Lessons Learned from Duchenne Regulatory Submissions

John D. Porter, Ph.D.
Chief Science Officer
Myotonic Dystrophy Foundation
(john.porter@myotonic.org)

MYOTONIC DYSTROPHY FOUNDATION

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Learning from Clinical Trials

Clinical trials primarily fail due to safety

Need a step-wise approach to de-risk trials (go/no-go decision points for safety/efficacy at all stages)

The only *truly failed* trial is a trial that we learn nothing from, & thus fail to improve patient health & design of the next clinical trial

Take Home: Essential to extract lessons learned from each clinical trial so that the massive efforts of the entire community are not wasted

Duchenne DYS Upregulation Programs

- **PTC Therapeutics**
  - EMA conditional marketing authorization (subject to Ph 3 data)Ph 3 with Genzyme (DB, P-C), failed 1° endpoint (6MWT)
  - FDA Refuse-to-File letter
- **BioMarin**
  - Ph 3, Prosensa/GSK, (DB, P-C) failed 1° endpoint (6MWT) plus safety
  - FDA Complete Response Letter
  - EMA informal feedback on intent to issue a negative opinion
- **Sarepta Therapeutics**
  - Ph 2b (DB, PC) 1° endpoint: % DYS+ fibers; sponsor & FDA differ on outcome
  - NDA filing based on *post hoc* analysis of open-label study (6MWT; major data for NDA was from non-PC studies)
  - Apr 2016 FDA AdComm negative recomendation; FDA decision pending

Understand Tractability

- **Lesson**: Can't wait for complete mechanistic understanding, but unresolved, key gaps in disease basic science can be disruptive
- Do you understand the loss- or gain-of-function & downstream cellular mechanisms to move forward?
  - Differential stability/functionality of skipped DYS
  - Genetic modifiers (SPP1, LTBP4)
  - Other functions of DYS
- A failure to understand the biology can negatively impact both candidate therapeutic rationale & clinical trial design

Rationale for Trials: Preclinical Efficacy

- **Lesson**: Understand & take what the preclinical models give you, but don't ignore or magnify their lessons
- DMD models affirmed the linkage between DYS levels/ distribution & functional benefit
  - Studies in mdx established both dose-response and PK/PD relationship
- Problem: the mouse 'doesn't have the disease' (see Dubowitz, V) & increases in DYS didn't translate
- Decision: understand mouse endpoint value; substantive level of effect >> simple statistical significance

FDA on DYS Quantification*

- 'Sample heterogeneity (intra & inter-patient/muscle); lack of high & consistent sample quality; lack of a reference standard' (e.g., purified DYS protein)'
- 'Need to test functionality of new [skipped, read-through] DYS'
- 'Inability to distinguish between revertant & drug-induced DYS'
- 'Need for robust assay reproducibility in a linear range & at very low levels of quantification'
- 'Co-expression of genes with potentially redundant functions (e.g., utrophin)'
- **Lesson**: Biomarkers essential in getting early signal of efficacy (see BIO); FDA biomarker qualification programs need to be pursued

*BioMarin Ad Com; similar in Sarepta Ad Com

Level of Effect

- **Lesson**: Limited level of effect is problematic for development programs
- Restoring DYS targeted by the 3 programs; preclinical & BMD data directly link DYS levels to functional outcomes—with low DYS, linkage not seen in trials
- Effect limited by adequacy of dosing/delivery—dose levels in trials < preclinical efficacious dose; dose-limiting toxicity & costs hindered full exploration of dosing; better exposure via improved backbone chemistries needed
- Acknowledge sampling errors with small biopsies from one of many muscles
- DYS levels in trials (FDA: 'trace' by WB) were variable & far below need established by mdx studies & BMD patient analyses
- By IHC, DYS distribution in trials limited to 'pockets' of fibers; Low DYS levels/ distribution make open label studies & post hoc re-analysis of functional data difficult for FDA to accept

Clinical Operational Readiness

- **Lesson**: Ensure sufficient trial readiness (understanding of the patient population, tool availability/validity, & capacity to conduct clinical trials) in order to facilitate design & decision making
- Do you have sufficient understanding of the patient population?
  - Limited natural history (progression patterns & heterogeneity) negatively impacts trials
  - Failure to share/consolidate (CPI model) silo'ed data, slowed progress
- Is system in place to manage samples/evaluate biomarkers, control for bias, & account for the sensitivity/specificity of analytic tools?
  - Handling of biopsy material
  - Assay reagents/methodology; including independent/blinded analyses
  - Value of qualified biomarkers
- Is GMP manufacturing capacity sufficient for an adequate trial size (adequately powered)?

