



June 13, 2014

Chairman Fred Upton
Representative Diana DeGette
US House of Representatives
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Upton & Representative DeGette,

The EveryLife Foundation for Rare Diseases applauds the launch of the **21st Century Cures Initiative** and your commitment to the millions of patients in need of lifesaving treatment. We respectfully submit the below recommendations in response to your request for comments on your white papers to spur the development of lifesaving therapies.

It is estimated that there are nearly 7000 rare diseases affecting more than 30 million Americans. While the science exists to treat many of these diseases, there are currently less than 400 treatments approved by the Food and Drug Administration for rare diseases. This is concerning not only for rare disease patients but for all patients with life-threatening illnesses. The science learned from treating rare diseases will likely lead to treatments and cures of more common diseases like Alzheimer's. Additionally, the challenge faced in developing rare diseases therapies will mirror the regulatory and development challenges for personalized medicine.

It is devastating when a parent learns that there is no treatment available for their dying child. The pediatrician sends them home with no hope, to watch their once healthy child lose the ability to see, walk, talk and eventually risk suffocation on their own saliva. This is torture for both the child and the family. This situation is even more tragic when a potential treatment is sitting on the shelf of a university lab or biotech company, but the cost and complexities of development has slowed or even prevented the treatment from ever being developed. Successful scientific advances made in recent years are currently inaccessible to thousands of patients with rare diseases, and they may never be available without improvements to the drug development process.

No Disease is Too Rare to Deserve Treatment

The EveryLife Foundation for Rare Diseases, a 501(c)(3) health advocacy organization was founded five years ago to address these challenges in the drug development and regulatory process. Our mission is to spur biotech innovation for rare disease treatments through science driven public policy. We are guided by the following three principles:

- No disease is too rare to deserve treatment
- All new drugs for rare diseases should be safe and effective
- We could be doing more with the science we already have

Additionally, we believe that small science-based policy fixes to the development and regulatory current process could have a huge impact in unlocking lifesaving treatments for patients. The Foundation has been leading the efforts on a number of policy changes that we will present below that have the biggest potential for the rare disease community. However, we offer just a few pieces of the puzzle; there are many other solutions needed to complete the drug development puzzle. We do feel however, that the best way to proceed is through smart & moderate change and that any radical overhaul of the system could have unintended effects.

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. However, the requirement for studies to meet clinical endpoints would require substantially more time and cost for clinical studies and 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. There was still uncertainty, but the acceptance of the T-Cell count opened the door to innovation both on the drugs to treat HIV and the biomarkers to assess the disease.

Over time, better science improved the biomarker choice to *viral load* although both biomarkers are useful, but the explosion in innovation was remarkable. As you can see in **Exhibit A**, over the following 16 years, 29 new drugs were approved that used six different mechanisms of action, devised by multiple startup companies generating approximately 78,500 new jobs¹. Four of those drugs were complex combinations that would never be developed without an efficient biomarker endpoint like *viral load*. More importantly, the FDA's small policy change of allowing the use of surrogate endpoints instead of a clinical endpoint changed HIV from a certain death sentence to a managed disease for many patients.

¹ BioMedical Insights report "Ultra-rare Therapeutic Employment Analysis" commissioned by EveryLife Foundation, June 15, 2010

RECOMMENDATIONS:

Below we present six policy solutions we believe will have the biggest impact on rare disease drug development; some of these are also recommended in the 2012 President's Council of Advisors on Science and Technology Report on Propelling Innovation in Drug Discovery, Development, and Evaluation.

