**Genetic Alliance Statement on Current Shortages of Enzyme Replacement Therapy**

Genetic Alliance believes the current shortage of enzyme replacement therapy (ERT) is a reflection of a larger, more serious, set of challenges and opportunities. We believe that the immediate decisions that need to be made can and should be made within this larger context. We are committed to joining in the process of catalyzing the dialogue and action required to address the challenges and seize the opportunities.

We recognize that all stakeholders—patients, advocates, companies, the Food and Drug Administration, and us, Genetic Alliance—are focused on the same thing: the best therapies for patients. We also recognize that we are all responding to very real fears of the consequence that a lack of ERT will have for each of us.

In order to make the best decisions for the whole, we have to address and overcome these fears, both in the immediate, practical response we make, and the longer term systemic response required to address the overarching issue of therapy discovery and development for rare conditions. This must be done with transparency, openness, and generosity for all stakeholders.

On a purely principled basis, Genetic Alliance prefers open access, including no exclusivity and no earmarking for funding for conditions. Yet, from the point of view of what is best for the whole system, including all the players identified above (and more), we are poignantly aware that no better system exists today.

FDA, before exercising its ability to revoke exclusivity, should consider what matters when getting drug to patients in the fastest possible manner. Using this as the yardstick, one must ask if patients will get ERT quickest if companies gear up from phase II and III trials to approved large scale production; or, will they get it faster if FDA accepts EU approvals on a temporary basis, or allows importation? It appears to us that alternatives to the current therapies, in the form of other biologics or small molecules in development, would take years to reach levels of production sufficient to reach the current population. We do not know the answer, but we do know shattering the exclusivity provision of the Orphan Drug Act undermines its premise.

As such, we recommend that the FDA not revoke exclusivity at this point in time.

Simultaneously, we believe in the need to open a dialogue in which all who are affected by these decisions address the larger system issues together.

The current situation calls for examination of a system that was built to respond to rare disease drug development issues more than 20 years ago. These lysosomal storage disorders are small opportunities to make a big impact and offer us the

**T:** 202.966.5557
**F:** 202.966.8553

4301 Connecticut Ave., NW
Suite 404
Washington, DC 20008-2369

info@geneticalliance.org
www.geneticalliance.org

opportunity to look at the system as a whole. We need to address the problems of which we are aware, as well as those we may not yet know.

Apparent challenges of the current paradigm include:

- Severe life threatening and quality of life aspects of the disease
- Difficulties amassing cohorts and characterizing them well and the resulting problems with regulatory approval processes for small cohort trials
- Lack of market incentives for rare disease therapies
- A focus on 'me too' therapies instead of therapies for the additional 6,000 conditions with no therapies (certainly to avoid risk on the part of biotech and pharma companies)
- Current need for exclusivity to guarantee return on investment
- Misaligned incentives and innumerable financial challenges
- Lack of global harmonization or regulatory standards

This crisis in the small world of lysosomal storage disorders is presenting all of us an opportunity to reflect upon, rethink, and revise the current system. The paradigm shift taking place in the move from blockbuster drugs to personalized medicine – creating many small subsets of responders in large disease states – fragments all diseases into multiple 'rare' diseases. Advances in newborn screening and better diagnostics will also create unprecedented worldwide demand for therapies for rare conditions. We must address systemic changes now so that we are not faced with a crisis of unprecedented magnitude later.

To this end, we recommend an urgent meeting of all who are affected by our present paradigm to discuss the best course of action for this situation and to determine a better system for the future. We are prepared to fully participate in this effort, and we look forward to taking this important next step with others who are as deeply concerned as we are about these issues.

Please feel free to contact us at any time:
Sharon Terry, President & CEO
sterry@geneticalliance.org
202.966.5557 x201

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