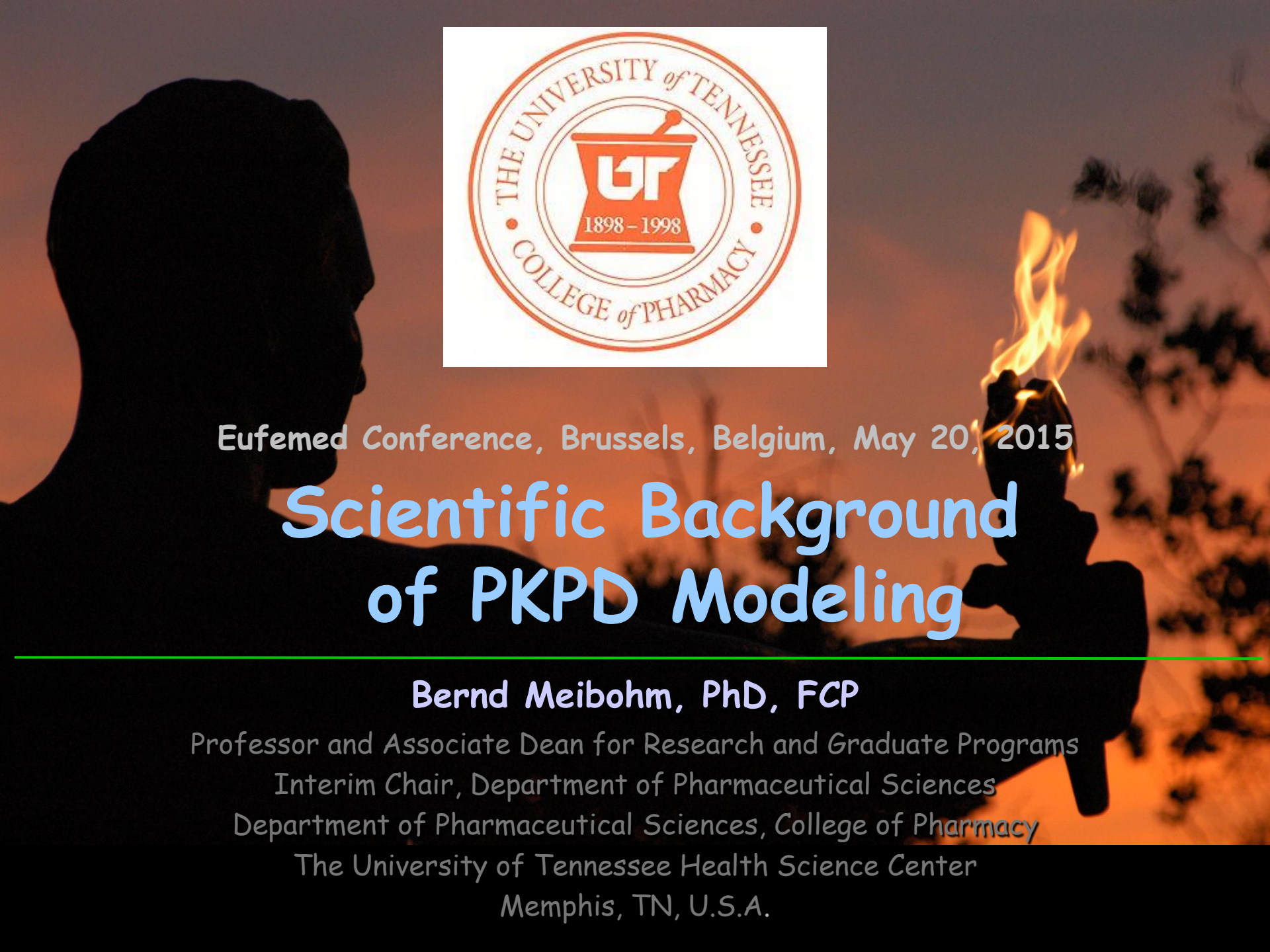

Eufemed Conference, Brussels, Belgium, May 20, 2015

Scientific Background of PKPD Modeling

Bernd Meibohm, PhD, FCP

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Interim Chair, Department of Pharmaceutical Sciences
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Models & Modeling

Model building is as much an art as it is a science

- Models are simplified descriptions of certain aspects of reality by mathematical means, thereby allowing to concentrate on the factors believed to be important.
- Models are a "mathematical representation of a system that can be used to explore the structure and behavior of the system" (Wastney et al., 1997).
- Modeling "provides a systematic way of organizing data and observations of a system at the cell, tissue, organ, or whole animal (human) levels" and "affords the opportunity to better understand and predict physiological phenomena" (Epstein, 1994).

