

Current Position and Expectation for use of M&S in Drug Development and Regulatory Decision Making

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(on behalf of EFPIA workshop contributors)

Current Position and Expectation for use of M&S in Drug Development and Regulatory Decision Making

- Current position:
 - Challenge for Pharmaceutical Industry
- Expectation for use of M&S:
 - Opportunities for greater utilization of quantitative approaches
- Drug Development and Regulatory Decision Making:
 - Challenges for greater utilization of quantitative approaches

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Attrition Rates for New Drug Development Projects have grown across all R&D Phases from 1990 to 2004

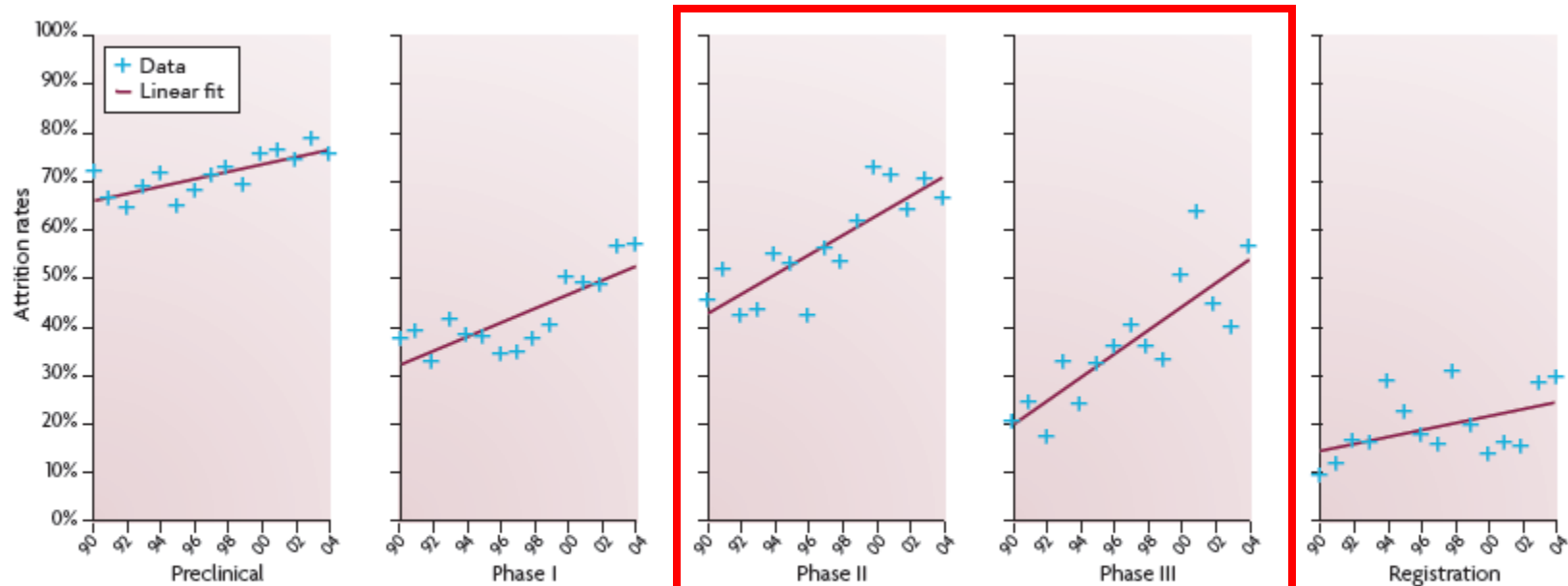
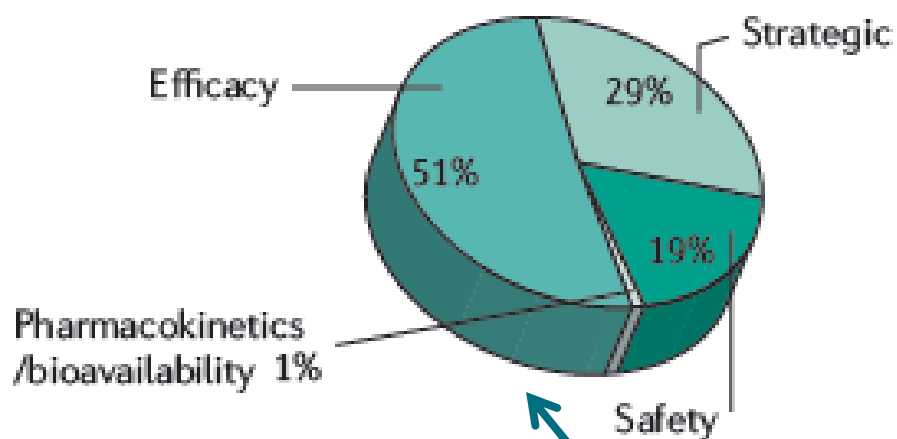


Figure 1 | Trends in attrition rates of drug development projects. Data are for projects started between 1990 and 2004 in the United States, Europe and Japan. Source: analysis of the Pharmaceutical Industry Database (BOX 1).

