLENGES IN RARE DISEASE DRUG DEVELOPMENT**

*Aldurazyme™ eventually approved after a 3 year delay*

- **Surrogate endpoint rejected**
- **Delayed again after Phase 3, related to statistics**
- **Advisory Committee voted drug effective 12-0 on 1/15/2003**

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**EXHIBIT D**

**FEW DISEASE CATEGORIES BENEFIT FROM ACCELERATED APPROVAL REGULATIONS**

*Usage of the Subpart H or E approvals: 64 NDA’s and 9 BLA’s since 1992*  
**ONLY 1 GENETIC DISEASE TREATMENT APPROVED IN 16 YEARS**

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Number of Accelerated Approvals</th>
<th>Surrogate Endpoint</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>26</td>
<td>Tumor load/PFS</td>
<td>Most pivotal studies without a control group</td>
</tr>
<tr>
<td>HIV</td>
<td>29</td>
<td>CD4 or viral load</td>
<td>Combination therapies also approved</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>Variety</td>
<td>PAH, MS, hormones, iron, Crohn’s, antibiotics</td>
</tr>
<tr>
<td>Genetic</td>
<td>1</td>
<td>Renal pathology</td>
<td>Fabrazyme</td>
</tr>
</tbody>
</table>

*Taken from the FDA.gov website table on accelerated approvals*
EXHIBIT E

Improving the Review of Treatments for Rare Diseases

- Food & Drug Administration
  Office of the Commissioner

- Center for Drug Evaluation (CDER)

- Office of New Drugs

- Office of Drug Evaluation

- Biochemical & Genetic Diseases

New Division of Biochemical & Genetic Diseases
- Improved specialization & expertise
- Focused drug review workload
- FDA reviewers with joint NIH appointments
- Increased academic responsibility
- Renewed priority to develop guidances

REGULATORY COLLABORATION

NIH
National Institutes of Health

NEW DRUG REVIEW DIVISION

EXHIBIT F

RAPID INNOVATION IS POSSIBLE

ACCELERATED APPROVAL HISTORY OF HIV DRUGS

29 NEW DRUGS

29 Drugs in 16 Years
All Accelerated Approvals


Accelerated Approval Regulations Implemented
Emil Kakkis, M.D., Ph.D.

Kakkis EveryLife Foundation, President

“No disease is too rare to deserve treatment”

Dr. Kakkis is best known for his work over the last 18 years to develop novel treatments for neglected rare disorders. He began his work in a research bungalow at Harbor-UCLA working with minimal funding and support to develop an enzyme replacement therapy (Aldurazyme®) for the rare disorder MPS I. The struggle to get the therapy translated from a successful canine model to patients succeeded due to the critical financial support of a new patient organization formed by Mark and Jeanne Dant for their son Ryan, called the Ryan Foundation.

Kakkis’ collaboration with the Ryan Foundation in the early development of Aldurazyme was highlighted in a 60 Minutes II segment aired in April 2001 (“Saving Ryan”), and Reader's Digest article in May 2001. Aldurazyme development was later supported by BioMarin™ and eventually their partner Genzyme™ leading to FDA approval in 2003.

During his tenure at BioMarin, Dr. Kakkis guided the development and approval of two more treatments for rare disorders, MPS VI and PKU and has contributed to the initiation of 7 other treatment programs for rare disorders, three of which are now in clinical development. Dr. Kakkis left his position as Chief Medical Officer of BioMarin in 2009 to pursue changes in the drug development and regulatory system. His focus is now on improving the diagnosis and treatment of rare disorders, specifically the process by which treatments for rare disorders are tested and approved.

Dr. Kakkis graduated from Pomona College, magna cum laude and received the Vaile Prize in Biology for his thesis research in 1982. He received a combined MD and PhD degrees from the UCLA Medical Scientist Program in 1989 and received the Bogen prize for his research on c-
myc oncogene regulation. He completed a Pediatrics residency at Harbor- UCLA Medical Center in Torrance, CA and completed his fellowship training there in the UCLA Intercampus Medical Genetics Training Program in 1993. He became an assistant professor of Pediatrics at Harbor-UCLA Medical Center from 1993-1998 where he initiated the enzyme therapy program for MPS I. He is board certified in both Pediatrics and Medical Genetics. He joined BioMarin in 1998 and held various positions including Chief Medical Officer from 2006 to 2009. He received the Lifetime Achievement Award from the National MPS Society for his work on Aldurazyme. He has authored numerous scientific articles on MPS I, immune tolerance during enzyme therapy, intrathecal enzyme therapy and studies on treatments for MPS VI and PKU.