Modeling & Simulation

Modeling

- Summarizing measured data by integrating different measures and prior knowledge about biological processes
- Identify the best model that sufficiently describes the data (Rule of Parsimony: simplest model)
- Purpose-driven: Level of model complexity defined by its intended use.

Simulation

- Modeling is a prerequisite for simulations: Application of the developed model
- Predictions beyond the measured data: inter- or extrapolations
- Validity of simulations depends on model (and the purpose is was developed for)
- Prediction error and uncertainty

Simulation Approaches

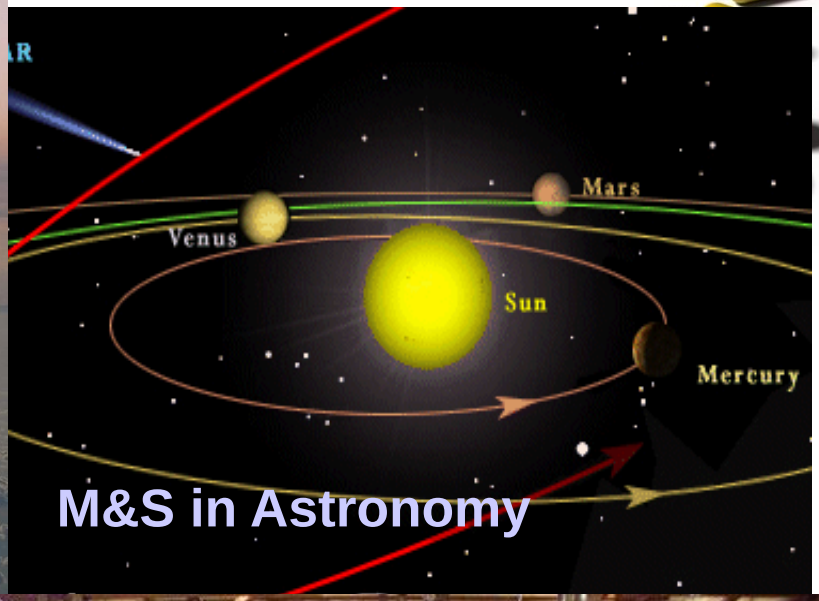
Deterministic vs. Stochastic

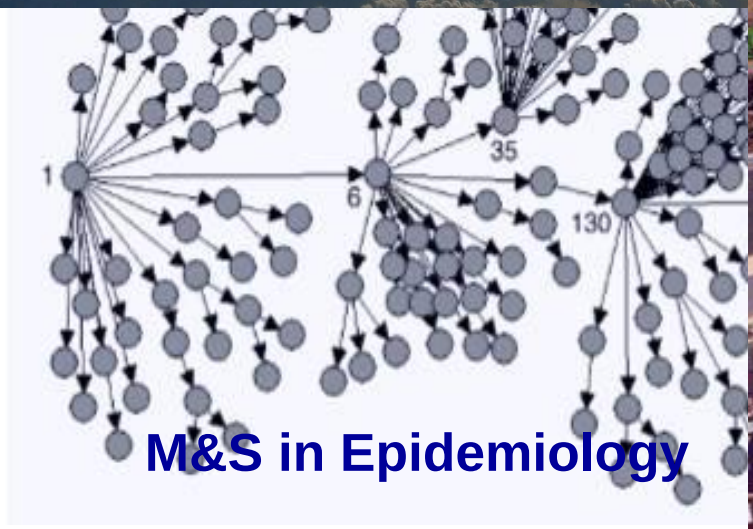
Deterministic

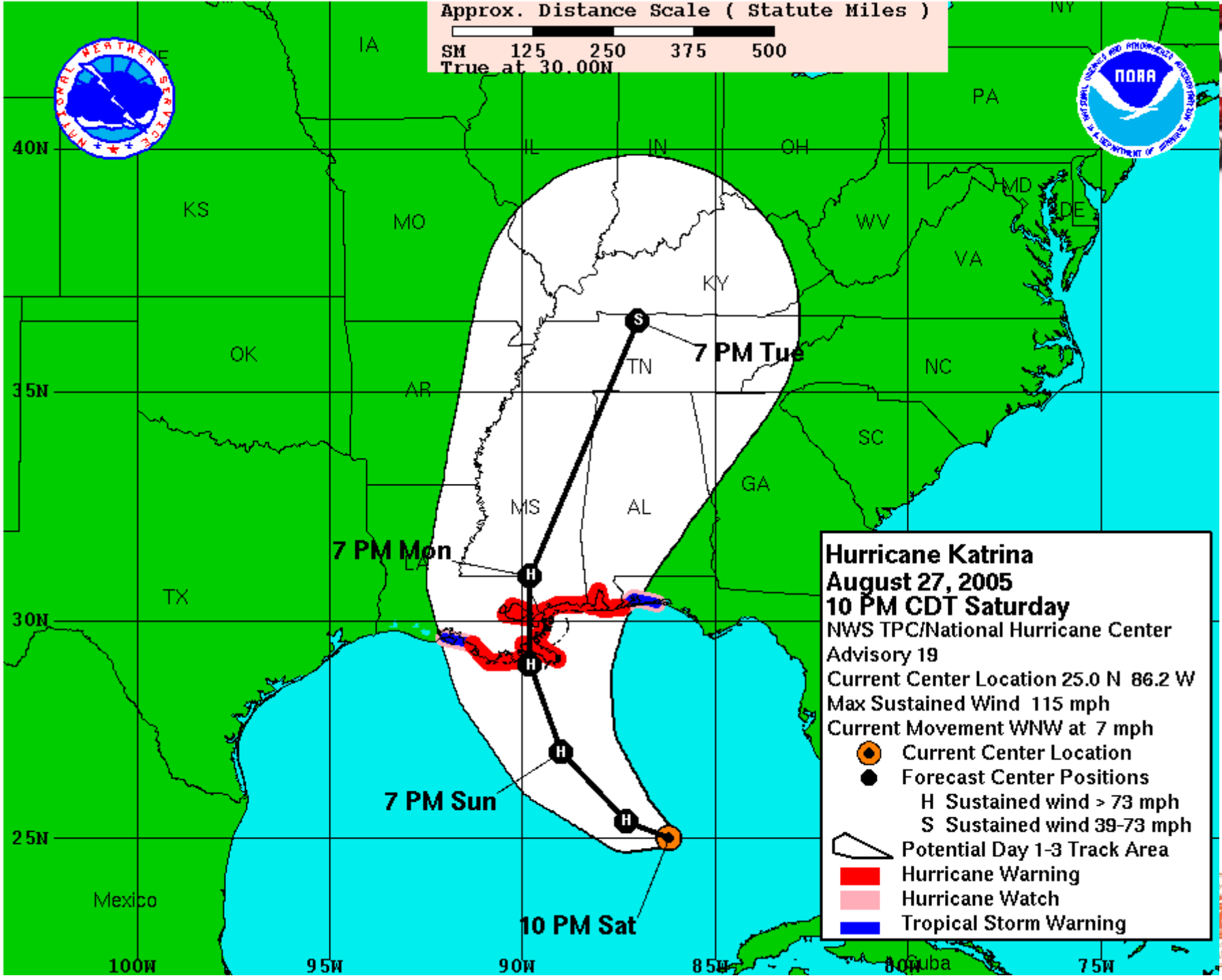
- "Best guess" parameter point estimates used for simulation
- One discrete outcome of simulation
  - E.g. a discrete drug concentration vs. time profile
- Parameters may be dependent on covariates
- Pro: Simplicity; ease of understanding
- Con: No uncertainty in parameter estimates considered

Stochastic (Monte-Carlo Simulations)

- Distributions for each specific parameter that capture the degree of uncertainty
  - Repeated random sampling of parameters from these distributions to simulate the outcome based on the underlying structural model.
- Distribution of outcomes with central tendency and spread
- Pro: provides inherently a measure of credibility and likelihood for simulation outcomes
- Con: increased complexity and thus difficult understanding and acceptance