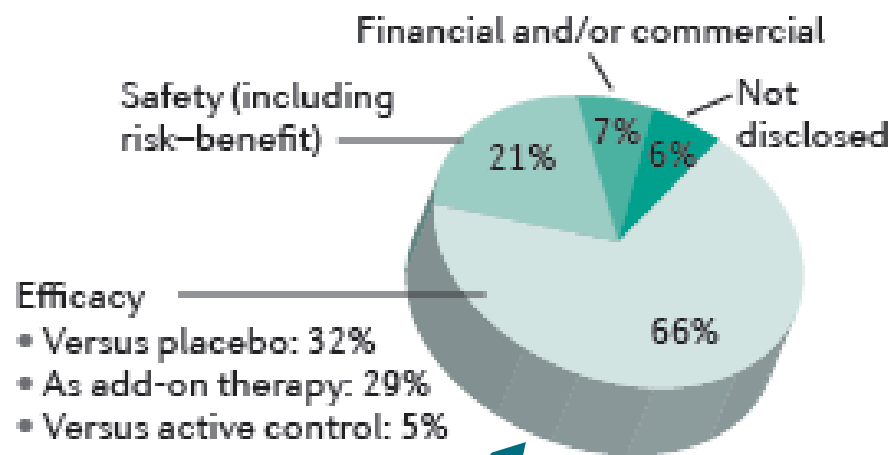
Pammolli F, Magazzini L, Riccaboni M. The Productivity Crisis in pharmaceutical R&D. Nature. June 2011. 10; 428-438.

Causes of Failure in Phases 2 and 3

Phase 2 Failures: 2008 – 2010
(N = 87 compounds)

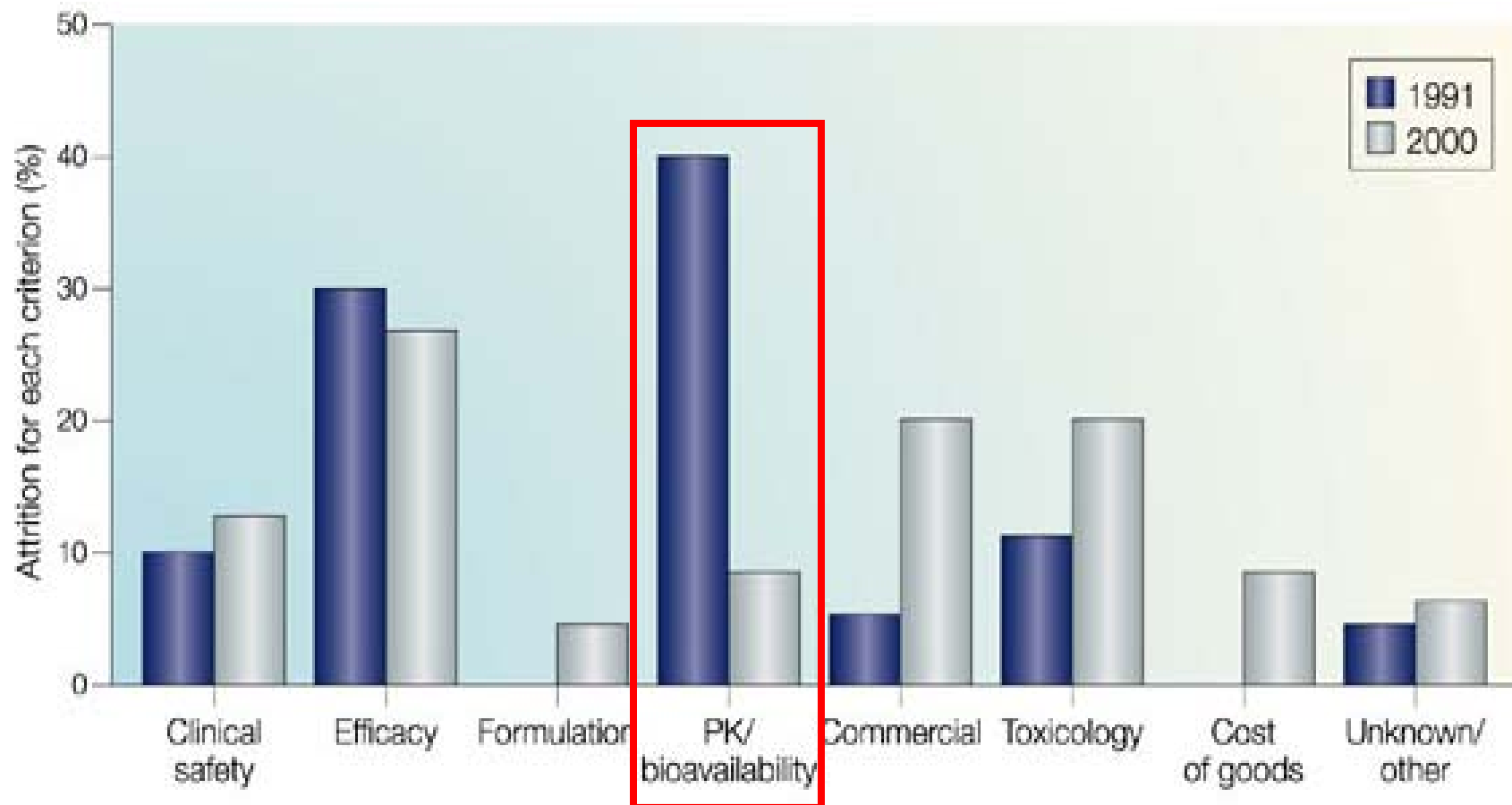


Phase 3 Failures: 2007 – 2010
(N = 83 compounds)



