Dose Selection in Drug Development and Regulation: Possible Future Direction
Concluding Industry Thinking

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Concluding thinking:

- What have we learned from this meeting?
- What is the “elephant in the room”?
- Possible ways to move forward.

What have we learned in this meeting?

- Much learning, an excellent meeting of content
- The 20 year old ICH E4 guidance does discuss Dose vs. Response, same with FDA documents
- Regulators care about Dose Response as much as industry!!
- The regulatory legal approval bar is risk vs. benefit, not dose
- The body of science to establish dose vs. response is well established and rich, many excellent examples and methodologies for most therapeutic areas
- The targets and diseases are harder

Jose Pinherio and our key points:

- Selection of dose for Phase 3 is an estimation problem and should not be addressed via hypothesis testing
- Model-based dose finding methods are more efficient than pairwise comparisons approaches
- Wider dose/exposure ranges (> 10 fold) and larger number of doses/regimens (> 3) should be routinely used in Phase 2
- Adaptive dose-ranging approaches, when feasible, can lead to substantial efficiency gains (time, number of patients, etc.)
- *Longitude data analysis (time vs drug effect) is extremely powerful and should be used more.*
- Having adequate Phase 2 study (with model-based demonstration of efficacy) serve as one of pivotal trials could greatly encourage better dose selection practices

What is the dead elephant in the room?

- We have done the experiment spending over $40 billion or more on industry R&D
- Over the past 20+ years, there has not been a distinct, significant improvement of Dose selection overall.
- The people who design, fund and control Phase 2 and 3 programs are not in this room.
- The “confirm” mentality is a driver of development plans, less so for “learning”
- Dominant behaviors of simplicity in design/statistics, focus on cost, speed, size and most recent regulatory path

Possible ways to move forward:

- A need to engage a different segment of the drug development process to improve dose selection
- Health authorities can have the largest and most immediate impact to change late phase drug development and dose issues
- Create more specific guidance on dose issues
- Create better incentives in development
  - Dose response as confirmatory evidence with one Phase 3 clinical trial
  - Partnerships of industry, academia and regulators
  - Simpler articulation of quantitative concepts and tools