KAKKIS EVERYLIFE FOUNDATION
No Disease is Too Rare to Deserve Treatment

Testimony Submitted by:

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Submitted June 23, 2010 to the United States Senate Subcommittee on
Agriculture, Rural Development, Food and Drug Administration, and Related Agencies
Committee on Appropriations
United States Senate
Washington, DC 20510
The Honorable Herb Kohl, Chairman
The Honorable Sam Brownback, Ranking Member

Chairman Kohl and Ranking Member Brownback:

Thank you for this opportunity to address the Subcommittee today and for your leadership in working to improve the treatment of patients 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 have spent the last 18 years focused on developing treatments for rare diseases working both as an Assistant Professor at UCLA, and as Chief Medical Officer at BioMarin. At BioMarin, I developed three approved products for rare genetic disorders, and 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 of many complicated rare diseases to treatment development. 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, I am here today to support an additional funding appropriation to the Food and Drug Administration (FDA) to create a more specialized drug review division focused on the rare biochemical and genetic disorders. We respectfully request an incremental **$10 million in the fiscal year 2011 Ag-Rural Development-FDA Appropriations bill for the FDA to establish a new review division for Biochemical and Genetic Diseases within the Center for Drug Evaluation Research, Office of New Drugs.**

This is the first step toward the larger goal of improving the rare disease drug development process. My testimony today 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 division or office is one core part of our three CURETHEPROCESS campaign goals (**EXHIBIT A**). The campaign is now formally endorsed by 128 unique patient organizations and physician societies. Our three goals are:

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

By making these three 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? There are more than 7,000 rare disorders that together affect over 25 million Americans and their families. The Orphan Drug Act (enacted in 1983) encourages pharmaceutical companies to develop drugs for diseases that have relatively small patient populations and has been very successful. Despite the success in the first 25 years with 1,892

orphan designations and 326 treatments approved[1], 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.

In **EXHIBIT B**, 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 category[2].

To understand how current science is only generating 2 or 3 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 little effort has occurred to translate this to patients. Some of these diseases are very rare, or they may have more difficult biology, but they could be treated. We must do more with the science we already have and turn the billions of dollars of promising research into life saving treatments.

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

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[1] Braun MM, Farag-El-Massah S, Xu K, Coté TR., 2010, Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years. Nat Rev Drug Discov. 2010 Jun 7. [Epub ahead of print].

[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.

help and support their efforts, but today I hope that we 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). 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. Only about 200 patients in the United States have MPS I and treated with Aldurazyme today. 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 CURETHEPROCESS 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 I[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.

Despite the ultimate success of Aldurazyme, our work on this enzyme highlights the difficulties encountered in development that our CURETHEPROCESS campaign aims to improve. There are only about 200 or so patients in the U.S. on Aldurazyme today, and this ultra-rare disease had never been considered for treatment prior to our efforts beginning in 1991. **EXHIBIT C** outlines

[3] Recounted by Margery Stein, "Saving Ryan", Reader's Digest, May 2001, p75

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. For rare diseases that have never been studied before, no prior clinical data exist. Somehow, we should still be able to use a biomarker and the Accelerated Approval pathway when the science is reasonable as it was in this case. The inability to use a reasonable marker that we believed (and still believe) "reasonably predicted clinical benefit", resulted in a substantial delay of the program. *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 in which 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 in order to best control of variation and extract the most information from the data, most 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, and with three drugs approved for three different rare genetic disorders, 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. The Agency has been unable to support the sufficient degree of specialization of their review divisions that would allow them to hire specialists trained in the rare disease areas that are currently not well covered. Aldurazyme was reviewed by a neurologist, an oncologist and a pulmonologist, with no experience in MPS or biochemical

genetic disorders. While they were intelligent and capable physicians, there is no adequate substitute for training and experience in the specific field of medicine. 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, 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[4]. 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.

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 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 division be established to lead the way in guidance formation and policy based on the joint work of experienced FDA reviewers and disease experts.

A dedicated FDA review division will improve the development path. Providing funding for a new review division for biochemical and genetic diseases will help create a more specialized

[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.
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ucm121597.htm

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. Cote', McNeil and other FDA staff will not be lost.