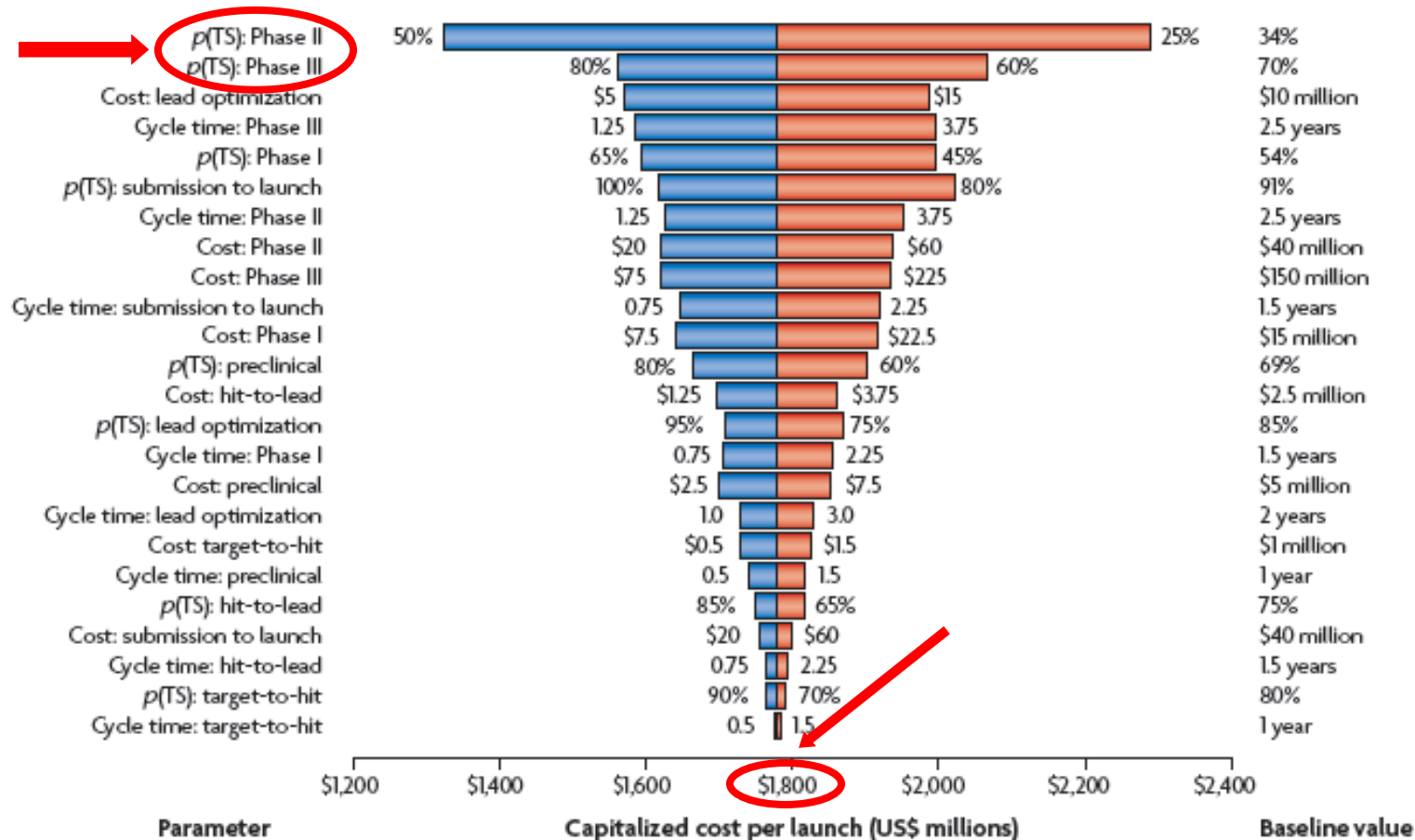
Efficacy is the major problem

Causes of Attrition in 10 Big PhRMA Companies



Kola and Landis. Nat Rev Drug Discov 2004;3:711-6.

High Failure Rates in Phases 2 and 3 are the most Important Determinants of Drug Development Cost



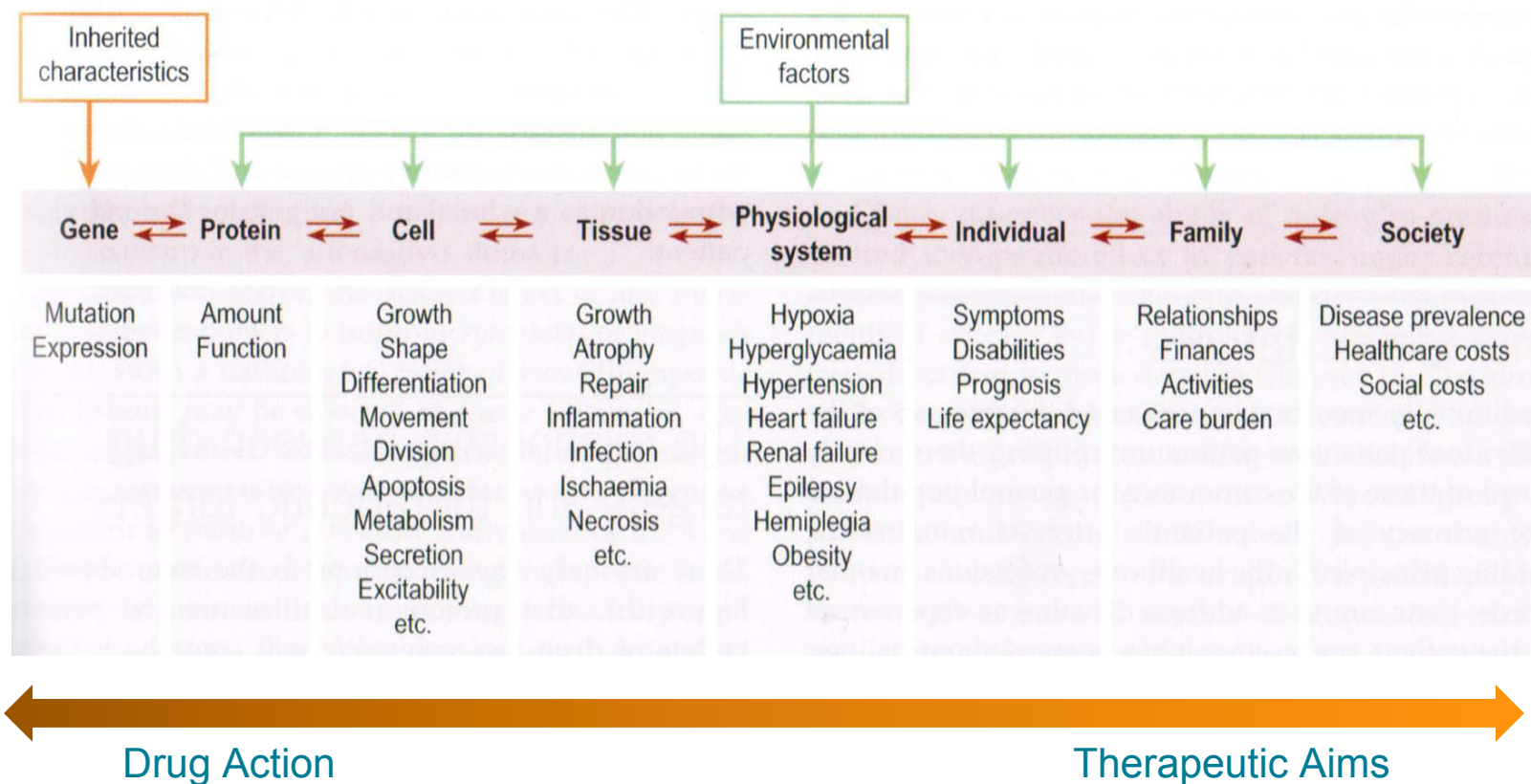
Opportunities for Greater Utilization of Quantitative Approaches