- 1) Improve the accessibility of the Accelerated Approval pathway by encouraging the FDA to allow new predictable scientific criteria for surrogate and biomarker endpoints used to evaluate treatments for rare disorders, consistent with FDASIA.
- 2) Facilitate the development of efficient clinical study design and analysis paradigms for rare disease clinical studies and encourage the FDA to allow these alternative clinical study designs and analyses.
- 3) Improve the specialization of the FDA drug review divisions by encouraging the recruitment of more specialist trained reviewers, allowing these reviewers to become specialized in the diseases they are reviewing, and have opportunities to keep up on the latest science.
- 4) Encourage the FDA to accommodate a more scientifically rational and flexible application of safety data regarding the initiation of clinical studies in life-threatening diseases as is practiced some regulatory authorities in the Europe.
- 5) Protect current and seek additional incentives for industry to ensure lifesaving medicines for rare diseases are economically viable to develop, while maintaining the Orphan Drug Act in its current form.
- 6) Ensure there is adequate funding for both the Food and Drug Administration and the National Institutes of Health.

Access to the Accelerated Approval Pathway:

Despite the success of Accelerated Approval in bringing about new treatments for AIDS and cancer patients, there remain very few approved treatments for rare diseases via the Accelerated Approval pathway even with the significant unmet need. The small number of patients with a particular rare disease make it virtually impossible under the current FDA requirements to qualify novel surrogate endpoints, since clinical data are required and no prior studies have ever been conducted. The absence of prior clinical data prevents rare disease treatments from using the Accelerated Approval pathway.

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The EveryLife Foundation report “The potential investment impact of improved access to accelerated approval on the development of treatments for low prevalence rare diseases” published in the Orphanet Journal of Rare Diseases in July 2011, showed the use of the Accelerated Approval pathway could lead to a decrease in cost to approval of 62%. Meaning with the same biotechnology company investment, three times as many rare disease drugs could be developed with Accelerated Approval than with traditional approval.

In 2012 the Foundation worked to ensure language was included in the Food and Drug Administration Safety and Innovation Act (FDASIA) [P.L. 112-144] to improve access to Accelerated Approval by empowering the FDA to use the best science available. Since prior historical clinical data does not and will likely never exist for these very rare diseases, FDASIA directed the FDA to issue a guidance that allows for achievable scientific criteria to qualify surrogate endpoints for rare diseases to use in clinical trials. The PCAST report echoes this in Recommendation #3 encouraging the FDA to “expand the scope of acceptable endpoints used to approve drugs for serious or life-threatening diseases with unmet needs” and to issue clear guidance on Accelerated Approval.

In June 2013, FDA issued a draft guidance for Industry on Expedited Programs for Serious Conditions-Drugs and Biologics to fulfill the Section 901 FDASIA mandate. The draft guidance failed to address the specific issues with rare disease drug development as clearly required by FDASIA. In October of 2013, 109 Members of Congress sent a letter to FDA asking them to revise the draft guidance to fulfill the intent of FDASIA and give rare disease access to Accelerated Approval.

During this time, the Foundation worked with industry and patient organization stakeholders to develop a white paper on “Recommendations for the Development of Rare Disease Drugs using the Accelerated Approval Pathway and for Qualifying Biomarkers as Primary Endpoints in Pivotal Clinical Studies” which the FDA could have used in developing their final guidance.

Just last week FDA issued the final Expedited Programs guidance, which was substantially improved from the draft released in 2013. However, the guidance still falls slightly short of providing a clear scientific framework on how rare diseases could use the Accelerated Approval pathway. While FDA reports more than 80 products have been approved via Accelerated Approval, in fact, only one rare disease has been approved via accelerated approval using a novel biomarker endpoint.

We urge Congress to ensure that FDA fulfills the FDASIA requirements and provides clear guidance on allowing access to Accelerated Approval for rare disease treatments.

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Alternative Clinical Study Designs

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. Variable and complex diseases often cannot be studied effectively with current trial designs and often make the effects of treatment hard to demonstrate. *Currently, there is no guidance on the acceptable or optimal design and analyses for rare diseases and FDA has been conservative in its approach to novel models.* For rare diseases, some understanding and agreement is needed to allow the very best and most powerful statistical 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.