We recommend that this new review division 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.** Due to the rarity of the disorders, the use of direct, relevant surrogate or biomarker endpoints as primary endpoints in clinical studies is essentially impossible for some rare disorders because none of these surrogates have been validated or ever evaluated in clinical studies and are therefore unavailable for development use. However, biochemical markers relevant to biochemical genetic disorders may be far better predictors of disease and treatment effect than many of the approvable surrogate markers currently accepted for use in drug approvals for more common disorders[6].

[5] Brownback Brown Amendment for Rare and Neglected Diseases in the FY 2010 FDA Appropriations Budget, H.R. 2997, Section 740

[6] Patricia Dickson, Maryn Peinovich, Michael McEntee, Thomas Lester, Steven Le, Aimee Krieger, Hayden Manuel, Catherine Jabagat, Merry Passage, and Emil D. Kakkis Immune tolerance improves the efficacy of enzyme replacement therapy in canine mucopolysaccharidosis I (2008), J. Clin. Invest. 118: 2868.

- **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.** While traditional randomized, controlled studies have been used in rare diseases, this design is relatively insensitive to changes in heterogeneous patients and fails to allow the assessment of all types of patients with all types of disease outcomes. A creative effort is needed to develop new paradigms in study design and optimal statistical analyses that capture individual benefit in a broad array of patients, utilizing all the clinical data to establish efficacy. The medical science needs to drive the statistical analysis.

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 also 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[7] 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 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 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[7]. Four of those drugs were complex combinations that would never be developed without an efficient marker endpoint like *viral load*. More importantly, HIV went from a certain death sentence to a managed disease for many patients.

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.

[7] BioMedical Insights report "Ultra-rare Therapeutic Employment Analysis" commissioned by Kakkis EveryLife Foundation, June 15, 2010

Mr. Chairman, thank you for your time. I commend your efforts to convene this hearing and your leadership to improve the FDA's review process for products to treat rare diseases. . 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 128 patient and physician organizations and support our request to **appropriate $10 Million to establish a new Division/Office of Drug Evaluation for Genetic and Biochemical Diseases** and start us down the path to an improved development process for rare disease treatments.

