

Pat Furlong's Questions for the Record Responses

Rep. Burgess's Questions

1. Why does the MD CARE Act need updating?

The Muscular Dystrophy Community Assistance, Research & Education Amendments – or MD CARE Act – is a shining success story. Since its enactment more than a dozen years ago, this law has leveraged limited federal resources to catalyze efforts that have:

- Increased by about 10 years over the same period of time the average lifespan of patients with the most common form of the disease;
- Dramatically improved and standardized clinical care helping drive improved health outcomes; and
- Transformed a barren potential therapeutics landscape into one that today counts 32 potential therapies in various stages of clinical investigation.

As a result of the program's success, a growing number of individuals with all forms of muscular dystrophy are now living into adulthood. Recognizing this and to maximize the sizeable federal commitment made over the years, targeted improvements need to be made to ensure the law is focusing on the most critical areas such as:

- **Research:** Expanding and sustaining research efforts across the muscular dystrophies including a greater emphasis on cardiac and pulmonary functioning and on the health care needs of adults with muscular dystrophies
- **Care Standards:** Updating existing Duchenne-Becker care standards, developing for the first time care standards for adults living with Duchenne and developing and disseminating care standards for those with other forms of muscular dystrophy
- **Surveillance:** Intensifying surveillance and tracking of all the muscular dystrophies and ensuring that this valuable data informs the biomedical research agenda
- **Adult Support:** Supporting adults with Duchenne and other forms of muscular dystrophy so they can live independent, productive and rewarding lives

2. Do you see the FDA as being a helpful partner or an impediment to progress?

We have been encouraged by the level of engagement the FDA has shown by their participation in the PPMD hosted policy forum this past December, the agency's willingness to meet with the muscular dystrophy community to discuss our views on the benefits and risk we're willing to

assume, and most recently, the invitation to develop a Duchenne draft guidance which was submitted to the agency in late June.

With regard to barriers, the most significant at this time would be the speed of FDA review of products. While FDA has multiple tools at its disposal, including new or strengthened tools provided via the FDA Safety and Innovation Act, our community shares the concerns of many regarding their limited use, particularly in spaces outside of cancer and HIV/AIDS. Challenges would include a dearth of clear guidance to industry in planning and implementing trials, particularly in small rare disease populations, a lack of flexibility around what is required to validate a surrogate endpoint in rare disease, and a benefit/risk paradigm that does not put enough weight on the risk of inaction. Such skewing is particularly troubling given a disease like Duchenne that lacks any disease-modifying treatments and is always fatal.

It has become clear to us that these challenges have at their root an ingrained culture at the FDA that simply does not account for the realities of a rare, progressive pediatric disease. Yet we remain hopeful that our efforts to quantify these issues through our benefit/risk study and our draft guidance can help evolve this perspective, and we have been encouraged by the agency's receptivity to both.

Finally, another challenge to FDA is significant under-resourcing of the agency.

3. What more can Congress do on this issue?

First and foremost, Congress must continue to support a robust biomedical research enterprise at the NIH and ensure adequate funding is available to advance our understanding of diseases we know little about, conditions that often fall into the rare disease category. Congress can also support programs and initiatives that span multiple institutes or centers while ensuring that all of the research is appropriately coordinated. Duchenne research, which is funded by multiple institutes, demonstrates that effective coordination via the Muscular Dystrophy Coordinating Committee is vital to avoid inefficiencies and duplication. Continuing to publicly report estimated and final levels of funding allocated to each disease is helpful and ensures continued transparency.

Congress should also look at some of the lessons learned elsewhere and apply them as appropriate to the biomedical research space. For example, the Defense Advanced Research Projects Agency or DARPA is widely regarded as an extremely effective entity for cracking high-risk but high-reward research questions. Developing more partnerships between NIH and DARPA, as well as other innovative approaches, may be warranted going forward.