In laymen's terms, requiring the same clinical trial model for a study of 1,000 patients of a common disease and a 40 patient study of rare disease creates major scientific obstacles and produces results that may not accurately show how well the drug is working. This causes biotech's to pull patients off drugs, abandon development, and sometimes close their doors completely, even if patients report benefitting from the treatments. This was the case for Seaside Therapeutics' Fragile X treatment. Patients were reporting major benefits, however the trial design failed to show efficacy. The emerging biotech failed, patients no longer have access to the drug, and jobs and investment were lost.

Additionally, there are many ethical concerns about the use of the required double blind placebo controlled trial designs. While it is clear that this design is robust when there are enough patients to populate a large study, it is hard to conduct in rare disease studies given the small populations and heterogeneity. In addition, when the drug is safe and there is some positive efficacy data in early phase studies, giving a dying child a placebo instead of drug is doing the child irreversible harm. While it is clear that this is understood by all parties, the next step of finding a way to manage the need for quality data, without putting patients through unnecessary harm is a challenge that needs resolution.

Industry should be encouraged to design and FDA should be encouraged to allow trials to include expanded access programs or supportive clinical studies that could accept patients who do not meet the main clinical trial entry criteria. This could eliminate the difficult and most often unsuccessful attempt of patients trying to gain access to treatments through the FDA's Expanded Access program.

Lastly, there has been a lot of progress being made on allowing for the patient community to help determine risk benefit for a treatment. Patients with no available treatment options are often

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willing to take more risk and less benefit than typical FDA standards require. As a parent recently explained to the FDA, they are just looking for a life raft; they don't need the Queen Mary. Parents often opt for a very risky bone marrow transplant to help prolong their child's life which has a 10-40% chance of death depending on the diseases and the tissue match. The transplant is not a cure, it will not stop the progression of the disease, yet parents are willing to take this risk. Stopping the disease from progressing would be a huge win for many patients. However, the FDA desires evidence showing the treatment reverses the effects of the disease, a much more difficult bar to reach.

The FDA should allow for alternative clinical study designs that are more sensitive to smaller patient populations, more inclusive of heterogeneous patient populations and allow for the patient community to help determine the meaningful endpoints and the desired risk benefit.

A More Specialized FDA Drug Review

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 consistently 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. For example, in the late 1990's Aldurazyme for MPS I, a complex pediatric metabolic disease 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. Nearly 15 years later, the FDA review divisions have still not increased their specialization. Biochemical genetic diseases are reviewed in Division of Gastroenterology and Inborn Errors Products, which up until 5 years ago was just named Division of Gastroenterology (GI). It's hard to understand why treatments for complex biochemical neurodegenerative, life threatening diseases are being reviewed by the same division as reviewers for drugs for ulcers and diarrhea.

There is growing concern that FDA reviewers do not even have enough time or funding to be able to attend scientific conferences. Surely, even if the FDA were to hire an expert in the field to review a drug, they would quickly lose their specialization if they are unable to keep up on the latest science. 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.

The EveryLife Foundation has proposed a model, see **Exhibit B**, that would greatly improve the specialization of the drug review divisions and allow for the FDA reviewers to become experts in the diseases they are reviewing. We believe that FDA could start by creating a pilot review

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division with reviewers who had joint appointments within the NIH's National Center for Advancing Translational Science (NCATS) allowing them to stay connected to the academic community. This is not a novel program; in the 1990's the reviewers in the FDA's Center for Biologics Evaluation and Research (CBER) had labs in academic institutions and NIH. However, most of the drug reviews were consolidated into the Center for Drug Evaluation & Research (CDER) and the reviewers were cut off from their academic ties. Many talented physicians left the FDA at that time. Our proposal would create more desirable positions at the FDA to allow them to recruit and retain top scientists who would handle more specialized drug reviews and maintain an active intellectual connection to the clinical and science world through their NIH joint appointment.

