Pharmacometrics/Modeling and Simulation

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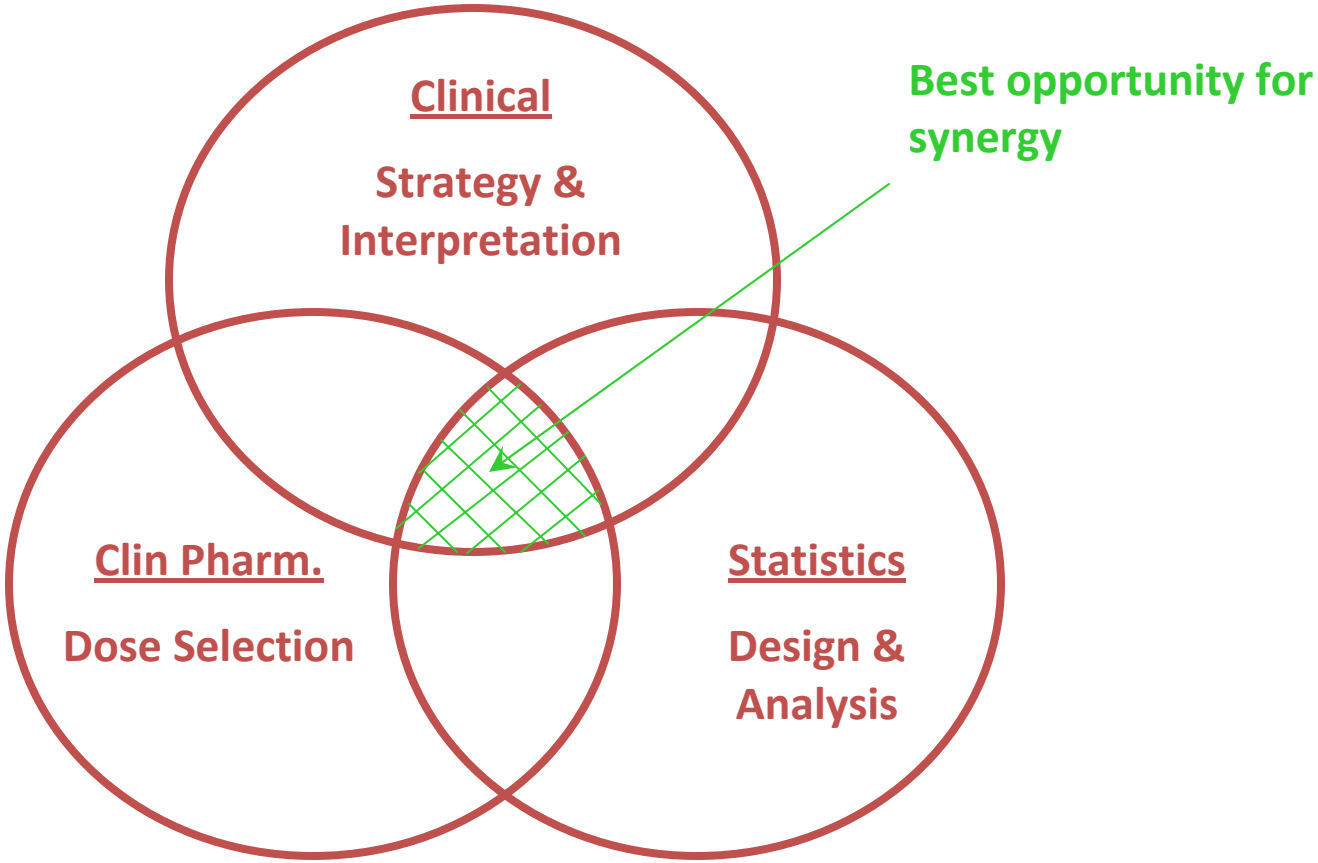
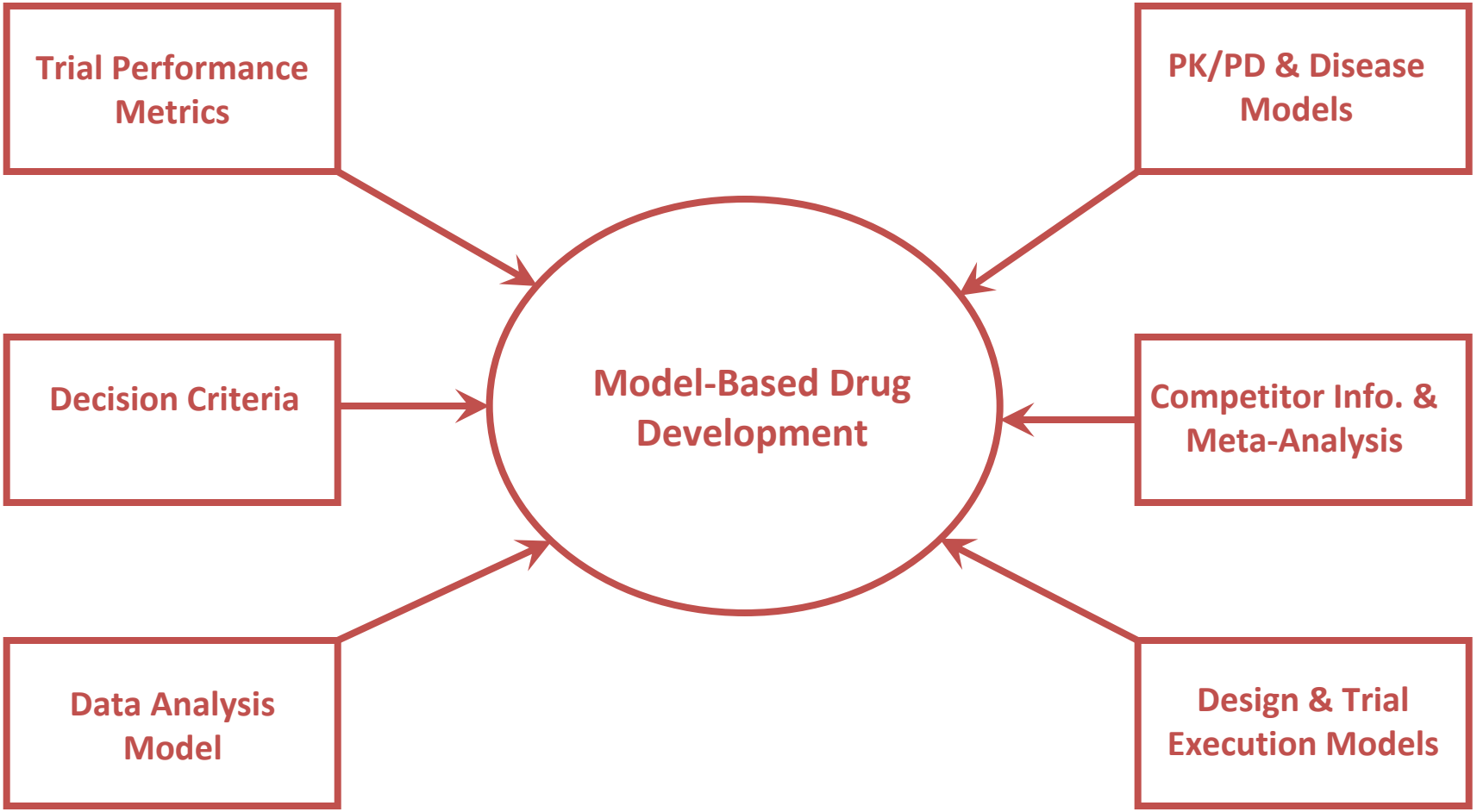
A Compartmental View of Clinical Drug Development



