



Selected Perspectives on Drug Development: Program Goals and Intermediate Elements

Challenges in Drug Development for Muscle Disease
August 2005

Marc K. Walton, M.D., Ph.D.


Director

Division of Biological Therapeutic Internal Medicine Products
ODE-6, CDER, FDA





Perspectives on Drug Development

- Goal of development programs
 - Challenges of First in Disease development programs
 - Role of Phase 2 Studies
 - Efficacy: Concept and Assessment
- 




Ultimate Goal

- Approved, Marketed, Available Therapy
 - Safety
 - Effectiveness
 - Favorable Risk-Benefit Assessment
 - Adequate Directions for Use
- 




Intermediate Steps

- Reasonably safe clinical studies
 - Effective clinical studies
 - ✦ Reliable information
 - ✦ Interpretable information
 - Efficient clinical development program
 - ✦ Studies not designed or used as isolated events
 - ✦ Studies combine to form a development program
- 




Safety

- Understanding the adverse events that may occur during or after period of use of drug
 - Nature and Frequency of expectable AEs
 - ✦ Both drug-related and drug-unrelated events
 - ✦ Including drug-related frequency for AE with a background rate
 - Sufficient depth of information to decide
 - ✦ To use drug or not
 - ✦ How to monitor patients using the drug
 - ✦ How to respond to patients who experience an AE
- 




Efficacy

- Establish nature of benefits that occur
 - ✦ Particularly with sustained use
 - ✦ Avoid extrapolation beyond actual use experience
 - Size (importance) of benefit that is provided
 - ✦ Individual patient effect
 - ✦ Population (group) effect size
 - ❖ Ultimately still need to relate to an individual patient's experience
- 




Adequate Directions for use

- Who to use drug in
 - ✦ What patient characteristics allow expectation of favorable risk-benefit
 - How to administer drug (dose, regimen)
 - How to monitor patients during use
 - How to manage AE occurring during use
 - How to decide when to discontinue use
- 




Challenges of Developing First in Disease Treatments

- Greater challenge than First in Class Treatments
 - No established paradigm to follow for disorder
 - ✦ Which patients capable of benefiting?
 - ✦ Which types of benefits feasible to obtain?
 - ✦ What is time course of achieving benefit?
 - ✦ What is time course of natural disease progression?
- 




Which Patients to Study

- Range of disease severity
 - ✦ Patient clinical status at time of study start
 - ✦ Patient prior disease course
 - Criteria for identifying disorder
 - ✦ If changed over time, patient population changes
 - ✦ Method(s) of diagnosis
 - Population studied likely to appear in regulatory labeling
 - ✦ May describe the appropriate population to treat with new drug
 - ✦ Broad vs Narrowed population for development
- 




Types of Benefits Feasible to Achieve

- Distribution of impairments in patient population should be considered
 - Mechanism of impairment in relation to mechanism of drug effect
 - Potential for reversibility of specific impairments
- 



Time Course of Observing Benefit

- Many muscle diseases long duration disease
 - ✦ E.g. myotonic dystrophy, FSH MD, LGMD
 - Objective is a treatment which is effective over long term
 - ✦ May need to demonstrate sustained benefit by study continued for extended period of time
 - Time course of action of drug
- 




Time course of natural disease progression

- For many muscle disorders disability progression is slowly occurring
- Affects ability to observe a stabilization of patient status by an effective drug






Strategy: Decision Guiding Phase 2 Studies

- Multiple questions regarding each new potential treatment exist at start of development
 - Decisions on many factors are necessary during development
 - ✦ Dose
 - ✦ Regimen
 - ✦ Patient population
 - ✦ Place within existing armamentarium
 - ✦ Concomitant care
 - ✦ Type of benefit expected
 - ✦ etc.
- 




Strategy: Decision Guiding Phase 2 Studies

- Successful development may depend on correct choices
 - Substantive Phase 2 studies offer opportunities to gain sufficient information to guide decisions
 - Phase 2 most valuable if full range of uncertainties are recognized
 - ✦ Employed as opportunity to try out multiple options
 - ✦ Patient population
 - ✦ Regimen
 - ✦ Outcome assessment method
- 




Decision Guiding Phase 2 Studies

- Consequence is need to analyze Phase 2 data in detail prior to design of Phase 3 study
 - Improve selections:
 - ✦ Which potential treatments to move to Phase 3 study
 - ✦ How to study potential treatments
 - ✦ Greater success in Phase 3 studies
 - ✦ Lesser missed opportunity loss of useful treatments
- 




Efficacy: Concept

- Efficacy: an effect of direct clinical meaning (importance) to a patient in how they feel or function (including survive)
 - Generally must be an effect of value to the patient directly
 - Not an indicator of a pharmacologic action
 - ✦ Pharmacodynamic endpoints
 - ✦ Activity endpoints
 - ✦ Biomarker endpoints
 - Exception: Validated Surrogate
- 