Congress should encourage the FDA to create more specialized drug review divisions and allow reviewers to keep up with the latest sciences. If FDA commits specialization, Congress should allocate more funding to allow the FDA to increase specialization of drug reviews.

Rational & Flexible Application of Safety Data

The safety of all treatments requires the conduct of safety testing including toxicology studies. The International Conference on Harmonization (ICH) guidelines on these studies provide an important framework for testing requirements and allows for flexibility. This allows regulatory authorities to interpret and apply these guidelines differently to meet the appropriate scientific standards for the specific treatment. One of most important ICH guidelines is the amount of testing required (before treating the first patients) to ensure the treatment is not toxic to humans. For many well understood protein therapeutics, like enzyme replacement therapies, we know the proteins naturally occur in humans and are much less likely to be toxic than a new chemical that has never been in the body. When a protein therapeutic is intended for a serious life-threatening rare disease, the ability to enter clinical studies after a reasonable amount of safety data from ongoing toxicology studies per the ICH guidelines is essential to ensure the company can proceed with development promptly.

Currently, FDA is applying more extensive and lengthy testing standards for toxicology studies than was applied by the FDA in the 1990s for well characterized biologic drugs and more than are applied in the EU currently which drives up the time and cost required to enter clinical studies in the US. This increase in requirements is not based on any safety issue in biologics that would be discovered by these studies. This is causing US companies to take their early clinical trials to the UK or Europe which are more willing to apply ICH guidelines flexibly and allow in-life testing of products. This movement of studies overseas can delay access to the experimental treatment in the US for as much as two years or longer, while patients in Europe get the earliest access to potential treatments. For rare disease patients in the US, especially children, a two year delay can mean missing any possibility of treatment.

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A more flexible application of ICH guidelines is needed by the FDA for naturally occurring biologic compounds, like proteins, normally found in the body that have a low probability of toxicity. This flexibility will enable the initiation of more clinical studies in the US for life-threatening rare diseases. This data standard is being applied in the UK for many studies. The toxicology requirements are not lowered but simply staged to allow US patients to have equal access to early clinical studies. The same safety testing requirements will still be applied for the final approval of the therapeutic.

The FDA should be encouraged to be flexible and apply the ICH guidelines based on the best available science and not a one size fits all approach in their requirements to allow US rare disease patients to have access to early stage clinical trials.

Incentives for Industry

For rare diseases in particular, the economic model of drug development for complex diseases with small patient populations is often not financially viable. New economic incentives have been essential to encouraging industry and venture capital to invest. The Orphan Drug Act provides a number of incentives for industry to develop treatments for rare diseases. These incentives such as the Orphan Drug Tax Credit have been essential in bringing lifesaving therapies to rare disease patients. Despite the Orphan Drug Act's success, 95% of rare diseases still have no approved treatments. We urge Congress not only to protect the incentives in the Orphan Drug Act but to seek additional incentives.

A new incentive is needed to encourage repurposing drugs for rare diseases. We know that a single targeted drug is likely to have multiple therapeutic uses and sponsors often repurpose drugs for different diseases. Repurposing drugs is faster, cheaper and less risky than traditional drug development. However, sponsors are unlikely to repurpose a drug for a rare disease because the patient population is so small. There is little economic value in having a few hundred additional patients taking the drug to justify the cost of even doing the study, when the major market for the drug is measured in the millions of patients. Even if the sponsor wanted to do the study for scientific or good will sake; there is just too great a risk to study the treatment in a population of patients who are very sick. The fear of having their major marketed product revenue decreased or eliminated because of an adverse effect in the rare disease population is too great for companies to allow their drug to be studied in rare diseases.

This leaves many rare diseases no options but to take the drug off-label. Because companies cannot legally release data or talk about potential off-label use, patients use these drugs with no evidence of effectiveness and no understanding about correct dosing. Furthermore, there is limited

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ability to get reimbursement from insurance for off-label use creating a huge financial burden on a patient for a drug that may or may not work.

