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Mr. Chairman, ranking member Pallone, distinguished members of the Subcommittee, I want to thank you for the opportunity to testify before you today. I am Diane Dorman, Vice President for Public Policy of the National Organization for Rare Disorders, or NORD.

Since 1983, the National Organization for Rare Disorders has served as the leading voice and advocate for the approximately 30 million men, women and children with rare diseases in the United States. NORD is a '501(c)(3)' nonprofit federation of voluntary health organizations dedicated to helping Americans with rare 'orphan' diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service.

NORD's mission is to foster a social, political, and financial culture of innovation that supports the basic and translational research necessary to develop new diagnostic tests and therapies for all rare disorders. This requires a regulatory environment that encourages the development of and timely approval of new safe and effective treatments for rare disorders.

To that end, reauthorizing the Prescription Drug User Fee Act (PDUFA) presents an opportunity for Congress to achieve that goal. In particular, some of the resources generated by the user fee program should be allocated to support the enhancement of regulatory science, to create greater clarity and predictibility for the review of novel therapies for rare disorders, and to empower patients to fully participate in the regulatory decision-making process where questions of benefit-risk assessment arise.

Of special significance in the draft agreement is the rare disease initiative that will enhance the development of drugs and biologics for the treatment of rare conditions. NORD supports these

efforts and looks forward to the opportunity to work with the Agency and Congress to guarantee the success of this initiative.

RARE DISEASE PROGRAM INITIATIVE

The Food & Drug Administration (FDA) has facilitated a series of open meetings for patient stakeholders, providing a forum for input from patients and consumers regarding the human drug and biologic review programs. NORD has been active participant in this process, voicing the concerns and priorities of patients with rare diseases.

Mr. Chairman, everyone within the rare disease community was heartened recently when the drug approvals summary for FY2011 was announced. Of the 35 innovative drugs approved by the FDA in FY2011, 10 were orphan drugs that treat rare diseases with few or no treatment options[1]. We hope and expect that further investment in orphan products will lead to continued development of therapies that address the unmet medical needs of patients with rare diseases.

We are encouraged that the Orphan Drug Act has brought about such successful innovation in the market for rare disease therapies. The reality is that we have barely started on the journey. There are still approximately 6,800 rare diseases that lack an FDA approved therapy. The reauthorization of PDUFA offers hope that we may build on previous successes by strengthening the review process still further and by creating an environment that encourages innovation and investment.

Particularly, we believe that the Rare Disease Program Initiative in the agreed upon PDUFA reauthorization performance goals will enhance the regulatory science needed to accelerate development of new therapies that treat rare diseases. This initiative allocates a small fraction of user fees for the expansion of the existing Rare Disease Program in the FDA's Center for Drug Evaluation and Research (CDER). In brief, the agreement completes the current staffing and implementation plan for the CDER Rare Disease Program in the Office of New Drugs, and establishes a rare disease liaison within the Office of the Center Director of the Center for Biologics Evaluation and Research (CBER). The patient community supports this initiative.

A key ingredient to successful innovation is how FDA views drugs for rare diseases. Last October, NORD released a landmark study that looked at all drugs for diseases other than cancer approved as orphans since 1983 to identify whether and when FDA exercised flexibility in the review process. Of the 135 drug approvals studied, NORD concluded that the FDA demonstrated flexibility in the review of effectiveness data on orphan drug therapies for two of every three orphan drugs approved. FDA clearly has demonstrated in its actions on orphan products over the past three decades that it recognizes the importance of therapies for people

[1] See report, "FY2011 Innovative Drug Approvals," US FDA, http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm276385.htm.

with rare disorders. (Several examples of flexibility in orphan product review are included in Appendix A).

NORD believes it would be helpful for such flexibility and importance to be recognized in a formal FDA policy, and for FDA officials to incorporate flexibility in a systematic way in their evaluations of each new therapy in development and under FDA review for Americans with any rare disease.

While NORD believes that the statutory standard for safety and efficacy should be the same for medical products for both rare disorders and prevalent diseases, enhancement of the Rare Disease Program will allow FDA to provide greater clarity in how it applies the standards for safety and effectiveness to orphan products. A formal policy setting forth the agency's view of flexibility in conducting orphan product review is likely to provide more certainty to innovators seeking to develop orphan products.