Approx. Distance Scale (Statute Miles)
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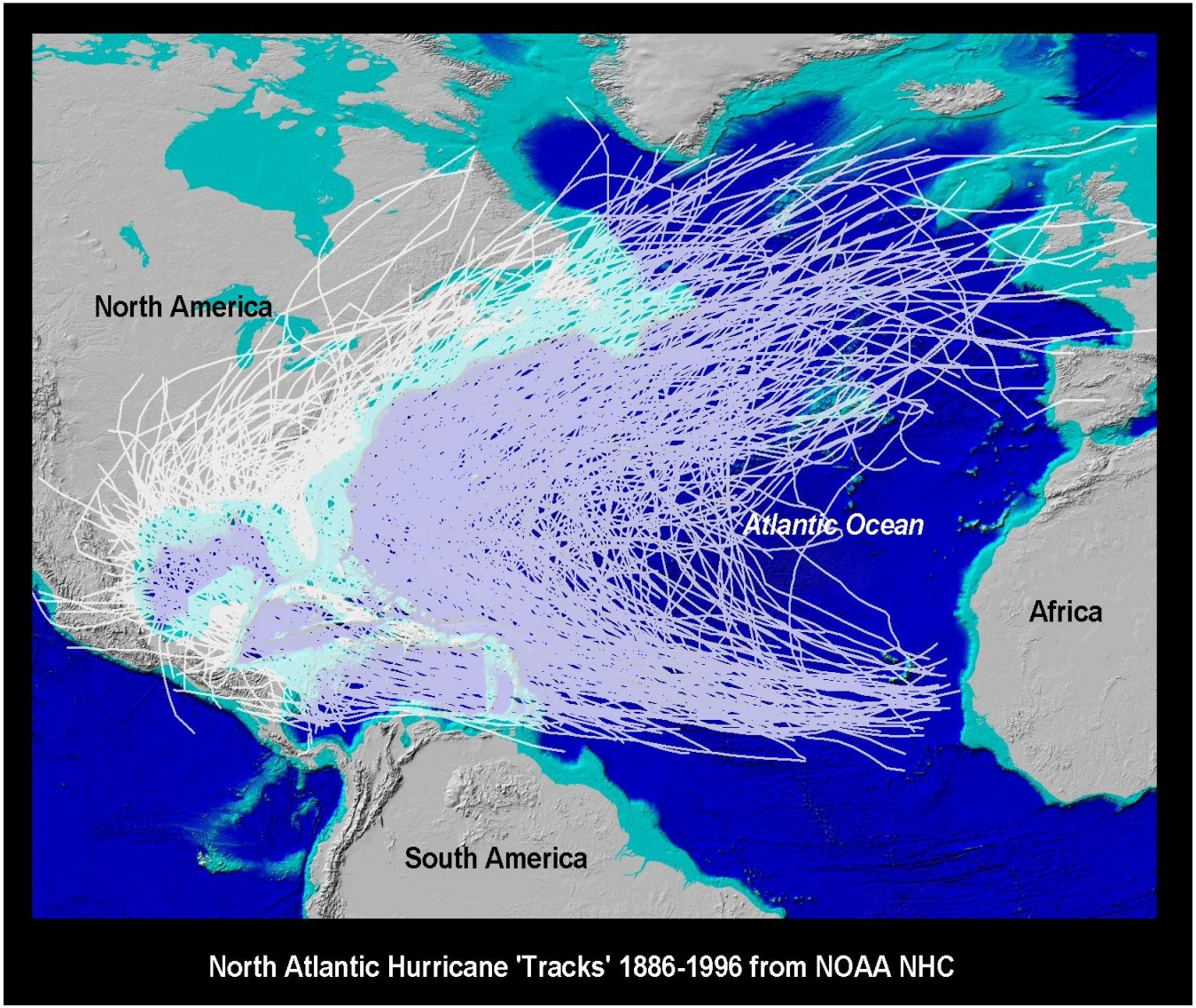
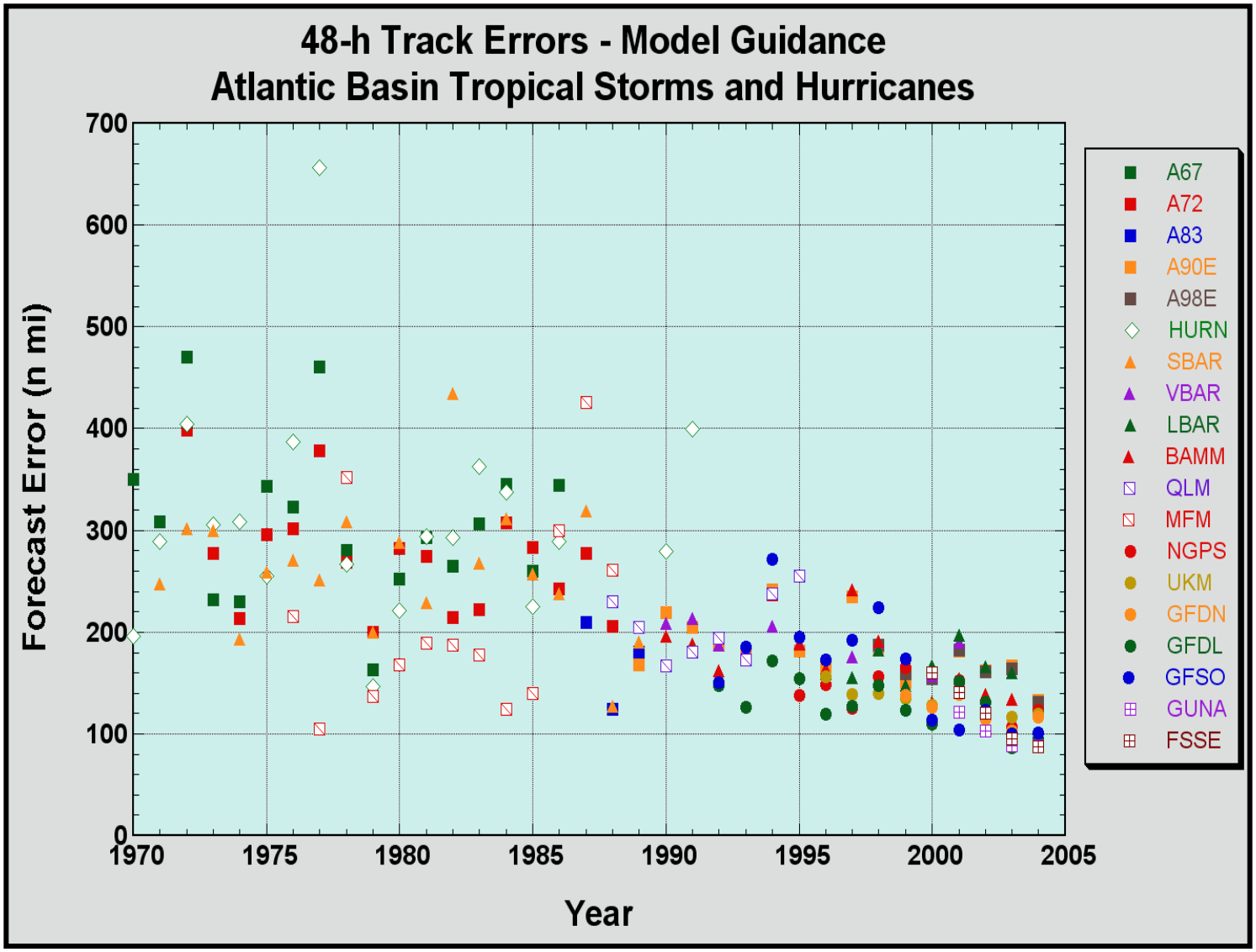
Hurricane Katrina
August 27, 2005
10 PM CDT Saturday
NWS TPC/National Hurricane Center
Advisory 19
Current Center Location 25.0 N 86.2 W
Max Sustained Wind 115 mph
Current Movement WNW at 7 mph
Current Center Location
Forecast Center Positions
H Sustained wind > 73 mph
S Sustained wind 39-73 mph
Potential Day 1-3 Track Area
Hurricane Warning
Hurricane Watch
Tropical Storm Warning

