Parent Project Muscular Dystrophy

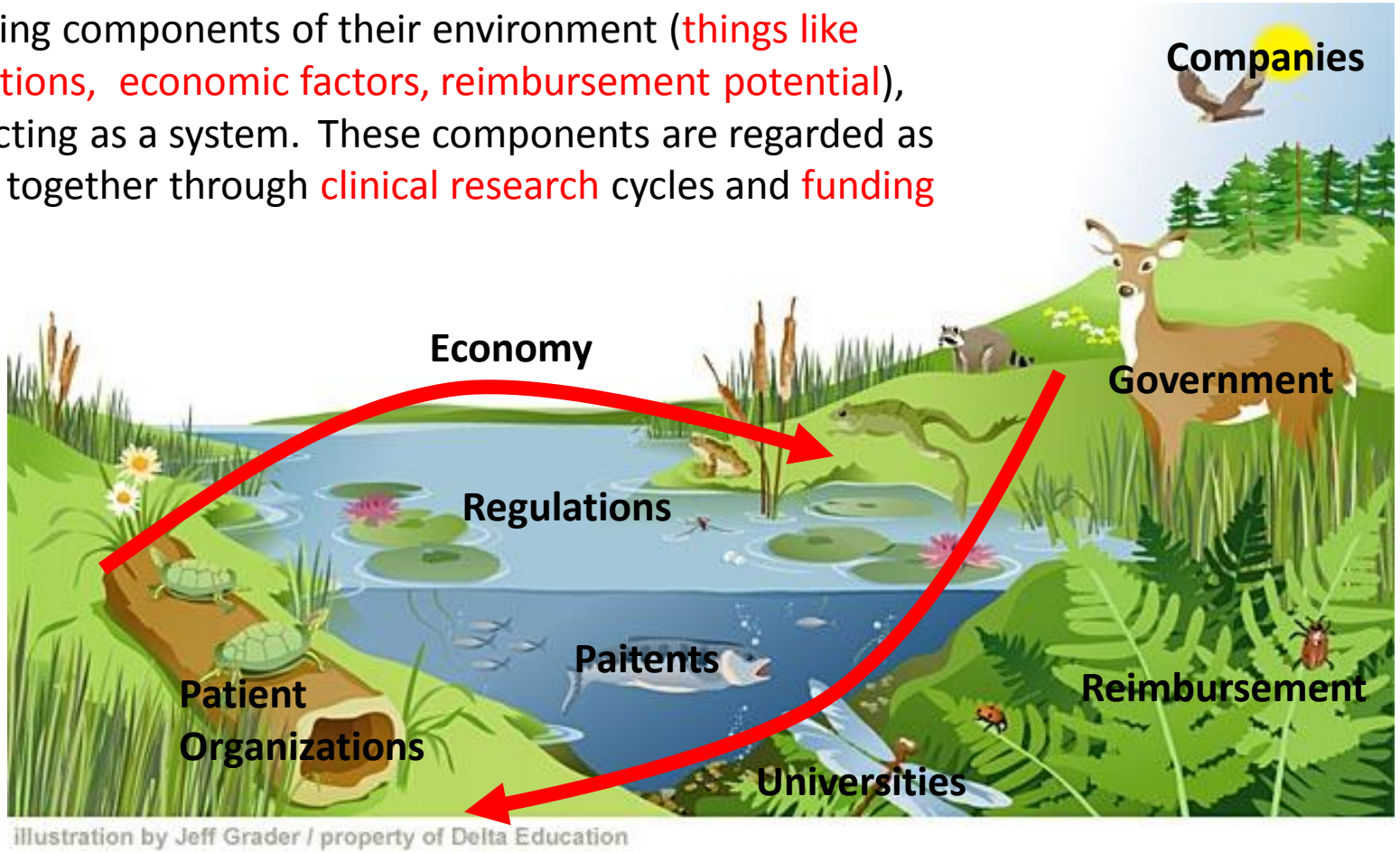
LEADING THE FIGHT TO END DUCHENNE

**The (im)Perfect Advocacy Organization**

Pat Furlong

# Why are we here?

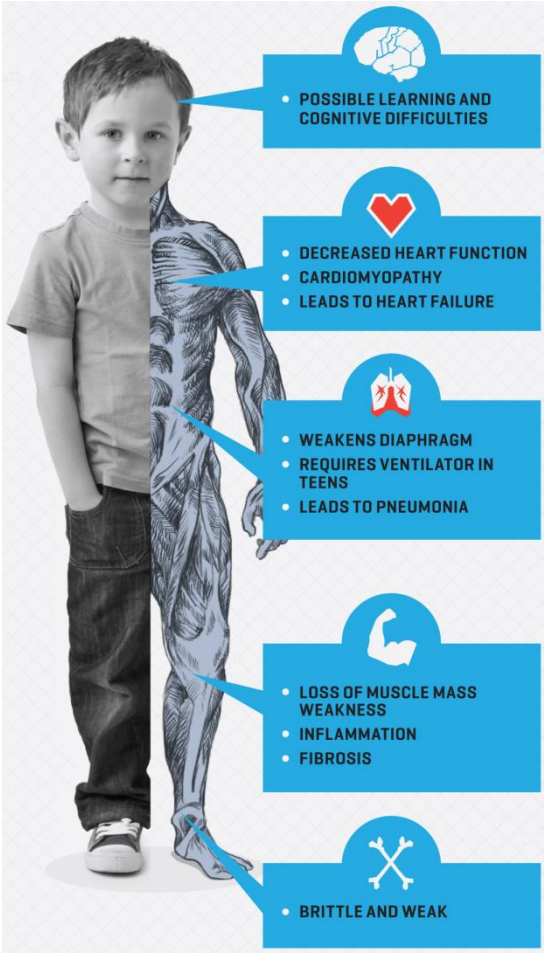
A drug development **ecosystem** is a community of stakeholders (universities, companies, patient organizations, patients, government organizations) in conjunction with the nonliving components of their environment (things like regulations, economic factors, reimbursement potential), interacting as a system. These components are regarded as linked together through clinical research cycles and funding flows



# About Duchenne Muscular Dystrophy

- X-linked, pediatric neuromuscular disease (onset in early childhood)
- Incidence 1:4600 boys (30% spontaneous)
- Predictable course
- Progressive loss of function
- 100% lethal

# Not just a muscle disease



Patient organizations
43 DMD specific in the US
Duchenne in Europe, Australia, Israel, Brazil, Mexico, S. Africa, India, soon China and Japan

Historical role of patient organizations was to bring peer sufferers together.
**The position from patient(organization)s has changed from 'sufferers' and users of care to PARTNERS in care, research and drug development**

# White Paper

- **Parent Project Muscular Dystrophy:**
- **Advisory Committee on Policies to Promote Responsible Access to New Therapies**

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**President EveryLife Foundation**

**H. Lee Sweeney, PhD**
Director, Center for Orphan Disease Research

**Susan L. Weiner, PhD**
Founder and President
Children's Cause for Cancer Advocacy

:

***Putting Patients First:***

***Recommendations to speed responsible access to new therapies for Duchenne muscular dystrophy and other rare, serious and life-threatening neurologic disorders***

To fully realize the potential to speed responsible access to new therapies for Duchenne, the FDA should:

1**. Expand the use of accelerated approval for therapies intended to treat rare diseases**, including Duchenne muscular dystrophy.