The EveryLife Foundation is proposing a simple economic incentive for industry to repurpose major-market patented drugs for rare diseases or “Rare-Purpose,” modeled after the Best Pharmaceuticals for Children Act (BPCA). BPCA allows companies to add 6 months of market exclusivity to life of their drug patent if they do a study on pediatric patients. BPCA’s Pediatric Market Exclusivity has been a great success - increasing the number pediatric indications and lowering the ‘off-label’ use of drugs in the pediatric populations by 20%. The Foundation suggests creating an Orphan Product Exclusivity Extension to provide an additional 6 month exclusivity on top of the patent life of the drug, see **Exhibit C**, if the Sponsor meets the 3 below criteria:

- Must be a Rare Disease, defined having a population less than 200,000 patients in the US
- Must qualify for Fast Track Designation, defined as life-threatening with an unmet medical need
- Must obtain the new rare disease indication on the drug label; meaning the Sponsor must do rigorous clinical study work to define the dose, safety and efficacy, and complete the regulatory process for FDA approval of the rare disease indication.

Sponsors that are Rare-Purposing a drug for a rare pediatric disease or cancer would receive a whole year of market exclusivity because the Orphan Drug Extension would be stacked on top of BPCA. While, the Orphan Drug Exclusivity Extension is modeled after BPCA, it does require the Sponsor to do more than just a study. It is our hope that the additional requirement for labeling will create a balance to the incentive in Rare-Purposing, especially for children, while also addressing critics of BPCA and still allowing timely generic competition. We do recognize this does not address the need to repurpose generic drugs for rare diseases; however patented drugs are the new drugs that are more highly targeted and better understood so they have the greatest potential for rare diseases. Patented drugs have sponsors with skilled personnel and resources to conduct the clinical research promptly. It is estimated that 120 drugs go off patent every year, so every year we lose these opportunities to rare-purpose these drugs.

Congress should pass legislation –Orphan Product Extensions Now (OPEN) - to create a new market exclusivity extension for Rare-purposing drugs.

Funding for NIH & FDA

While the majority of our proposed policy solutions can be done with little cost to the government, we must stress the importance of the need for adequate funding for the FDA & NIH. We understand the difficulties and the political realities that comes with the need to reduce the Federal budget deficit. However, funding for these core government agencies is essential to foster the

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development of life-saving treatments. Policies like sequestration that implement across the board funding cuts are very harmful. It would be best to consolidate funding toward programs and agencies that provide the most benefit to spurring the development of treatments and cutting funding from the programs that do not. It is especially important that industry funded User Fees be exempt from sequestration. Lastly, a trust fund or guaranteed funding stream to maintain and increase funding for the FDA and NIH is a potential solution that would protect the agencies from the budget crisis. This could be established through public-private funding models like the Prescription Drug User Fees.

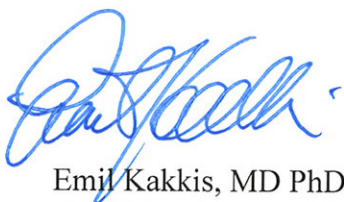
Congress should prioritize NIH and FDA funding and seek new streams of revenue to ensure adequate funding for essential health agencies.

OUTCOMES:

A more science-based and predictable FDA regulatory process will lead to a surge in investment and development activity for even the most rare disorders. More patients with rare diseases will get earlier access to safe and effective treatments. Improved public policy will bring down the cost of developing treatments and lead to lower cost treatments. Increased investment in early-stage biotech companies focused on rare diseases will have a positive economic impact in local communities and bring new high paying biotechnology jobs.

While we understand the political process is very slow, we must urge you to move this legislation in the next Congress as many patients will not make it to their next birthday. You will have our support both as an organization and as leader in the grassroots patient community. If you have any questions or would like further information on the above comments, please contact Executive Director Julia Jenkins at (415)884-0223 or via email at jjenkins@everylifefoundation.org. Thank you again for considering the needs of rare disease patients.