- Failure rate in Phase 2 can be attributed to target selection
 - Animal models of disease are often not predictive of efficacy in humans
 - H. Bart van der Worp et al. PLOS Medicine 2010;7:e1000245
- Once target and compound are selected the benefit: risk in humans is largely pre-determined
 - Clinical development serves to uncover the drug's inherent properties sooner or later
- Better understanding of human biology, pathophysiology can be achieved via mechanistic models
 - Increased confidence in drug targets that have evidence of human validation
- Failure rate in Phase 3 can be attributed to inadequate “risk decisions”
- The systematic integration of compound specific (direct) and mechanism and disease area (indirect) relevant information is required in order to create a comprehensive, complete and contemporary body of evidence

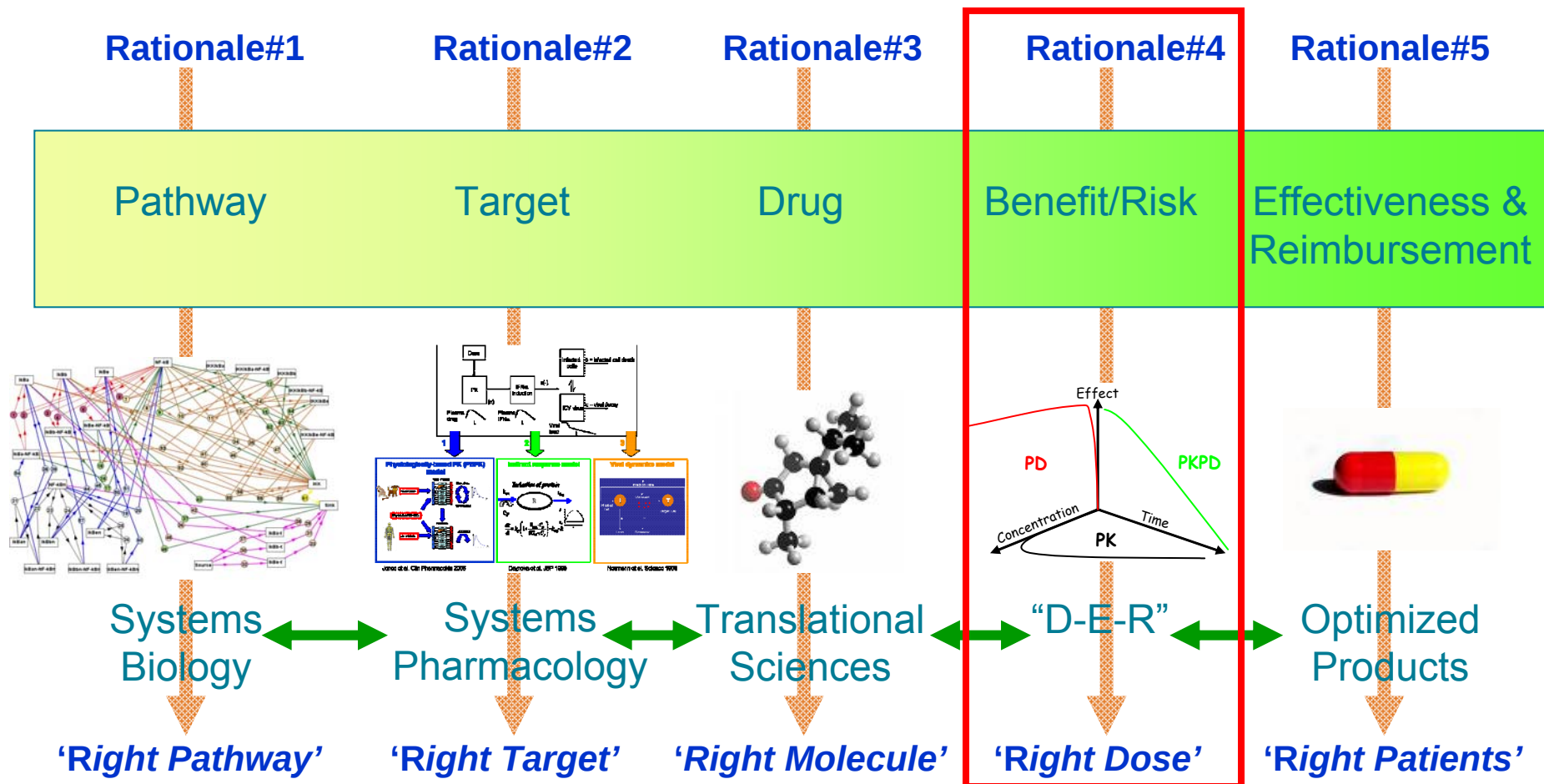
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 - Opportunities for greater utilization of quantitative approaches
 - Increase confidence in rationale for human efficacy
 - Decision-making efficiency supported by data totality & fit for purpose quantitative analyses