Clinical Status Assessment Tools

- Methods to evaluate selected clinical features
 - Ideally sensitive and reliable
 - ✦ May be not readily available for some disorders
 - Development of new clinical endpoints may be needed
 - ✦ Improved tools may aid in identifying and proving new treatments
 - Variety of approaches conceivable (ADL scales, composites, etc.)
- 




Clinical Status Assessment Tools

- New tools require rigorous validation to serve as phase 3 primary efficacy endpoint
 - ✦ Validation requires effort and time, but may serve to improve therapy development
 - ✦ Meaningfulness
 - ✦ Reliability
 - ✦ Often requires explicit development program to formulate and validate new tools
 - ❖ Outside of drug development program
 - Less experience may be sufficient to justify use in phase 2 studies
- 




Biomarkers and Surrogate Endpoints

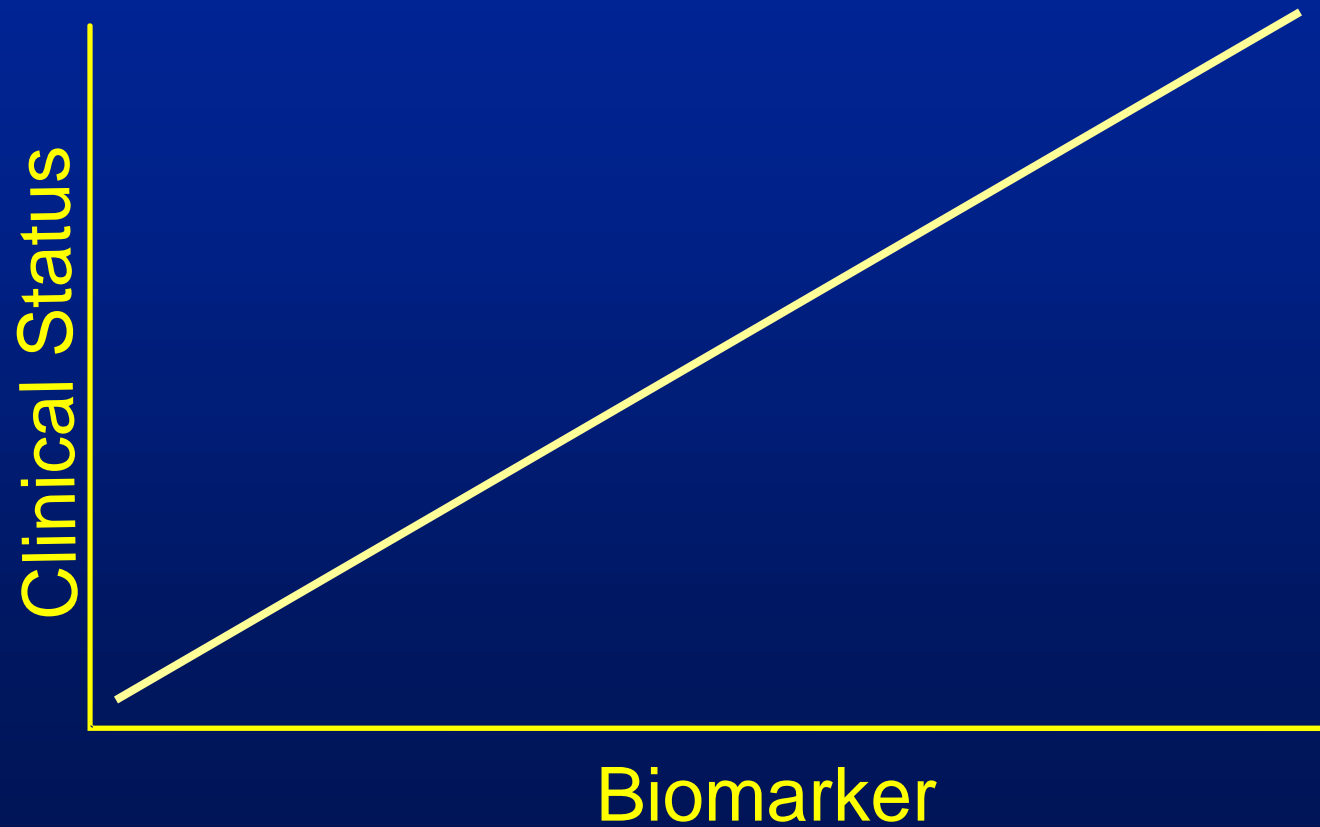
- Biomarkers may guide early decision making
 - ✦ Does not need to be rigorously validated, BUT
 - ✦ If inadequately linked to clinically relevant activity of product then may mislead
 - Surrogate Endpoints (as Phase 3 primary endpoint)
 - ✦ Conceptually attractive
 - ✦ Require advance validation
 - ✦ Validation difficult; may be limited to class of agent the validating data is derived from
 - ✦ Generally not feasible to validate a surrogate for the first effective therapy for the disease
- 