Kowalski, Ewy, Hutmacher, Miller & Krishnaswami, *Biopharmaceutical Report*, Vol 15, Summer 2007, pp 2-22.

A New Paradigm: Model-Based Drug Development



Kowalski, Ewy, Hutmacher, Miller & Krishnaswami, *Biopharmaceutical Report*, Vol 15, Summer 2007, pp 2-22.

Comments/Questions on Presentations

Pravin R. Jadhav, FDA

- Provided a general overview of the value of quantitative pharmacology to inform regulatory and drug-development decision-making
- The FDA's Critical Path Initiative and Pharmacometrics Group have played a major role in promoting model-based drug development activities both within the FDA as well as industry
  - Very receptive to novel M&S approaches leveraging contributions from pharmacokineticists, clinicians and statisticians

Comments/Questions on Presentations

Munni Begum, Ball State U.

- PBPK models tend to have more relevance in the preclinical setting.
  - May be useful for translation to humans when interspecies scaling based on body size is inadequate
    - e.g., when nonlinearity in the kinetics are species-dependent
- Even when PBPK models are identifiable, it is still a challenge to conduct experiments with rich enough information to estimate all the parameters of the system
  - Often blood flows are held fixed based on estimates reported in the literature for a particular specie
  - Partition coefficients and rate constants for certain tissues/organs may be estimated from other experiments (e.g., tissue distribution studies)

Comments/Questions on Presentations

Jim Rogers, Metrum Research Group LLC

- Longitudinal model-based meta-analyses pose numerous, challenging statistical issues
  - E.g., How do we account for correlation in treatment means over time when the only summary information provided in the literature are means, SDs and sample sizes?
    - If independence is assumed this can lead to estimates of standard errors that are too small.
- I applaud Rogers' and Gillespie's efforts to leverage patient level data to account for correlations across time when performing longitudinal model-based meta-analyses
  - Assumes correlation structure for the in-house patient level data is representative of the underlying correlation structure for all the studies reported in the literature used to obtain the meta-data
- Longitudinal model-based analyses offer numerous opportunities for statistical research
  - Perhaps a sensitivity analysis to alternative <u>assumed</u> correlation structures may be informative and lead to more robust decisions

Comments/Questions on Presentations

Chuanpu Hu, Centocor

- Promotes a confirmatory approach to population PK and PK/PD analyses
  - A Phase 3 pop PK example is provided
- There are many challenges to applying Hu's approach more broadly in pop PK/PD analyses
  - Iterative development/updating of a global PK/PD model versus development of separate "fit-for-purpose" PK/PD models
  - May be difficult to design a study to confirm/validate all aspects of a global PK/PD model which is continuously being updated as new data emerges
- Consider MBDD as a series of learn-predict-confirm cycles
  - Design studies to confirm the predictive performance of the model

Comments/Questions on Presentations

Kuenhi Tsai, Merck

- Proposes a CTS system to address many statistical issues in the design, execution and analysis of trial designs
  - Assumes empirical approach for data-generation models
    - Piecewise linear models
    - AR(1) process for repeated measures within a subject
  - Focus is on traditional design operating characteristics (e.g., power)
- Consider a broader application of CTS leveraging information from all three disciplines (statistics, clinical, and clinical pharmacology)
  - Use of pop PK/PD models are likely to be more informative and predictive than the authors' proposed empirical data-generation models
  - Focus on trial performance metrics such as probability of success (POS) and probability of a correct decision (POCD)
    - Integrate information regarding design OCs (e.g., power) with uncertainty in the predictions of effect sizes based on predictive models

References

1. Kowalski KG, Ewy W, Hutmacher MM, Miller R, and Krishnaswami,S. "Model-Based Drug Development – A New Paradigm for Efficient Drug Development." *Biopharmaceutical Report* 2007;15:2-22.
2. Lalonde RL, Kowalski KG, Hutmacher MM, Ewy W, Nichols, DJ, Milligan PA, Corrigan BW, Lockwood PA, Marshall SA, Benincosa LJ, Tensfeldt TG, Parivar K, Amantea M, Glue P, Koide H, and Miller R. "Model-Based Drug Development". *CPT* 2007;82:21-32.