2. **Issue clear guidance outlining the level of evidence required for the use of surrogate endpoints in order to expand the scope of acceptable endpoints**, including novel surrogate and intermediate clinical endpoints, used to approve drugs for serious or life-threatening diseases with unmet medical need.

3. **Pilot the use of adaptive approval** for serious and life-threatening disorders with significant unmet medical need, using existing authority under current law.

4. **Give greater weight to the demonstrated benefit/risk preferences of patients, as well as caregivers in the case of pediatric illness**, when making risk benefit determinations. Subpart D considerations must be evaluated here, yet benefit/risk should also be addressed within the context of patients living with Duchenne.

# A caregiver's perspective

*"When it comes to terminal illnesses [the FDA's] job should be to make sure a product is safe and that the risks and benefits presented by the producer are accurate. Our job should be to determine, given all that information, whether to give it to our children. It is an intensely personal decision that involves the parents and the child with Duchenne."*

Source: **Parent of an individual with DMD**,

PPMD "Tell your story"

# DMD caregiver survey

- To promote **patient-centered drug development** in the area of DMD, PPMD conducted a national survey caregivers of a child with DMD.
- To quantify **treatment preferences** of caregivers of a child with DMD for the potential benefits and risk of potential treatments we utilize a cutting edge stated-preference method: Best-Worst Scaling (BWS)
- In our BWS experiment, we presented caregivers with **potential treatments** (profiles) and asked them to select the best and worst features.
- Features included **benefits, risk and other characteristics** of potential treatments

# Community-centered research

- PPMD led the study, guided by an **advocacy oversight team** comprising PPMD staff members who collaborated with the **research team** to design and implement the study.
- The broader DMD community was engaged to develop the survey (clinicians, sponsors, families).
- The oversight team made **study-related decisions** through a consensus process.
- Contributing authors included **PPMD staff** and academic collaborators from **Johns Hopkins**.