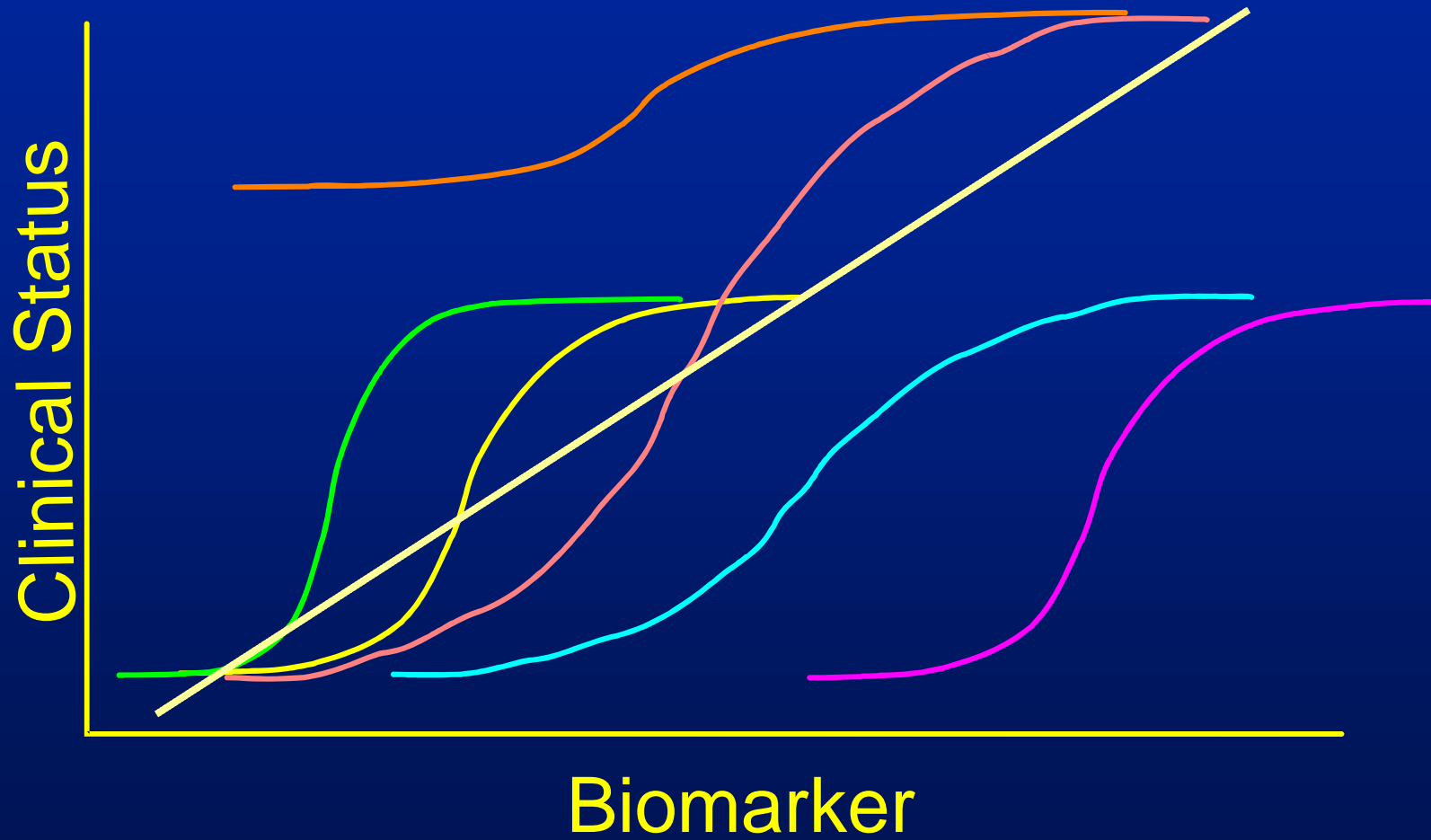
Biomarkers and Surrogate Endpoints

- Risk of selecting Biomarker/Surrogate which is unsuitable for a new treatment mechanism
 - Consider the quantitative biomarker/surrogate vs clinical relationship
- 

Surrogate Measure – Clinical Relationships



Surrogate Measure – Clinical Relationships





Summary

- Development programs complex & may be long
 - ✦ Absence of successful examples to follow
 - Tailor development program to specific agent
 - ✦ Study designs suitable for some agents, not others
 - Step-wise development important
 - ✦ Informative phase 2 studies prior to phase 3
 - ✦ Consideration of information gained prior to proceeding
 - Understanding both disease mechanism and natural course valuable for therapy development
- 