

National Organization for Rare Disorders, Inc.®

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out of the darkness
into the light

NATIONAL MEMBER ORGANIZATIONS

Alagille Syndrome Alliance
Alpha 1 Association
Alpha 1 Foundation
American Brain Tumor Association
American Laryngeal Papilloma Foundation
American Porphyria Foundation
American Syngomyelia Alliance Project
Aplastic Anemia & MDS International Foundation, Inc.
Association for Glycogen Storage Disease
Association of Gastrointestinal Motility Disorders, Inc. (AGMD)
Batten Disease Support & Research Association
Benign Essential Blepharospasm Research Foundation
Charcot-Marie Tooth Association
Chromosome 18 Registry Research Society
Cleft Palate Foundation
Cornelia De Lange Syndrome Foundation
Cystinosis Foundation, Inc.
DEBRA of America
Dysautonomia Foundation, Inc.
Dystonia Medical Research Foundation
Ehlers Danlos National Foundation
Epilepsy Foundation
Families of Spinal Muscular Atrophy
Foundation for Ichthyosis and Related Skin Types
Genetic Alliance
Guillain Barre Syndrome Foundation International
Hemochromatosis Foundation
Hereditary Colon Cancer Association
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Immune Deficiency Foundation
International FOP Association, Inc.
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Interstitial Cystitis Association
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National PKU News
National Spasmodic Torticollis Association
National Tay Sachs & Allied Diseases Association
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Neurofibromatosis, Inc.
Osteogenesis Imperfecta Foundation
Parkinson's Disease Foundation, Inc.
Platelet Disorder Support Association
Prader Willi Syndrome Association, USA
Pulmonary Hypertension Association
PXE International, Inc.
Reflex Sympathetic Dystrophy Syndrome Association
Scleroderma Foundation
Sickle Cell Disease Association of America
Stevens Johnson Syndrome Foundation
Sturge-Weber Foundation
The Erythromelalgia Association
The Oxalosis and Hyperoxaluria Foundation
The Paget Foundation
Tourette Syndrome Association
Trigeminal Neuralgia Association
United Leukodystrophy Foundation
United Mitochondrial Disease Foundation
VHL Family Alliance
Wegener's Granulomatosis Association
Williams Syndrome Association
Wilson's Disease Association

July 13, 2004

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

Re: Docket No. 2004-N-0181, Critical Path Initiative

To Whom It May Concern:

In response to the Federal Register Notice (Vol. 69, No. 78, Thursday, April 22, 2004), the National Organization for Rare Disorders (NORD) provides comments on activities that may reduce existing hurdles in research and development of new drugs, biologics, and medical devices.

We wish to congratulate the Food and Drug Administration (FDA) for its excellent report, "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products," especially the report's recognition that the Orphan Products Research Grants Program provides "an instructive example of a successful targeted intervention." To that end, NORD and the entire rare disease community requests that the FDA recognize that success and insure increased funding in FY 2006 for that program as authorized by the Rare Diseases Act (PL 107-280).

The Orphan Drug Act of 1983 (PL97-414), and the Rare Diseases Act provide financial incentives and authorize funding for research on new treatments for rare disorders. The extraordinary success of the American orphan drug program has led to replication of the law in Europe and Asia.

We assume that the pharmaceutical, biotech, and device industries will provide detailed comments on the "most pressing scientific and/or technical hurdles causing major delays and other problems in the drug, device, and/or biologic development process." As the representative of patients and families with rare "orphan diseases", however, NORD wishes to comment on these issues from a patient perspective, as follows:

1. **Priority of new product approvals for new drugs, biologics and devices should be based on scientific and clinical superiority to already existing products on the market, and to promote the development of new medical advances in order to address unmet or underserved medical conditions.** This is not to say that innovators should not be permitted to develop "me-too" products. Rather, industry should be encouraged, in cooperation with all stakeholders, to develop a strong pipeline of innovative products. The Orphan Drug Act (PL 97-414), requires that any new orphan product that is similar to an existing orphan drug, must prove it is "clinically superior" to the first drug in order to break the exclusive marketing rights of the first drug. This promotes head-to-head research on new products, resulting in improved therapies for patients.

2004N-0181

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Associate Member Organizations

Acid Maltase Deficiency Association (AMDA)	Canadian Organization for Rare Disorders (CORD)	Family Support Network of North Carolina	National Spasmodic Dysphonia Association	Shwachman - Diamond Syndrome International
American Autoimmune Related Disease Association	Children's PKU Network	Freeman-Sheldon Parent Support Group	Organic Academia Association	Society for Progressive Supranuclear Palsy, Inc.
American Behcet's Disease Association	Chromosome Deletion Outreach Inc.	Hydrocephalus Association	Osteoporosis and Related Bone Diseases National Resource Center	Sotos Syndrome Support Association
American Self-Help Group Clearinghouse	Chronic Granulomatous Disease Association	Incontinentia Pigmenti International Foundation	Parent to Parent New Zealand Inc.	Takayasu's Arteritis Association
Amyotrophic Lateral Sclerosis (ALS) of Greater Philadelphia Chapter	CLIMB	K-T Support Group	Rare & Expansive Disease Management Program (REM)	Taiwan Foundation for Rare Disorders
Association for People with the Van Lohuzen Syndrome (CMTC)	Consortium of Multiple Sclerosis Centers	Late Onset Tay-Sachs Foundation	Recurrent Respiratory Papillomatosis Foundation	Associations are joining continuously. For newest listing, please contact the NORD office.
A-T Children's Project	Contact A Family	Les Turner ALS Foundation Ltd.	Restless Legs Syndrome Foundation	
(The) CDG Family Network Foundation	Cushing Support & Research Foundation Inc.	Mercy Medical Airlift	Sarcoid Networking Association	
	EURORDIS	National Lymphedema Network Inc.		
	Family Caregiver Alliance	National Niemann-Pick Disease Foundation		

Dedicated to Helping People with Orphan Diseases

This is a successful paradigm that can serve as a model for treatments aimed at common medical conditions. Speedy approvals should be awarded to true medical advances, and "me-too" drugs should be a slower priority for the agency. The pharmaceutical, biotech and device industries cannot thrive if marketing departments, rather than medical experts, drive new product development.¹ If the industry notices it will take longer to get "me-too" drugs approved, they may eventually redirect their R&D budgets to innovative products that patients need.