Dimensionality and Longitudinal Scaling Problem

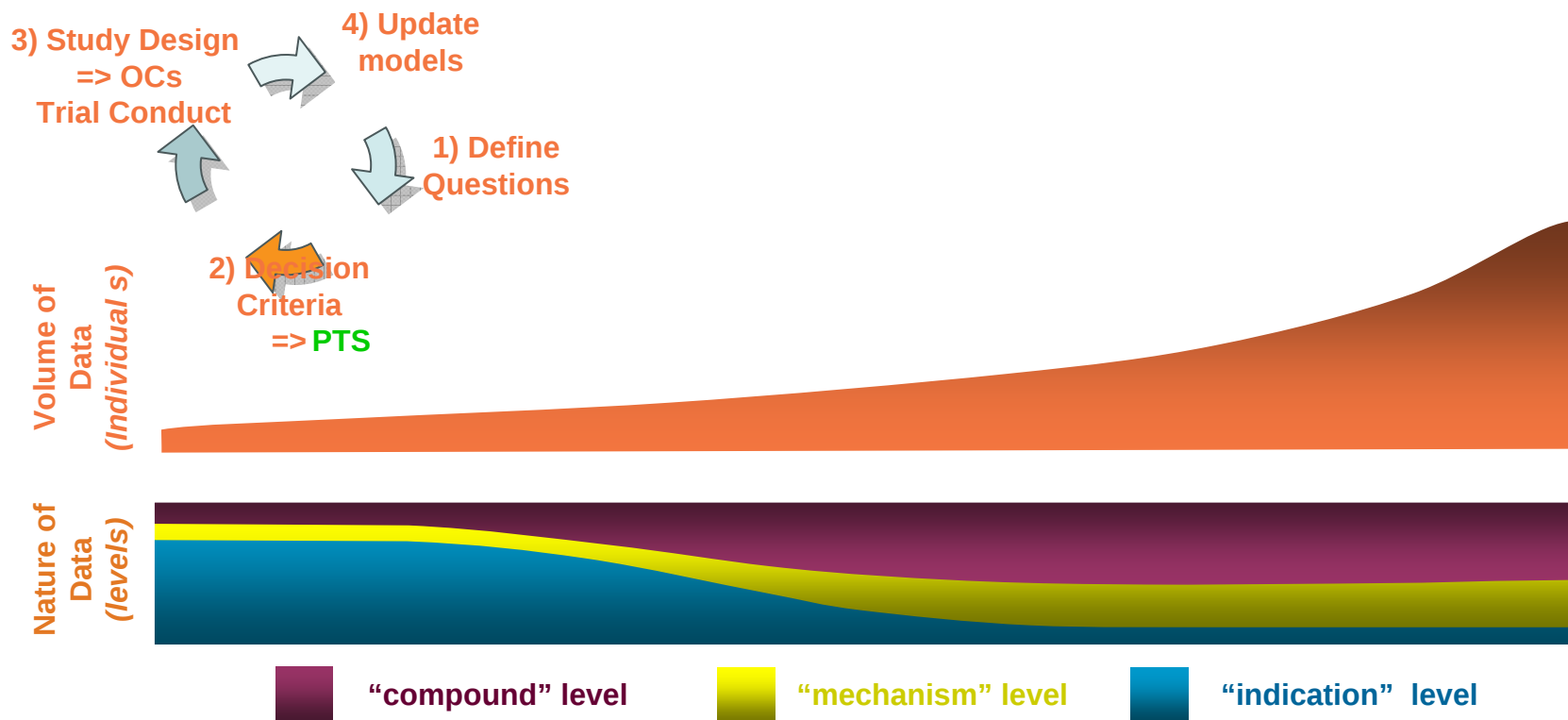


Decision Making: Vertical and Horizontal Challenges for Data/Knowledge Integration