EXHIBIT A

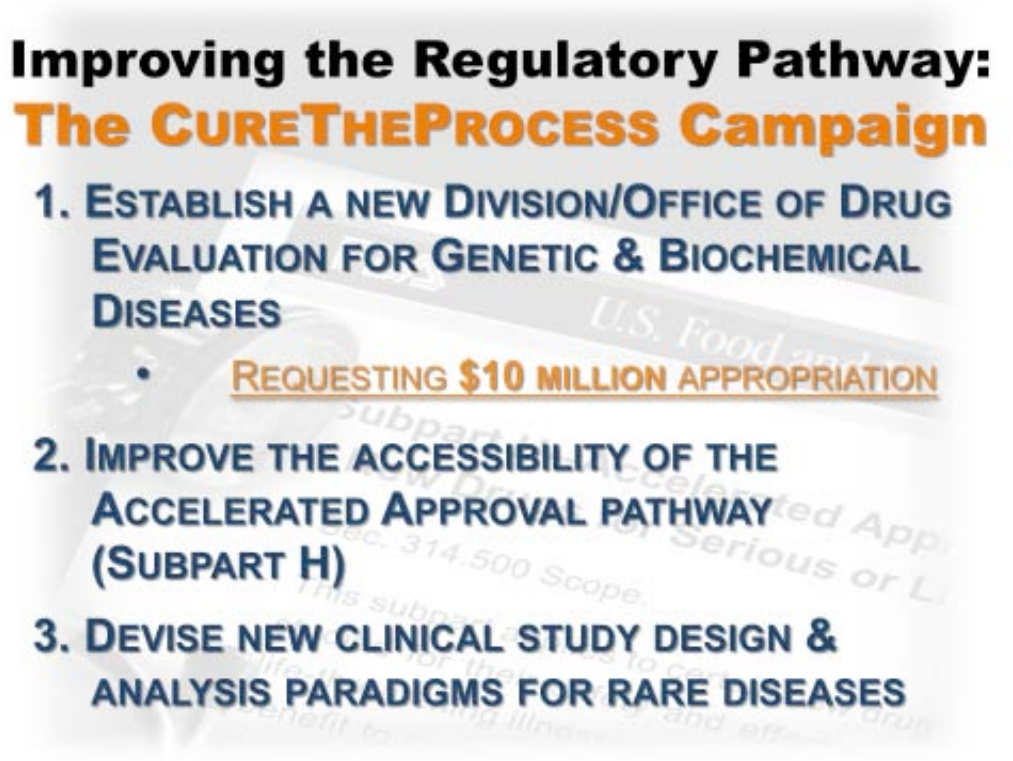


EXHIBIT B

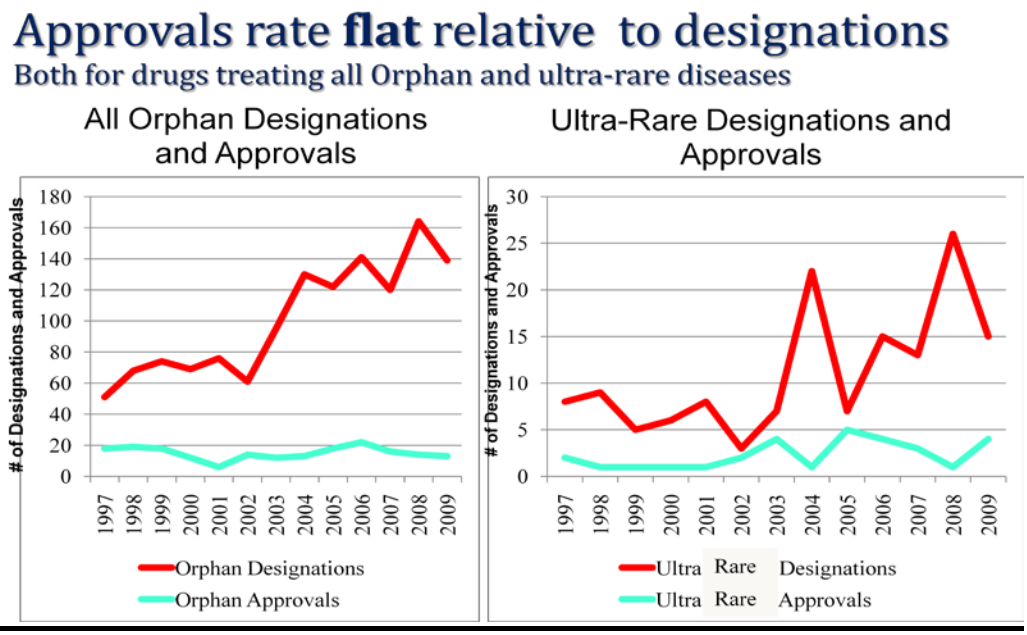


EXHIBIT C

Aldurazyme eventually approved after a 3 year delay

- Urine GAG surrogate endpoint rejected
- Delayed again after Phase 3 related to statistics
- Advisory Committee voted drug effective 12-0 on 1/15/2003
- Approved in April 2003

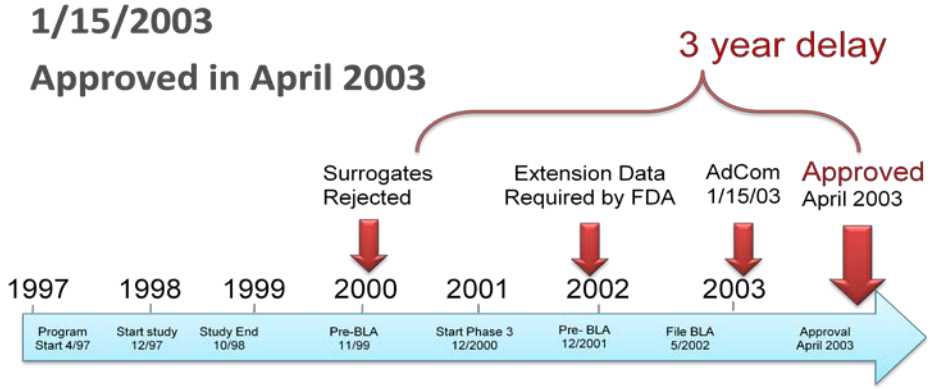


EXHIBIT D

Few diseases 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

Therapeutic Area	Number of Accelerated Approvals	Surrogate endpoint	Other
Cancer	26	Tumor load/PFS	Most pivotal studies without a control group
HIV	29	CD4 or viral load	Combination therapies also approved
Other	17	Variety	PAH, MS, hormones, iron, Crohn's, antibiotics
Genetic	1	Renal pathology	Fabrazyme