Sincerely,



Emil Kakkis, MD PhD
President/Founder



Julia Jenkins
Executive Director

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Exhibit A

RAPID INNOVATION IS POSSIBLE ACCELERATED APPROVAL HISTORY OF HIV DRUGS

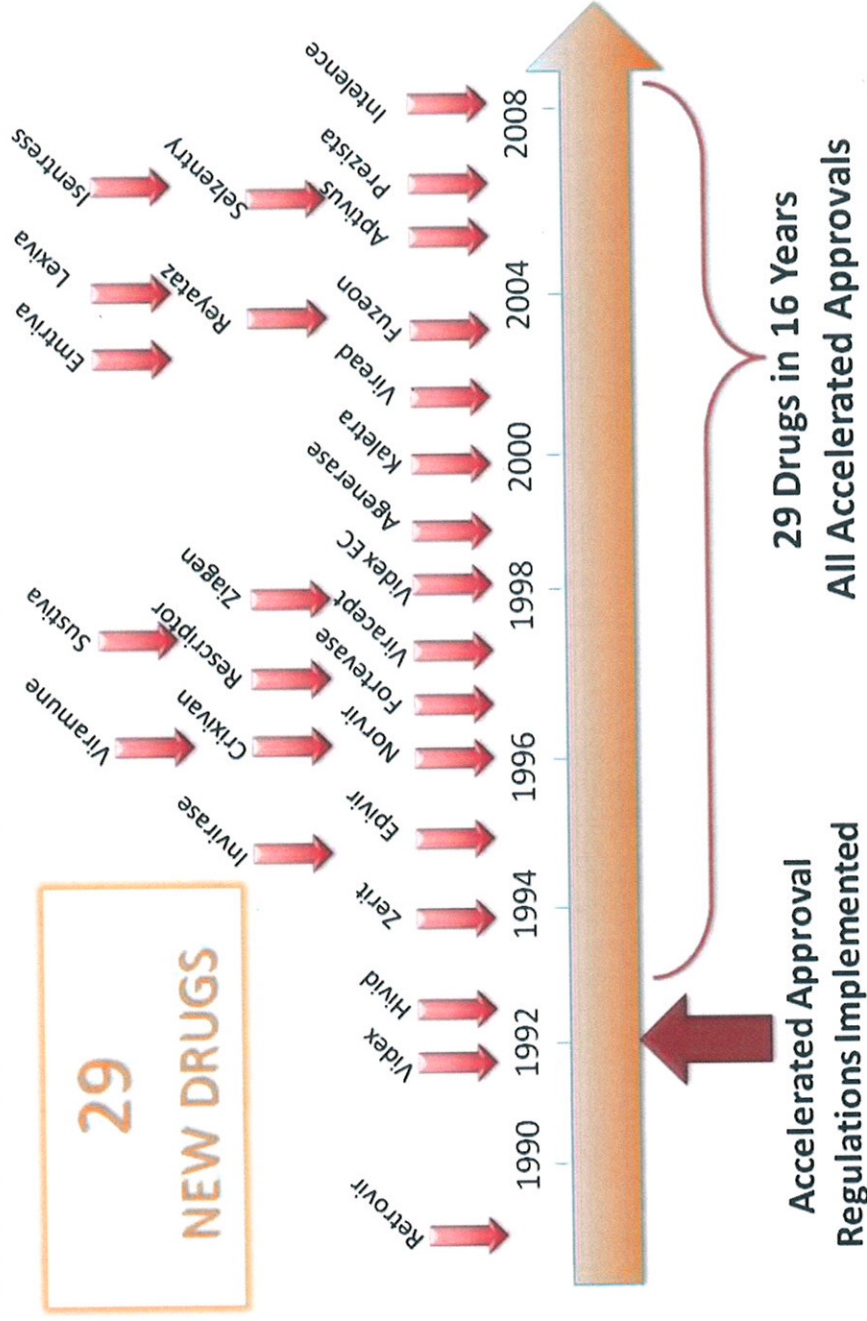
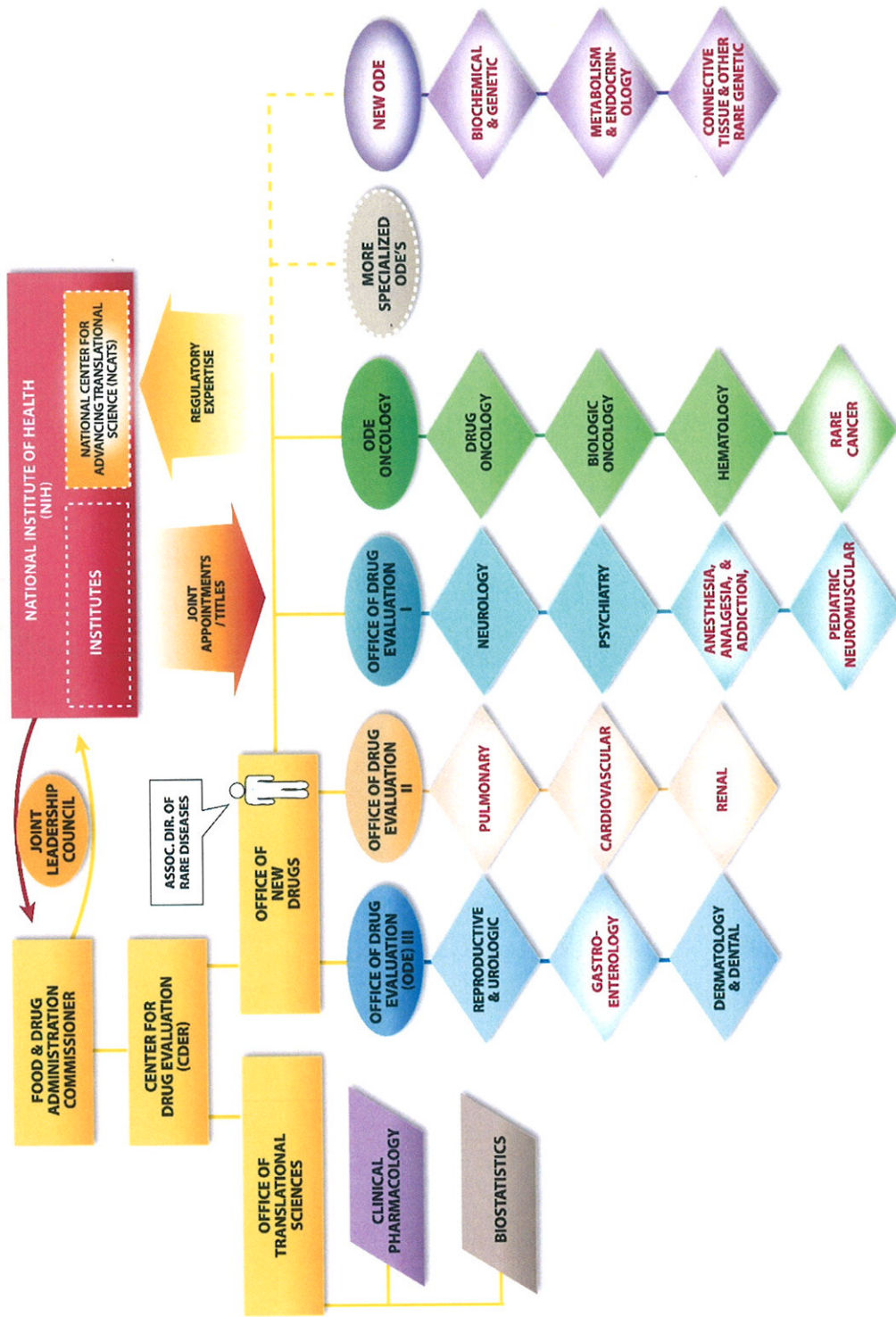