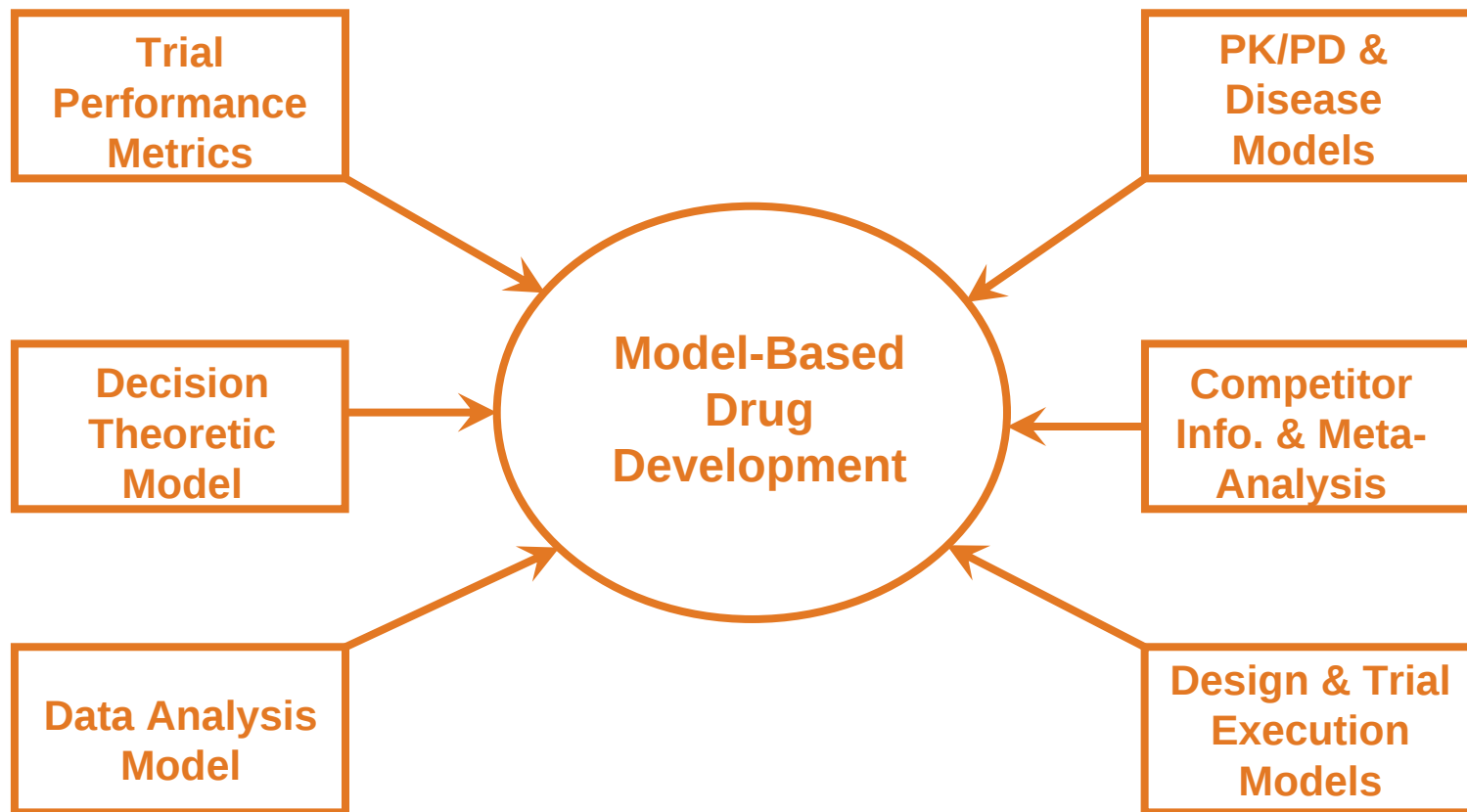


Framework for Improving (Confidence in) Predictions, De-Risking and Accelerating Compound Delivery

CAN FIH FIP POC P3 Registration P4



Elements of Model Based Drug Development (MBDD)

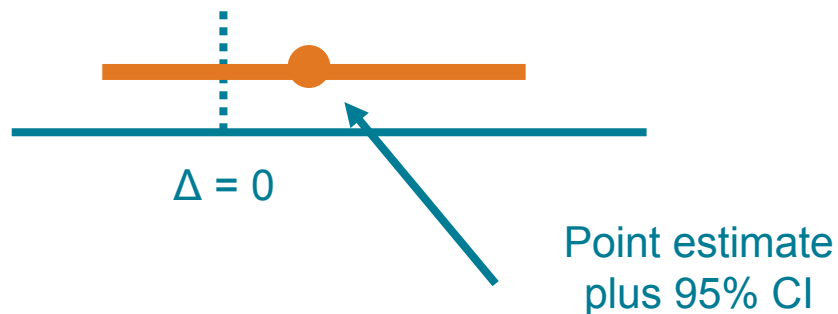


Kowalski KG et al "Model-Based Drug Development – A New Paradigm for Efficient Drug Development". *Biopharmaceutical Report* 2007;15(2):2-22

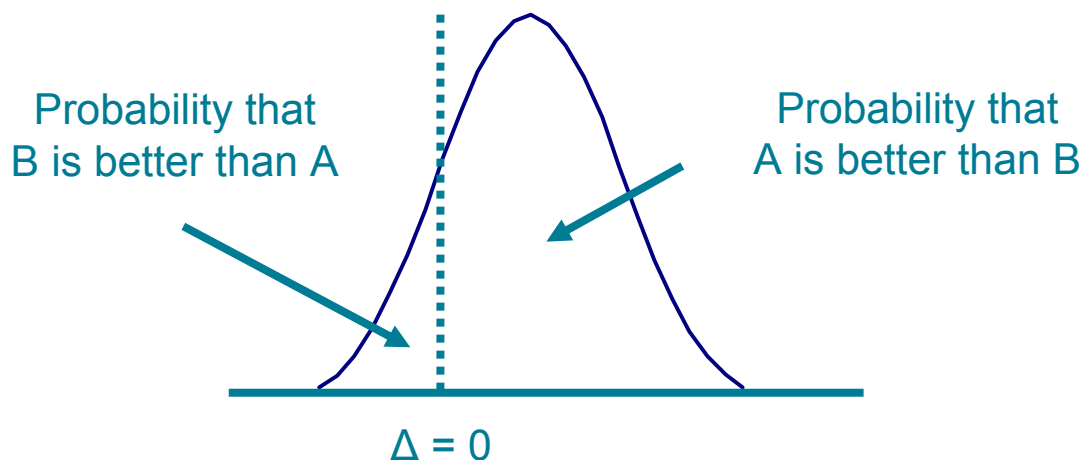
Accumulation of “Evidence” via Meta Analysis