# Treatment preferences

- A pool of **treatment features** (attributes) identified and refined in consultation with parents, clinicians, and industry
- **Six attributes** were chosen to cover the potential benefits, risks and other features, each varying across **three levels** each.
- A main-effects orthogonal array was used as the basis of the **experimental design** - identifying 18 potential treatments that systematically varied across the six chosen attributes.

# Attributes and levels

- **Effect on muscle function** (none, slows, stops)
- **Gain in expected lifespan** (none, 2, 5 years)
- **Post-approval information** (none, 1, 2 years)
- **Nausea** (none, loss of appetite, loss of appetite and occasional vomiting)
- **Risk of bleeds** (none, risk of bleeding gums and increased bruising, risk of hemorrhagic stroke)
- **Risk of heart arrhythmia** (none, risk of harmless heart arrhythmia, risk of dangerous heart arrhythmia and sudden death)

# Conclusions – Treatment priorities

- Within the context our preference experiment:
  - Stopping/slowing the **progression of muscle weakness** accounted for the largest proportion of the variation.
  - The presence of a serious **risk** could be compensated for by a treatment that stops/slows progression to muscle function.
  - **Nausea** was viewed negatively, but not nearly as negatively as a risk for a serious health event.
  - Caregivers *marginally* valued **post-market data**

# Overview

We have continued to engage the FDA to demonstrate our approach as a model for **advocacy-academia partnerships** in promoting patient-centered drug development:

- The work of PPMD
- Meetings with the FDA
- FDA policy forum
- Drafting FDA guidance for industry

# Other Impact…

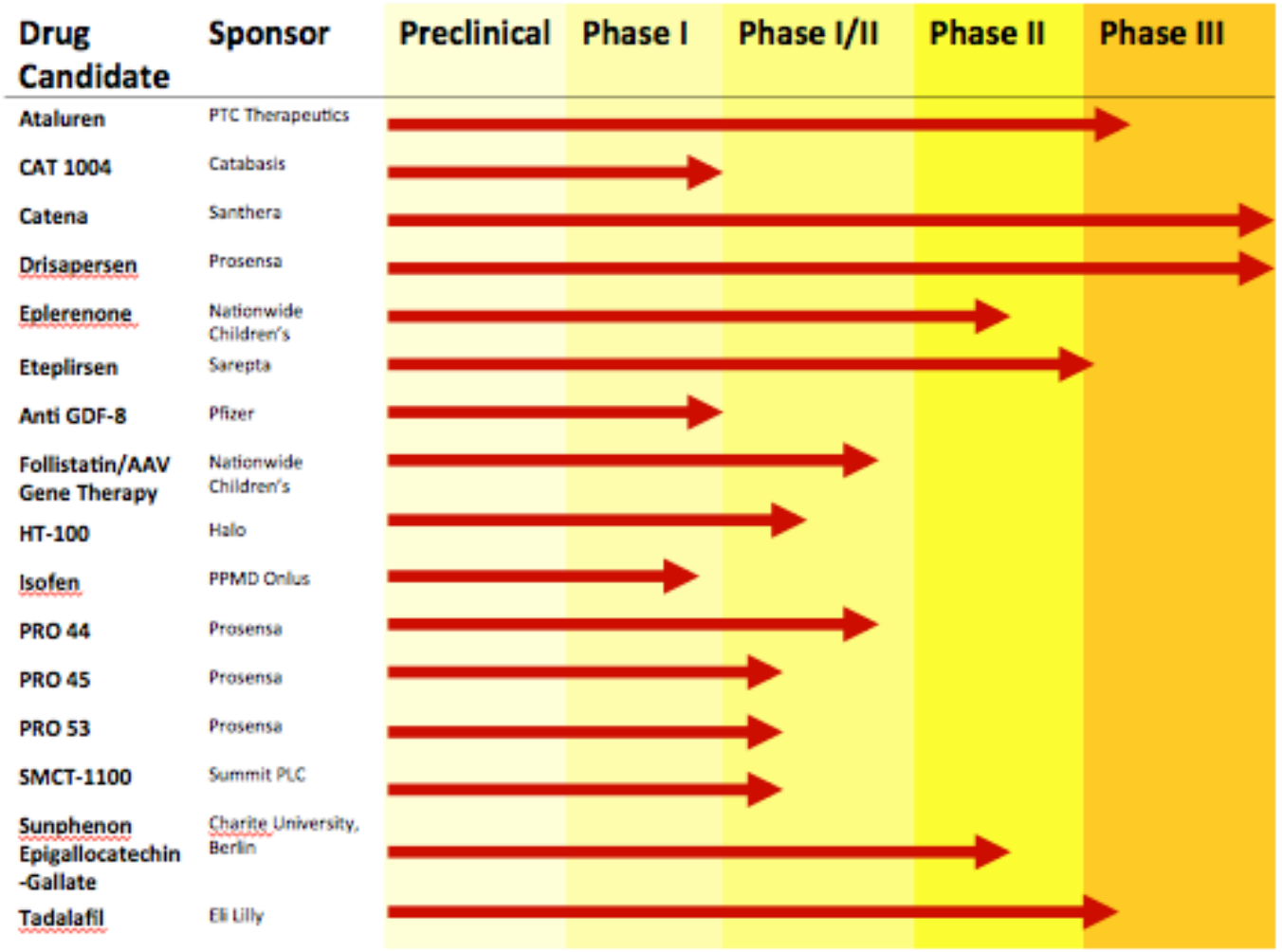
The appropriations bill that funds the FDA includes:

*"**Duchenne Muscular Dystrophy**—The Committee commends the collaboration between FDA and the Duchenne Muscular Dystrophy community to advance useful regulatory tools for benefit-risk considerations in this disease population and drug development guidance. The Committee supports the agency's engagement with the patient population for these purposes and to enable the appropriate use of regulatory flexibility as provided in FDASIA."*

-House Committee on Appropriation

# Why Would the Duchenne Community Develop a Guidance for Industry?

# A Drug Development Pipeline in Duchenne Full of Potential



# And yet, in 2013, there had been some setbacks

- **Ataluren seemed to be in regulatory limbo (in 2014 Conditional Approval in Europe)**
- **A couple drugs were halted or held up because of side effects in human or animal studies**
- **Disappointing trial results were announced on drisapersen—a drug that previously had been granted 'breakthrough therapy designation'**
- **Eteplirsen's NDA was reportedly to be held up due to questions about the use of dystrophin quantitation as a biomarker**

# Why Would the Duchenne Community Develop a Guidance for Industry?

- **The understanding of the Duchenne natural history, biomarkers and appropriate clinical endpoints was evolving alongside drug development process**
- **Danger that if pharmaceutical companies felt regulatory goal posts kept moving they might leave field**
- **Community felt that the FDA wasn't taking their experiences/preferences into consideration**
- **Rare childhood neurologic diseases cannot be held hostage to conventional regulatory policy and procedure**

# EMA Develops Draft Guidance For Duchenne & Becker MD

- **Important first step, but…**
  - Had been drafted without community consultation
  - The community, and its scientific experts, had a number of problems with the guidance
- **The Duchenne community in Europe held scientific meetings — inviting academic and industry experts, regulators, parents and patients to discuss to improve guidance**
- **The Duchenne community provided the EMA with their feedback, and that guidance is being revised**

# FDA Engagement

- **PPMD had been meeting with the FDA**
- **Asked FDA to draft guidance for Duchenne**
- **Agency said it couldn't, but invited community to develop draft guidance and submit it for FDA's consideration**
- **FDA worked with community to develop Duchenne Policy Forum**
  - 19 FDA officials in attendance
  - 200 stakeholders- research, clinical, patients, caregivers, industry

**Agreement with agency that the Duchenne community would create draft guidance on Duchenne

# Draft Guidance on Duchenne

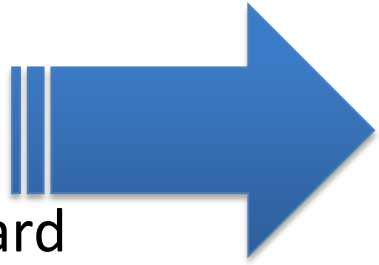
- Draft guidance submitted to FDA docket June 25th
- Community engagement throughout process
- Historic/unprecedented undertaking by a patient community