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

EXHIBIT E

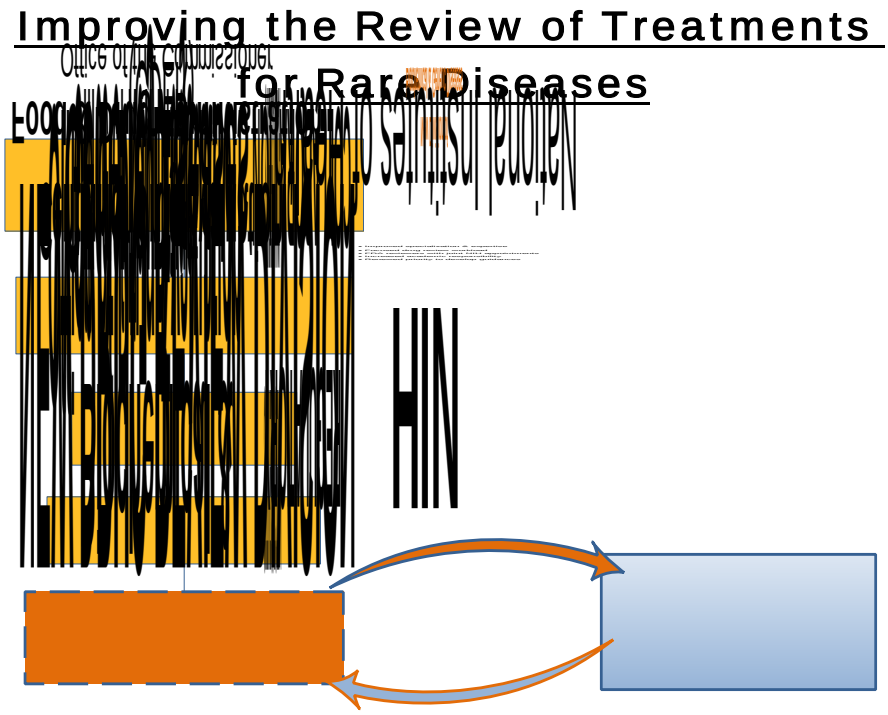
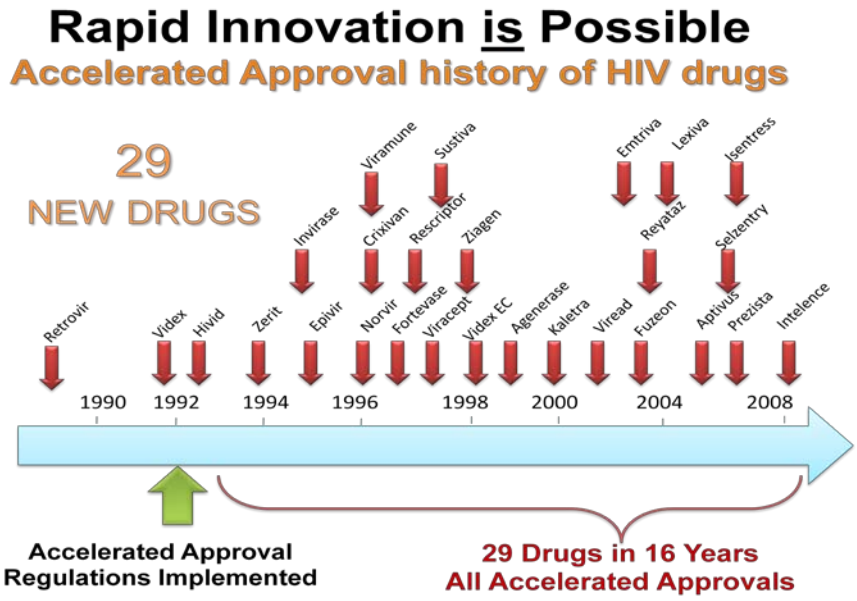


EXHIBIT F



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