Exhibit B

CONCEPT FOR A MORE SPECIALIZED ORGANIZATIONAL STRUCTURE



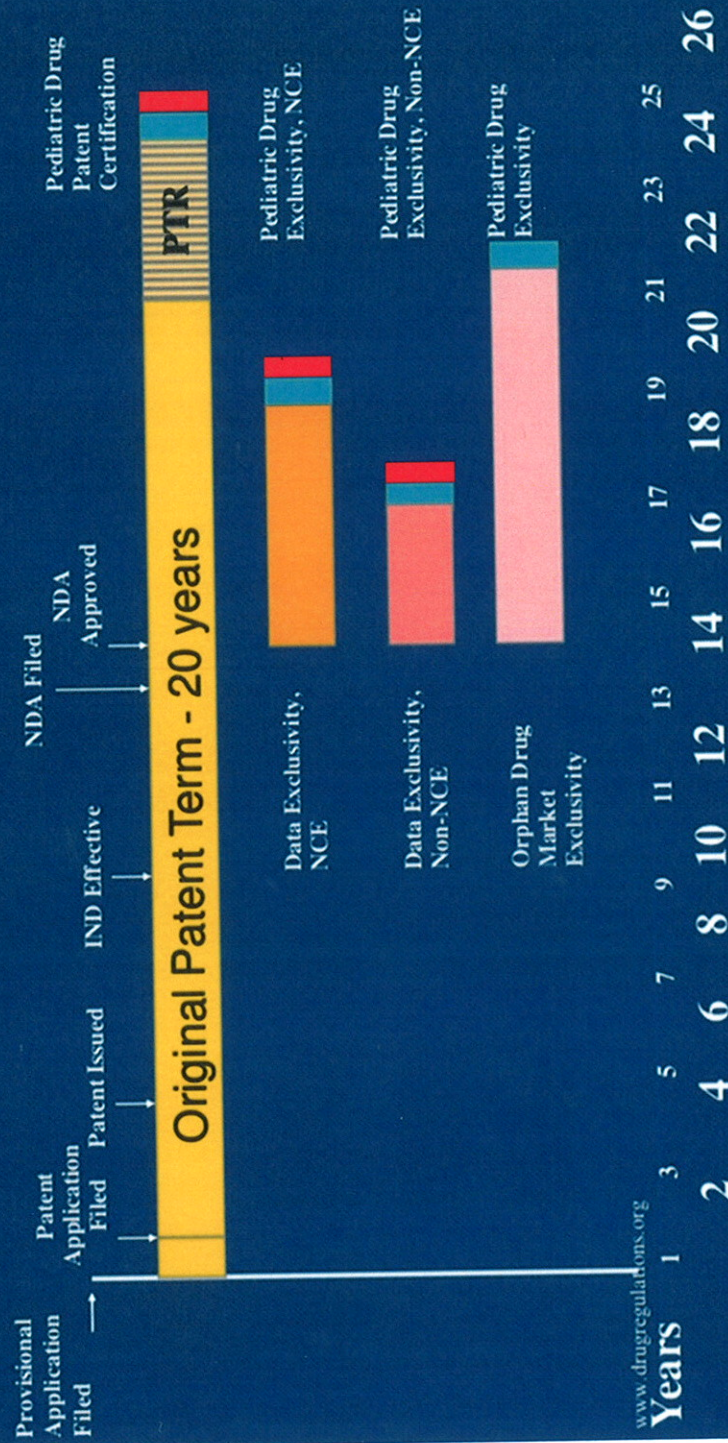
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Exhibit C

Patents & Market Exclusivity



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