Missing in the draft agreement is increased coordination between CDER and CBER and two other key FDA Centers. Although the regulatory schemes differ between CDER, CBER, CDRH and CFSAN, there are underlying themes of commonality – geographically dispersed small patient populations and, of course, the challenges of trial design. Because humanitarian use devices and medical foods for inborn errors of metabolism and other rare conditions are equally critical to rare disease patients, increased collaboration and education of reviewers in CDER and CBER with CDRH and CFSAN is strongly supported by NORD.

Further, we would like to see the proposed public meeting and staff training implementation dates in the PDUFA reauthorization performance goals moved forward, to occur no later than the end of FY 2013.

Additionally, we think that the American public is served well by a strong FDA that continues to review safe and effective therapies and approve them for marketing in the United States first, faster than in Europe, (as demonstrated by a recent study of new oncology therapy approvals at the FDA and the European EMA[2]). Likewise, our own analysis comparing orphan drug approvals over the last decade indicates that a total of 106 more orphan products have been brought to market in the United States compared to the European Union, (see Appendix B).

PDUFA V will provide FDA with the resources needed to maintain a strong professional staff that is necessary for the development of clear guidances and the expedited review of innovative drugs.

ADVISORY COMMITTEES AND CONFLICT OF INTEREST

During FDAAA negotiations, NORD argued that because patient populations are very small, and the number of researchers who study a particular rare disease is limited, identifying experts not

[2] This study, by Friends of Cancer Research, indicates that a sizeable majority of new cancer therapies approved for marketing by both the US FDA and European EMA from 2003-2010 were approved by FDA first.

financially conflicted to sit on an Advisory Committee would be difficult, if not impossible. Those concerns were realized in 2008 when it took the FDA nearly six months to identify an expert to review a life-saving therapy to treat infantile spasms[3].

To address those concerns, NORD has joined forces with over 50 organizations who are deeply concerned about the current conflicts-of-interest statutory provisions and their impact on the appointment of experts, particularly researchers and patients, as Special Government Employees on FDA Advisory Committees and as otherwise needed. As a group, the organizations promote efforts to bring better treatments and cures to those struggling with diseases. Many of these conditions have no adequate treatments and, therefore, it is imperative that we challenge hurdles that impede the quality and efficiency of the treatment development process.

It is our belief that protections must be in place when persons are appointed to positions where their own financial interests might influence their service to the federal government. However, it is also our strong belief that the current conflict-of-interest statutes that apply to the FDA have resulted in a system that is out of balance to the point that conflict avoidance is the primary driver of who serves on Advisory Committees, regardless of the extent of the conflict, the uniqueness of their expertise, or the government's need for their services.

As you know, FDA SGE's are subject to an additional layer of statutory conflict-of-interest provisions beyond those that already govern SGE's for all other departments and agencies in the executive branch. Specifically, under current law, the FDA must analyze potential committee members pursuant to Section 712 of the Food, Drug, & Cosmetic Act (FDCA), in addition to the government-wide provisions found in the Federal Advisory Committee Act and the Ethics in Government Act of 1978. This additional FDA-specific provision appears to drive the FDA to look only for individuals to serve as SGE's who have virtually no financial ties to any issue that might be addressed by a given Advisory Committee.

While that may sound wise at first glance, in fact those with expertise in a given area often have foreseeable and unavoidable ties to the community as a result of their expertise. Yet, under the current structure, the FDA is not allowing those individuals to serve as SGE's, despite the fact that by doing so the FDA is being deprived of expertise by those who are best qualified. Accordingly, we support any effort to eliminate the additional conflicts of interest restrictions that apply only to the FDA[4].

Our view is that the existing provisions in the Federal Advisory Committee Act and the Ethics in Government Act of 1978 are adequate to safeguard against conflicts of interest, while still

[3] The details of this delay are outlined in an article appearing in Pink Sheet Daily, August 27, 2008. See references.

[4] http://www.accessdata.fda.gov/FDATrack/track?program=advisory-committees&id=AdvComm-waivers&fy=all. While FDCA does give the FDA authority to issue waivers for those with conflicts of interest (with an annual cap on the number) it frequently selects for SGE service those who need no waivers, often meaning they have little direct involvement in an issue or a field.

allowing those with the necessary expertise and perspective to serve on these very important committees. In fact, the specific standard for SGE's found in 18 U.S.C. 208(b)(3) recognizes that potential SGE's may have conflicts-of-interest, but allows for their service nevertheless when the need for their services outweighs the potential for a conflict-of-interest created by the financial interest involved.

That standard is clear, reasonable, and balanced and appropriately recognizes that some potential SGE's may come to the FDA with ties to the community that may pose some conflict-of-interest, but that the primary issue must be the government's need for their services. The main goal of these committees, after all, is to help the FDA to make the best decisions possible. The FDA can only do that if it has the best, most well-informed researchers, clinicians, and patients advising it.