2. **Input on a "Critical Path Opportunities List," which is intended to bring concrete focus on tasks that can modernize the critical path, should not be exclusive to industry, academia, FDA and other federal agencies.** This "List" should be developed with the input of all stakeholders. With at least a third of drugs marketed by the major drug companies being licensed from universities or small biotech companies, and orphan product development being driven in large part by academia and rare disease patient organizations, excluding any stakeholders would be a disservice to all patients throughout the United States².

An example of inadequate stakeholder cooperation was the *Orphan Products Board* (Sec. 227), established when the Orphan Drug Act was signed into law on January 4, 1983. Although no longer a functioning Board, its mission was to "promote the development of drugs and devices for rare diseases or conditions and the coordination among Federal, other public and private agencies in carrying out their respective functions relating to the development of such articles for such diseases or conditions." Other provisions of Sec. 227 were to "assure appropriate coordination among all interested Federal agencies, manufacturers, and organizations representing patients, in their activities related to such drugs." In the years when the Board functioned, no consumer groups were invited to participate, and the Board eventually became inactive.

3. **There is an urgent need to improve the efficiency and effectiveness of the clinical trial process, including trial design, endpoints, and analyses.** According to the Critical Path report, if a company could see a ten percent improvement in predicting failures before clinical trials, it could save \$100 million in development costs per drug. For orphan drugs, however, patient recruitment is often one of the biggest hurdles for clinical trials.

Orphan drugs must be tested on small patient populations, and it seems that the standard methodology used for statistical analyses was developed for trials on large numbers of people. It is very difficult and sometimes impossible for sponsors to find a large number of patients with a target orphan disease, which is required by FDA statisticians. There has got to be a better way to analyze efficacy! This problem greatly delays, and sometimes prevents, orphan drug development. Moreover, patients with rare diseases are called on repeatedly for clinical research and ultimately they feel they are "used" by the system because researchers cannot find an ample number of new subjects.

The FDA requires control groups in clinical trials, which generally means some people will receive placebo. But people with life-threatening diseases often refuse to enter a placebo-controlled trial, making it even more difficult to find enough patients. Ideally, FDA should accept historical controls, but this is very rarely accepted by the agency. Moreover, academic scientists are unable to obtain funding for historical studies; neither FDA nor NIH will fund this type of study.

One of the best ways for sponsors to find enough patients for a clinical trial is to list their study on: clinicaltrials.gov. Even though all studies (publicly and privately funded) are required to be listed, FDA has not enforced the law (FDA Modernization Act, 1997) and very few private manufacturers have listed their studies. FDA should support an enforcement mechanism in the law so patients will have an opportunity to locate clinical trials on the Internet that may affect them, and companies will spend less time and money-soliciting patients.

4. **Patient Protections:** Another hurdle to patient participation in clinical trials is public distrust of the patient protection system spurred by press reports of research tragedies. FDA is not a signatory to the *Common Rule*, and until recently it has not even had a staff bioethicist. Federally-funded studies must comply with comprehensive patient protection rules, but FDA is the only enforcer of protections for privately-funded research. The agency must do a better job of ensuring the public that privately-funded companies must adhere to human subject protection rules; for serious and life-threatening diseases, all patients should be allowed to cross over from placebo to active drugs; and FDA should never require a procedure that is not acceptable to IRBs. We have heard of several instances where FDA required a protocol design that was unacceptable to a university IRB. Investigators wasted months renegotiating the problem with the agency and commercial sponsors.
5. **Staff Training:** Besides the manufacturing issues that can slow the progress of new product development, clinical testing problems can greatly delay availability of safe and effective treatments. Since many FDA reviewers are unfamiliar with rare diseases, there can be confusion about selecting appropriate endpoints, surrogate markers, etc. Independent experts on these unusual diseases should be asked to provide training to FDA staff so they will become familiar with the symptoms and progression of a rare disease. Otherwise there is a risk of selecting inappropriate endpoints, or requiring painful procedures that are unnecessary.
6. **The Major Delays in Drug Development:** In terms of priorities, we are convinced that FDA's highest priorities should be placed on enhancing patient protections; speeding enrollment in clinical trials; finding a solution to the "statistical significance" problem for small populations of patients; and finding substitutes for control groups (e.g., published case studies of untreated patients, or funding studies of "historical controls" that the agency would accept as viable); and processing true breakthrough treatments more quickly than standard "me-too" drugs.

Division personnel should call on ad hoc disease experts to educate them about unusual diseases early in the process, when they are first exposed to a new product for that disease. Such independent experts are asked to participate on Advisory Committees for unusual diseases, but they should be called on earlier so they can enhance reviewers' understanding of appropriate endpoints and trial design.

Very truly yours,



Abbey S. Meyers
President

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cc: Diane Dorman, NORD Vice President for Public Policy

¹ Angell, Marcia. *The Truth About the Drug Companies: How They Deceive Us and What To Do About It*. The New York Review of Books. Volume 51, Number 12. July 15, 2004.

² Angell.