- A quantitative review and synthesis of results from related but independent studies (*Normand, 1999*)
- Aggregate data (AD) meta-analysis
 - Based on summary statistics from each trial
 - Mean response, proportion of responders, hazard ratio
- Individual patient data (IPD) meta-analysis
 - Observed response, time-to-event
- If data are collected longitudinally, either approach can be applied at a single time point or as a longitudinal model
 - IPD is better suited for longitudinal models than AD
- Address uncertainty and heterogeneity of studies, increase statistical power, improve estimates of treatment effect, “new” knowledge & questions

Decision Theoretic “Types”



*No significant difference
Between A and B*



*75% Probability that
A is better than B*

Chuang-Stein C., Kirby S, French JL, Kowalski K, Marshall S, Smith MK, Bycott P, and Beltangady M.
A Quantitative Approach for Making Go/No-go Decisions in Drug Development. *Drug Information J.* 45: 187–202. 2011

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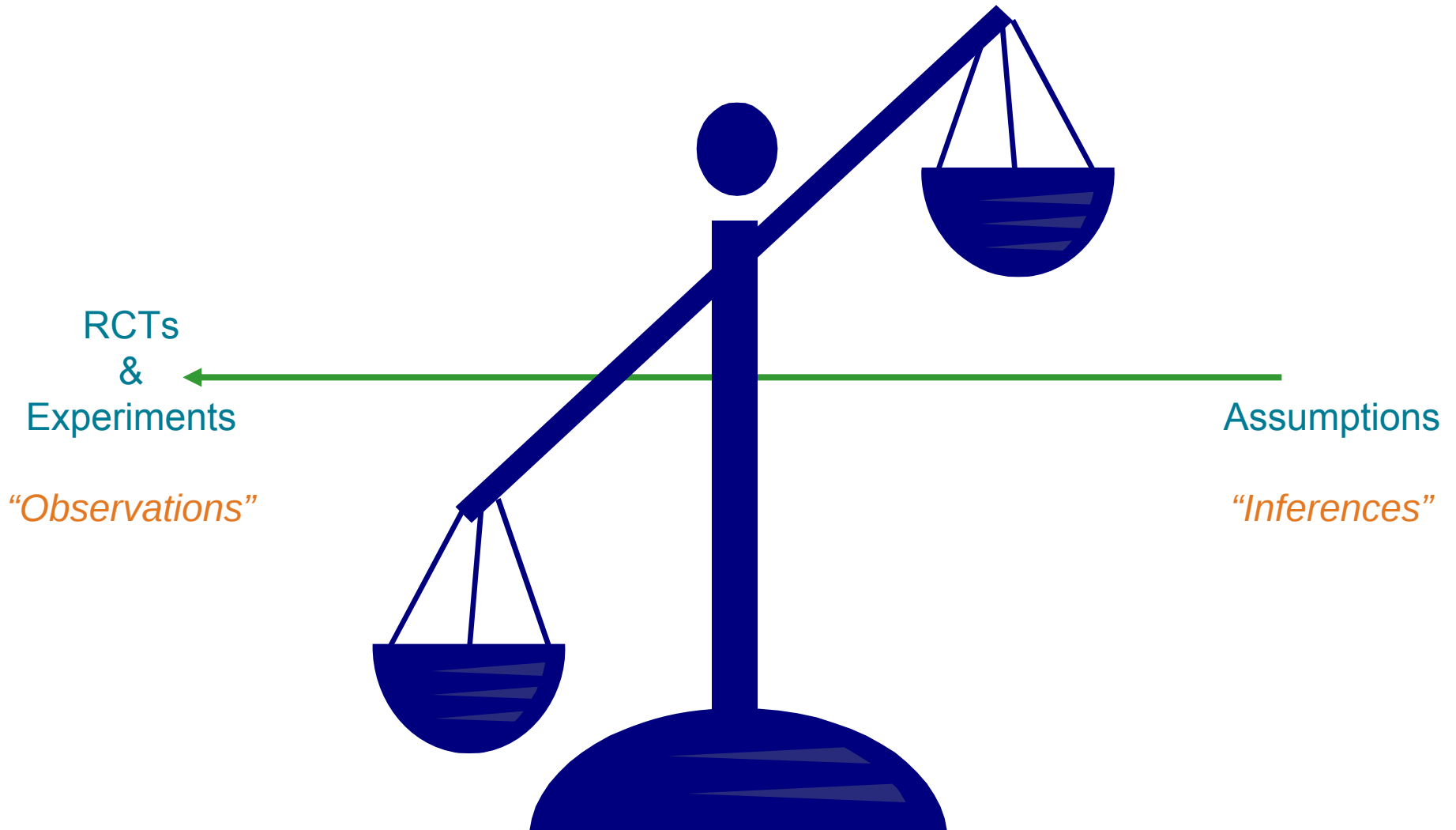
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“Evidence based medicine is the conscientious explicit, and judicious use of **current best evidence** in **making decisions** about the care of individual patients” taking into account “individual patients predicaments, rights and preferences using **best evidence** from clinically relevant research.”