RISK TOLERANCE IN THE PATIENT COMMUNITY

Early this year, NORD convened a meeting of like-minded members of the patient community to discuss the willingness or reluctance of patients and their families to tolerate a greater degree of risk in the use of therapies to treat chronic and rare conditions. Our goal was to develop a proposal to be submitted to the FDA as to how the patient community can communicate on a more frequent and periodic basis with medical reviewers and other relevant FDA staff as they are making risk tolerance and other decisions regarding specific product applications or making policy decisions.

The 32 organizations who signed the letter submitted to CDER on September 27, 2011[5], are in full agreement that it is essential that patients have the opportunity to provide such input to product and policy decisions made by the FDA, particularly with regard to risk tolerance associated with the use of specific products. Mechanisms currently exist for patients and other external audiences to provide input to the FDA – e.g., at the public sessions of advisory committees – but the input does not necessarily occur at the time that risk tolerance and other critical issues are being deliberated, and does not necessarily represent a broad spectrum of patient views.

As the FDA commits to a more patient-centric posture, and as patients themselves become more knowledgeable and sophisticated about diseases and their treatment options, we advocate that more systematic processes be established at FDA to enable contributions from the patient community at the time that critical decisions on risk tolerance are being made, and from a representative sample of patient views.

We believe the process should be well-defined and well-understood within the review divisions, and provide a universally applied opportunity for patients to make such input. We are conscious that FDA reviewers and other relevant FDA staff have many demands on their time, but strongly

[5] A copy of the letter may be found on NORD's website:
http://www.rarediseases.org/docs/policy/MullinRiskToleranceletter..pdf

believe that a new process for input will improve product analysis and approval and access to necessary treatments in a timely manner.

We recognize that risk tolerance and other critical decisions are made at many points during the regulatory life cycle of a product - from initial clinical trials through marketing. However, at some points of the review process when risk assessments are made, patient contributions would be of value to the FDA decision-makers.

We also recognize that continuous interaction with the patient community is not feasible. At the same time, the patient community believes that specific milestone events should be designated at the times at which FDA, as a matter of policy, seeks formal input from the patient community.

We do not seek to create a burdensome or time-consuming process. Rather, we want to be sure that patients across the country, whether they belong to a patient organization or not, have the opportunity to share their views with the FDA.

Our hope and expectation is that the kinds of information that patients and patient organizations can share with the FDA will contribute toward its decision-making in assessing the benefit-risk equation of new products as well as the amount of risk patients at various stages of their condition are willing to take, the quality-of-life challenges they face, the ways they receive information about the proper use of their therapies, how often they see and receive information from their physicians, and other information that FDA medical reviewers and other relevant FDA staff may benefit from knowing directly from patients.

CLOSING

In closing, I want to thank the Subcommittee again for giving NORD the opportunity to testify today regarding the reauthorization of the Prescription Drug User Fee Act. The rare disease community believes that engaging Congress and FDA officials in the process has, and will continue to lead to practical, detailed improvements to the regulatory process that will accelerate the development of orphan products– from concept to access.

Thank you.

Respectfully Submitted,

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References

1) Samantha A. Roberts, Jeff D. Allen, and Ellen V. Sigal. "Despite Criticism of the FDA Review Process, New Cancer Drugs Reach Patients Sooner in the United States Than in Europe." *Health Affairs*. July, 2011, 30:1375-1381.
2) Frank. J. Sasinowski, "Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Cataloguing FDA's Flexibility in Regulating Therapies for Persons with Rare Disorders." 11 Oct. 2011. Accessed 30 Jan. 2012. <<http://www.rarediseases.org/docs/policy/NORDstudyofFDAapprovaloforphandrugs.pdf>>
3) Kate Rawson and Michael McCaughan. "The Longest Review: Inside Ovation's Wait for Sabril." *The Pink Sheet Daily*. 27 Aug. 2008. Print.

Appendix A

Selected CDER Rare Disease Product Approvals from 2007 to 2012

1. Voraxaze (glucapidase) – New Biologic

On January 17, 2012 FDA approved Voraxaze (glucarpidase) to treat patients with toxic levels of methotrexate in their blood due to kidney failure.