Clinical Trials 1

- **Lesson**: Doing things in a hurry can delay, rather than accelerate, a definitive regulatory outcome (e.g., DMD vs. SMA)
- FDA legally requires 'adequate and well-controlled trials"
- In trial design, attention to sample size & control/comparator populations is critical
- Problem of un-blinding by social media
- Limitations of post hoc analysis
- Notable differences between FDA and EMA (particularly conditional approval with rapid pull back with EMA)

FDA on Natural History Controls*

- FDA ICH E10 Guidance; design limitations:
  - 'Inability to control bias is the major & well-recognized limitation, & is sufficient in many cases to make the design unsuitable'
  - 'It is always difficult, & in many cases impossible, to establish comparability of the treatment & control groups'
  - 'It is well documented that untreated historical-control groups tend to have worse outcomes than an apparently similarly chosen control group in a randomized study'
  - 'An external control group is often identified retrospectively, leading to potential bias in its selection'
- **Lesson**: Every therapeutic candidate needs a comparator; the key question is which comparator; understand nat hist limitations

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Clinical Trials 2

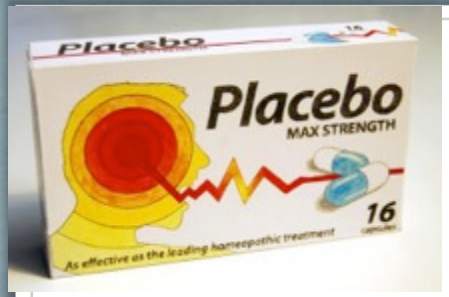
- **Lesson**: Registration endpoint, study group choices & implementation strategy need to be objective & clear
- Plan to evaluate outcome that is clinically meaning to patient
- 6MWT endpoint difficult—poor reliability, non-linear progression & susceptible to motivation; need for other endpoints (other timed function or respiratory?); loss of ambulation call to exclude = 'subjective'
- Standardized protocols essential (site to site variability problematic)
- Potential biases in endpoint measure protocols need to be recognized
- FDA wasn't as 'directive' on endpoints as assumed

FDA on Trial Design

‘I would prefer seeing randomisation very, very early" in the drug testing process, Woodcock remarked, adding "even if there's a small, tiny effect, it may be meaningful to that patient population. If they can show there is definitely a small effect in a terrible disease, we will approve that drug.’

FDA Feedback

- **Lesson**: Essential to work with FDA & EMA to facilitate the controlled studies needed for clear answers; Regulators legally constrained on public comments—sponsor's communication must be transparent & clear
- FDA consistently advised for P-C trials & for pre-defined analytic strategies in DMD; strategy of accelerated approval with limited data/analyses not pre-defined can delay drug approvals
- FDA has stated 'flexibility' granted them in FDASIA is for indications with unmet need; understand that flexibility is in *interpretation of science*, not in *circumventing need for scientific evidence* (regulatory bar has not gone down)



Final Thoughts

- Were DYS-targeted drug candidates sufficiently de-risked at each stage of development? Assays & data independently validated? Candidate & dose fully optimized? Need to mitigate well-known reasons for many clinical failures!
- For DM:
  - Develop adequate preclinical rationale
  - Optimize endpoint selection & trial design
  - Biomarkers/PD markers, existence & technology, are essential
  - Attend to level of effect (go/no-go)
  - Mitigate therapeutic misconception
  - Appreciate the impact pushing poor rationale, trial design, & weak data may have upon progress in the disease