Sackett et al, 1996

*Acknowledging Deborah Ashby,
Dept of Epidemiology and Public Health, Imperial College London*

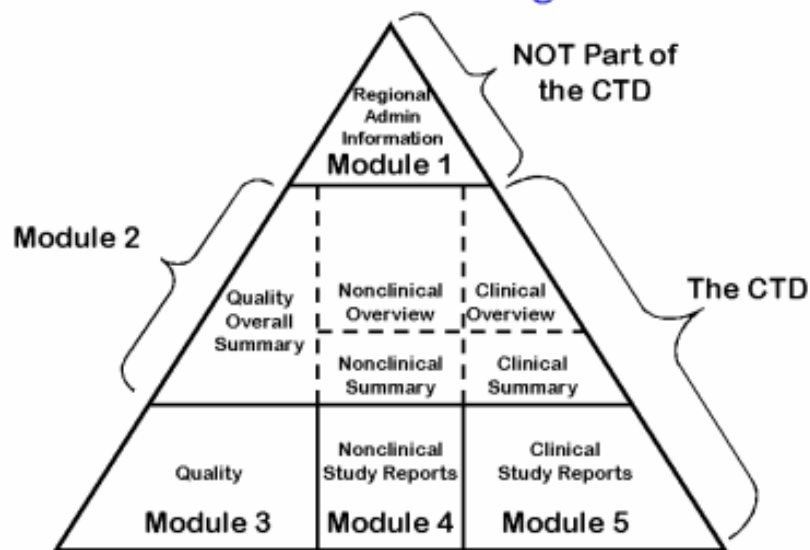
Evidence Based Medicine



Regulatory “Structure vs Function”

- Regulators decide on quality, safety, efficacy and benefit: risk (to individuals and “the public health”)
 - In the interest of public health, authorisation decisions [...] should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations. REGULATION (EC) No 726/2004

The CTD Triangle



BOS1: M&S in early development (to support FTIM)

- Can the EMA partner with Companies to improve success and efficiency of Preclinical & Early Clinical Development (PD/ECD) through M&S-based approaches?
 - Preclinical mechanistic PoC and toxicity signal detection (exp. design regulatory studies).
 - First-in-Human (FIH) dose selection
 - Early clinical development: early selection of safe and efficacious drugs
- How does EMA see its role to assist Companies in making better (internal) decisions that ultimately result in faster access for patients to safe and effective new medicines?
 - is this an internal issue for the Companies only?
- Would the EMA be open to discuss model-based approaches for FIH dose selection beyond the classic NOAEL approaches such as PBPK predictions, PKPD-based margin setting?
- What are EMA expectations on reporting standards for M&S-based data compilation in PD/ECD documentation (e.g. FIH, PoM and PoP/C studies)?
- What is the vision of EMA for M&S in PD/ECD for 2015-2020?
 - Sharing data, database development, model library (for translational M&S).
 - Acceptance of model-based approaches in FIH and Phase I/II dose selection.
 - Standards for Translational M&S (i.e guidance on acceptance criteria for quantitative integration of all available information including in vitro data, physiological/mechanistic knowledge, preclinical and clinical data from literature and in house.
 - Other?

BOS2: M&S in clinical pharmacology and dose finding

Communication/Exchange

- Proposals how in the future the interaction between the Pharmacometricians and the authorities could be improved – in general and for specific projects
 - How can M&S strategies and results be scientifically discussed between companies and authorities to agree on acceptance criteria and level of necessary documentation
 - Possibilities of guidelines/white papers that would summarize the state of the art

Efficient use of M&S in clinical pharmacology

• Dose-Exposure-Response

- Identify pre-requisites and acceptable assumptions when M&S can be the primary analysis to establish doses for phase II/III
- Identify pre-requisites and acceptable assumptions when M&S results can be used to interpolate or extrapolate doses

• Integration of data by M&S to provide evidence of efficacy and safety for untested scenarios

- Identify situation when M&S should be used to come to the best study design for an untested scenario and when M&S results on its own might be sufficient for label recommendations

BOS3: M&S as a tool to bridge PK, efficacy and safety data in special populations, ethnic groups and rare diseases

Assumption	Probability to violate	Clinical Consequences	Implications for evidence synthesis	Impact of M&S on development programme
PK properties	Definitely Likely Unlikely Improbable	Minor Major Unknown	No additional evidence required More evidence from large/small subset Accept risk if further evidence gathering is unfeasible	Reduce trial burden Reduce sampling frequency
PD properties	Definitely Likely Unlikely Improbable	Minor Major Unknown	No additional evidence required More evidence from large/small subset Accept risk if further evidence gathering is unfeasible	Incorporation of biomarkers Better dose rationale
Disease	Definitely Likely Unlikely Improbable	Minor Major Unknown	No additional evidence required More evidence from large/small subset Accept risk if further evidence gathering is unfeasible	Population selection Stratification Different recommendation (e.g., contraindication)
Patient population	Definitely Likely Unlikely Improbable	Minor Major Unknown	No additional evidence required More evidence from large/small subset Accept risk if further evidence gathering is unfeasible	Estimation of covariate effects Define appropriate inclusion criteria
Statistical aspects	Definitely Likely Unlikely Improbable	Minor Major Unknown	No additional evidence required More evidence from large/small subset Accept risk if further evidence gathering is unfeasible	Reduce sample size Higher statistical power Eliminate need for a study

BOS4: M&S to optimizes the design of confirmatory trials, to analyse Ph3 data and support claims in SPc

- Improve how **Companies and EMA interact** with respect to the use of M&S in the design and interpretation of Phase 3 studies
- It is important for EFPIA to understand where **application of M&S** would be acceptable to the EMA in order to guide future activities in the following areas:
 - In Phase 3 design (dose, comparator, selection, N etc)
 - Model based primary or key secondary analysis
 - Acceptability in estimating risk benefit **including** where this replaces the need for further studies
 - In creation of development path guidance for novel or existing disease areas