Methotrexate is a commonly used cancer chemotherapy drug normally eliminated from the body by the kidneys. However, patients receiving high doses of methotrexate may develop kidney failure. Voraxaze is an enzyme that rapidly reduces methotrexate levels by breaking this chemotherapy drug down to smaller, inactive components that can be eliminated from the body by the liver. Voraxaze is administered as a single injection directly into a patient's vein (intravenously). Prior to approval of Voraxaze, there were no effective therapies for treatment of toxic methotrexate levels in patients with renal failure.

The effectiveness of Voraxaze was established in 22 patients from a single clinical study, in which all patients received Voraxaze treatment (open-label, single-arm trial). Patients ranged in age from 5 to 84 years, and the most common cancers being treated were a form of bone cancer (osteogenic sarcoma) and blood cancers (leukemia and lymphoma). The treatment was considered successful if the methotrexate level fell below a critical level within 15 minutes and stayed below the critical level for eight days. Ten of the 22 patients achieved this standard. Although not all patients experienced this result, Voraxaze reduced methotrexate levels by more than 95 percent in all patients.

Voraxaze was given a priority review by FDA, which is a shortened review time of 6 months for drugs that may offer major advances in treatment or that provide a treatment when no adequate therapy exists, instead of the standard review time of 10 months for other drugs. FDA exercised regulatory flexibility in evaluating efficacy based on rapid and sustained clearance of toxic methotrexate blood levels, a novel endpoint for drug approval. The use of this endpoint in a selected patient population allowed efficacy to be demonstrated in a single arm study.

2. Erwinaze (asparaginase) – New Biologic

On November 18, 2011 FDA approved Erwinaze (asparaginase) to treat patients with a form of blood cancer, acute lymphoblastic leukemia (ALL). Erwinaze is a component of multi-agent chemotherapeutic regimens for the treatment of ALL.

ALL is a malignancy arising in the bone marrow, and most commonly affects children. Epidemiologic data from 2004-2008 show that the median age at diagnosis for ALL was 13 years of age, and 60% of newly diagnosed patients are under age 20.

The effectiveness of Erwinaze was established in one trial in 58 patients, in which all patients received Erwinaze treatment (open-label, single-arm trial). All patients were enrolled in NCI-sponsored cooperative group trials conducted by the Children's Oncology Group. Patients in the study ranged in age from 2 to 18 years (median 10 years). The main outcome measure in the trial was the level of asparaginase activity in serum, an accepted surrogate measure for clinical benefit, which supported a full approval for Erwinaze.

3. Zelboraf (vemurafenib) – New Molecular Entity (NME)

On August 17, 2011 FDA approved Zelboraf (vemurafenib) to treat patients with metastatic melanoma that has a specific abnormality of a gene know as BRAF. It also required coordination with CDRH on the simultaneous approval of a diagnostic test for the gene abnormality, which was the first-ever approval by FDA of a drug + a "companion diagnostic".

Zelboraf's effectiveness and safety were established in one Phase 3 randomized, open-label (not blinded to treatment) trial and one Phase 2 open-label, single-arm trial. In the Phase 3 trial, patients were randomized to Zelboraf or treatment with the chemotherapeutic agent dacarbazine. The results showed an increase in median overall survival (OS) and progression-free survival in patients treated with Zelboraf vs. dacarbazine, and an overall response rate of 48% in the Zelboraf group vs. 6% in the dacarbazine group.

Due to the results of these studies showing a significant benefit in overall survival in patients with melanoma with the BRAF mutation, Zelboraf was given a priority review. In addition, because of the paucity of effective therapies for patients with this disease, this application was given an expedited review and approved by FDA more than 2 months ahead of the PDUFA priority review goal date.

This application is also notable in that FDA became aware of preliminary results in the sponsor's Phase 2 study as well as published results of the Phase 1 study with Zelboraf that showed impressive objective response rates of >50% in this patient population. In published literature reports of patients with metastatic melanoma treated with a variety of chemotherapy agents, objective response rates ranged from 11% to 24%. Given these noteworthy results with Zelboraf, FDA proactively communicated with the applicant to modify the statistical plan for the Phase 3 trial, adapting the impressive observed activity of Zelboraf in the Phase 1 and 2 studies. With this adaptation, the applicant was able to successfully conduct the analysis early in a planned manner with the timely adaptation of the clinical trial.

4. Carbaglu (carglumic acid) – New Molecular Entity (NME)

On March 18, 2010 FDA approved Carbaglu (carglumic acid) for the treatment of NAGS deficiency, a rare, serious inherited disorder. Less than 20 patients in the US are known to have NAGS deficiency.