Rep. Lance's Questions

- 1. In the first panel I questioned Dr. Woodcock on the effectiveness of ClinicalTrials.gov. I would like to get your thoughts on the effectiveness of ClinicalTrials.gov. Is this**

something any of you use as a resource? What can be done to improve the site and what role can it play in modernizing clinical trials?

PPMD does use clinical trials.gov, which provides timely information for families interested in participating in clinical trials and is easily searchable. Like most any database, it is not perfect and must be refined continually over time to provide interested patients and caregivers with the necessary information in an accessible format without being overly burdensome. One suggestion would be to list trials in chronological order, with the most recent listings appearing first. Doing so would more easily spotlight new potential trials. Another suggestion would be to separate or differentiate trials that are currently active from those that are no longer recruiting or that are complete or terminated. Additionally, the site should more carefully consider or more clearly define certain key terms. For example, in studies where “results” are listed as available, parents may interpret the term “results” as pertaining to the outcome in terms of positive or negative and next steps, rather than the general description and statistics of the study.

For the Duchenne Community, PPMD operates DuchenneConnect, a patient/caregiver registry that began in 2007 with funding from the CDC. Since 2011, it has been funded entirely by PPMD. The registry includes data on about 3,000 patients and is a community resource, offering educational materials, information about upcoming and recruiting trials, and access to a genetic counselor. Sponsors of clinical research use DuchenneConnect for feasibility planning, study recruitment, and communicating updates and results. Last year alone, the registry was used to recruit for a dozen clinical trials.

2. It was clear from our discussion that more needs to be done to increase patient engagement in the clinical trial process. Will you walk me through the process for recruiting and selecting patients for clinical trials? What information is provided to patients? How can researchers and physicians make patients more comfortable with participating in clinical trials?

Duchenne is rare disease, with a small patient population which makes recruiting the appropriate number of boys that meet the clinical trial criteria quite difficult. This is all-the-more challenging because Duchenne is not homogenous but rather multiple mutations at different points along the gene, and some of these mutations are ultra-rare. Additionally, most trials rely upon the six-minute-walk test as the primary outcome measure of success, which means non-ambulatory boys are unable to participate in such studies.

The Duchenne Community wants trials that are inclusive of people with Duchenne of all ages across the spectrum of the disease. Such decisions are up to the sponsors of the trial, yet the FDA can play a role here by providing guidance on this and other important issues that would embrace more inclusive or flexible trials designs. In addition, sponsors should pre-specify plans for extension studies as well as their interest in permitting access via expanded access or compassionate use. In specific instances where families have more than one child with

Duchenne and only one of the children fit the inclusion criteria, sponsors should be required to agree to include the other child or children once safety is established.

As mentioned above, the DuchenneConnect educates patients and caregivers who want to participate in clinical research about these issues. This platform allows for targeted messaging and reduces concerns about sending patients and families unwanted information or requests for participation. In addition, sponsors receive anonymous feasibility information about – and can deliver their recruitment materials to – a community that wants to participate in such projects.

Additionally, many families have shared their experiences in clinical trials (including their decision-making process, perception of benefits and satisfaction levels) with PPMD through a study funded by the NINDS. Understanding the decision making process and clinical trial experiences allows PPMD to advocate for regulatory changes, protocol flexibility and communication approaches that meet needs identified by participants and to improve the process for future participation. We have also learned through focus groups with Duchenne trial sponsors what specific challenges they see in conducting trials in this space, including the need to aggregate trial data in a central repository, the use of a central institutional review board and provide better resources and training for trial site administrators.

Finally, the draft guidance referenced earlier includes a detailed section on clinical trial design, outcome measures and considerations. This section addresses barriers to clinical trials such as inclusion criteria, the need to validate existing patient reported outcome measures, and the Duchenne Community's desire to move away from placebo-controlled trial. This guidance, if adopted by the agency, has the potential to change the landscape of Duchenne clinical trials, and quite possibly other rare diseases that encounter similar challenges.