**<u>Overall Structure</u>**

Steering Committee

Working groups
over 80 stakeholders

Community Advisory Board



# Organizational structure

| Expertise | Steering committee members | | |
|---|---|---|---|
| | Name | Title | Affiliation |
| Industry Representative | Lawrence Charnas, MD, PhD | Medical Director | Shire |
| Policy Specialist | Tim Franson, MD | Principal | FaegreBD Consulting |
| Patient Advocate | Pat Furlong | Founding President, CEO | PPMD |
| Patient Advocate | Neera Gulati, MD | Family Medicine | Suneel's Light Foundation |
| Scientific/Clinical Expert | Craig McDonald, MD | Director Neuromuscular Disease Clinics | UC Davis Health System |
| Scientific/Clinical Expert | Lee Sweeney, PhD | Director, Center for Orphan Disease Research and Therapy | University of Pennsylvania |
| Academia | John Bridges, PhD | Associate Professor | John Hopkins University |
| Scientific/Clinical | Kevin Flanigan, MD | Neurologist | Nationwide Children's |

# Guidance Working Groups

| Working group topic | Working group chair | Title | Affiliation |
|---|---|---|---|
| #1: Benefit/risk analysis | John Bridges, PhD | Director of the MHS in Health Economics, Department of Health Policy & Management | Johns Hopkins Bloomberg School of Public Health |
| #2: Diagnosis | Kevin Flanigan, MD | Professor | Nationwide Children's Hospital |
| #3: Natural history | Craig McDonald, MD | Director Neuromuscular Disease Clinics | UC Davis Health System |
| #4: Biomarkers I Molecular genetics and Muscle Biopsy | Justin Fallon, MD | Program Director, Neurogenetics Cluster | National Institutes of Health |
| #5: Biomarkers II MRI; Serum; Urine | Lee Sweeney, PhD | Director, Center for Orphan Disease Research and Therapy | University of Pennsylvania |
| #6: Clinical trial designs & outcome measures | Lawrence Charnas, MD, PhD | Medical Director | Shire |
| #7: Imperatives | Pat Furlong | Founding President, CEO | Parent Project Muscular Dystrophy, Parent |

# Support Team

## Professional Writer

**Theo Smart**

*Medical Writer*

HIV/TB treatment activist and treatment journalist

## Project Management

Mark Krueger & Associates, Inc.

Mark Krueger, MPH- President
Project Coordinator - Pritha Kuchaculla

## Regulatory Consultation

Tim Franson, MD- Faegre BD

# Community Advisory Board

**Patient and Parent Reps, and Foundation Representatives**

# Duchenne Drug Develop Panel

**Industry were provided with an opportunity to provide input on the usefulness of the guidances to sponsors**

# Guidance for Industry

# Duchenne Muscular Dystrophy

# Developing Drugs for Treatment over the Spectrum of Disease

# Community Imperatives/ Cover Letter for Guidance

Industry

- Trials should be inclusive of people with Duchenne of all ages and disease stage
- Move away from placebo-controls or to use trial designs that minimize exposure to placebo

FDA

- Consider the benefit risk preferences of the Duchenne community when evaluating potential therapies
- Encourage the agency to use maximal flexibility when reviewing future NDA applications.

**Guidance submitted to the FDA June 25th 2014**

# What next?

**FDA docket. Comment period closed 10/6/14**

**Meeting scheduled with FDA to discuss Phase 2 benefit/risk and when we might anticipate FDA's release of guidance**

**Continue to strongly urge the FDA and EMA** on need for flexibility in review

# Dr. Janet Woodcock Quote

*"We share your goal of getting disease-modifying therapies onto the market as rapidly as possible. We understand 'the clock is ticking' for the kids and for the community. We understand the urgency"*

**- Dr Janet Woodcock,**

**FDA Director**

**Center for Drug Evaluation and Research (CDER)**

***December 2013, PPMD Policy Forum***

# Consider: Patient Dilemma

- One shot on goal –clinical trials typically 48 weeks. Extension phase ? Analysis. Approval = 3 years of a patient's life
- Burden of participation and next steps
- Impact of Social networks
  - Phase II study. 12 patients
  - Sub-study – MRI
  - Closed FB account
  - Analysis of results