NAGS deficiency is one of a group of diseases known as urea cycle disorders. Urea cycle disorders most commonly present in infancy and early childhood. The urea cycle is responsible for removing ammonia from the blood stream. Ammonia is toxic, and high levels in the blood can cause brain damage and death. NAGS is a required cofactor which combines with an enzyme in the first step in the urea cycle, and a deficiency in NAGS results in severe impairment in the urea cycle. Carbaglu is a closely related drug to the naturally occurring NAGS, and acts as a replacement for the deficient cofactor.

Carbaglu's effectiveness and safety were demonstrated in a retrospective case series in which the clinical course of 23 patients with NAGS deficiency who were treated with Carbaglu for a median of 8 years (range 0.6 months to 21 years) was evaluated. Patients included in the analysis started Carbaglu treatment at ages ranging from less than 1 year to 13 years. This retrospective analysis was unblinded and had no concurrent control group, so no meaningful statistical analysis could be performed. The results showed stable or favorable neurological outcomes in most patients over time, which was notable when compared to historical descriptions of the clinical course of the disease ("historical control"). In 13 of the 23 patients, laboratory data on blood ammonia levels was available, which showed decreases in ammonia levels in both short-term (1 day) and long-term (median 6 years) follow-up.

Carbaglu was given a priority review of 6 months. Although non-specific treatments for urea cycles have been available for many years in the US, prior to the approval of Carbaglu, no targeted and specific treatment was approved for NAGS deficiency. Carbaglu represented an advance in treatment for NAGS deficiency patients.

5. Arcalyst (rilonacept) – New Biologic

On February 27, 2008 FDA approved Arcalyst (rilonacept) for the treatment of cryopryin-associated periodic syndromes (CAPS), a group of rare inherited disorders affecting approximately 200-300 patients in the US.

CAPS is a deficiency in a protein "cryopyrin", which is part of the innate immune response. Deficiency in cryopyrin results the body's over-production of another protein, IL-1, which leads to the development of recurrent rashes, fever and chills, joint pain and other symptoms. In severe forms, it can lead severe organ damage, such as deafness, protein accumulation in vital organs, joint and bone deformities, and nervous system impairment. Depending on disease type, CAPS can manifest in neonates, children or adults. Arcalyst is a protein product, which was developed to interfere with IL-1, and hence, to decrease the signs and symptoms of the disease.

Arcalyst's safety and effectiveness profiles were described in one randomized, double-blind, placebo-controlled trial in 47 patients. The effectiveness of Arcalyst was evaluated using a daily symptom questionnaire, which was a novel endpoint developed for this study with the drug developer and FDA working in collaboration.

Arcalyst was given a priority review. Prior to the approval of Arcalyst, there were no targeted products approved for the treatment of CAPS, and Arcalyst represented an advance in the treatment of this disorder.

6. Soliris (eculizumab) – New Biologic

On March 16, 2007, FDA approved Soliris (eculizumab) for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), a rare, serious, acquired disorder estimated to affect several thousand people (or fewer) in the US.

PNH is a deficiency in a blood component "terminal complement inhibitor", which results in an over-activation of other proteins in the complement system. This over-activation leads to the breaking apart of red blood cells in the blood stream (hemolysis). Hemolysis can lead to blood clots, abdominal pain and other signs and symptoms. The formation of blood clots is the most serious manifestation of the disease and can lead to death and severe complications, such as stroke or liver failure. Soliris is a monoclonal antibody, which was developed to specifically target the over-activation of one protein in the complement system (C5). Soliris' mechanism of action is intended to result in less hemolysis and longer red blood cell survival.

Soliris' safety and effectiveness were demonstrated in one randomized, double-blind, placebo-controlled trial in 87 patients, with supporting evidence provided by a second, open-label study in which 97 patients all received treatment with Soliris. Soliris' effectiveness was assessed in the first study by changes in laboratory values, including stabilization in measures of red blood cells (e.g., hemoglobin) and whether blood transfusion could be avoided. These endpoints were significantly improved with treatment with Soliris.

Soliris was given a priority review. Prior to the approval of Soliris, there were no targeted products approved for the treatment of PNH, and Soliris represents an advance in the treatment of this disorder.

Appendix B

Year	EU Orphan Marketing Authoriziations	US Orphan Drug Approvals
2001	8	6
2002	7	14
2003	4	12
2004	6	13
2005	3	20
2006	8	23
2007	15	16
2008	6	14
2009	8	20
2010	4	15
2011	4	26
TOTAL	73	179

These data taken from publically available database access, FDA & EMA, 27 Jan. 2012.