Model Development Based on Prior Data



North Atlantic Hurricane 'Tracks' 1886-1996 from NOAA NHC

Prediction Error & Model Refinement

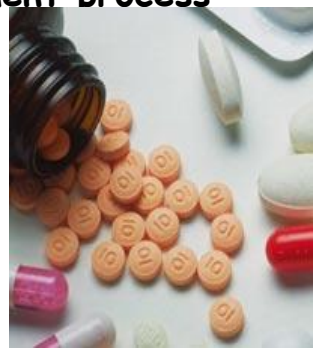


Model-Based Drug Development

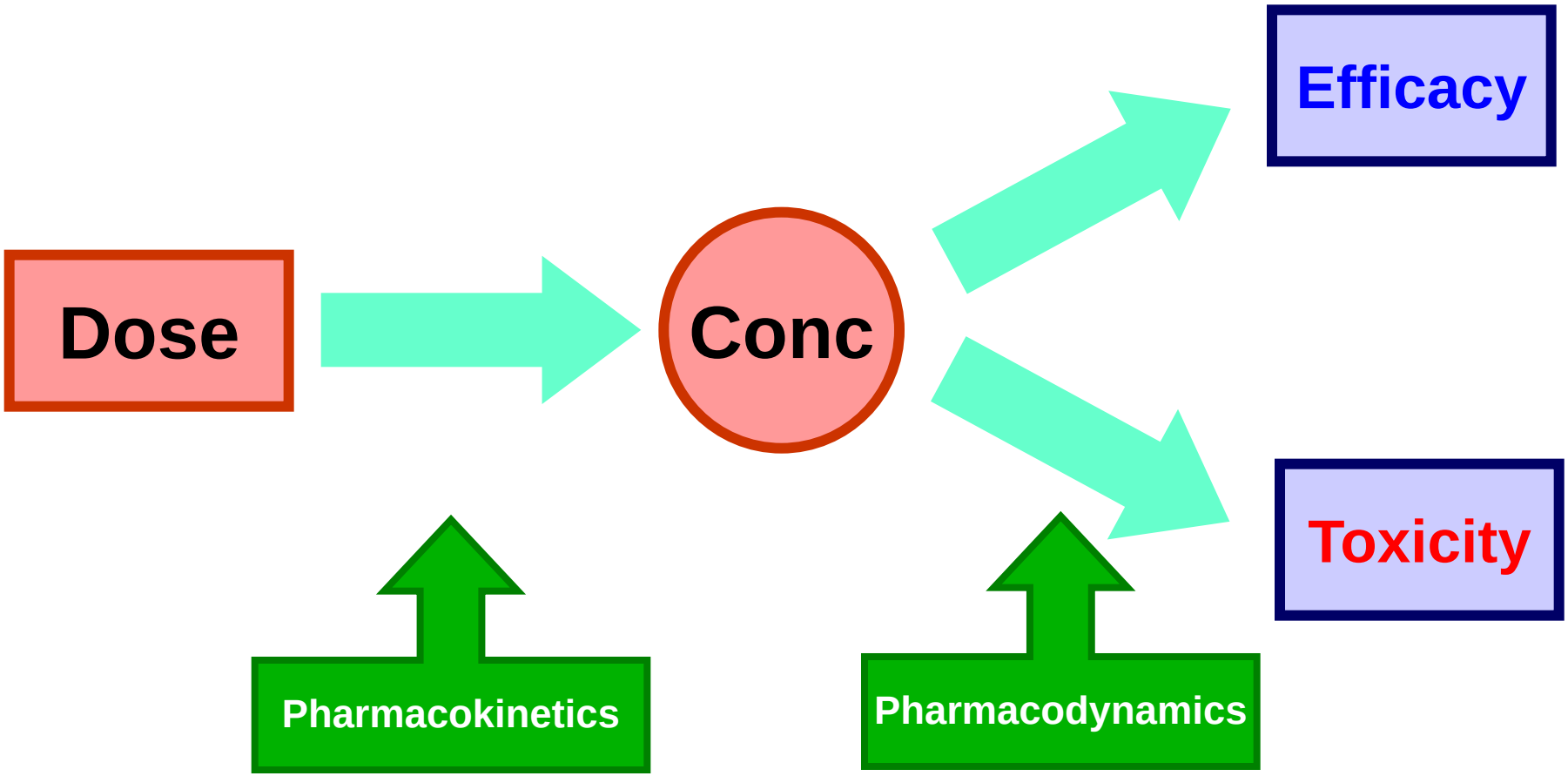
M&S provides the framework for a rational, scientifically-based drug development program

Model-based drug development strongly promoted by FDA's Critical Path Initiative

M&S as a tool for a rapid, cost-efficient, and more focused drug development process

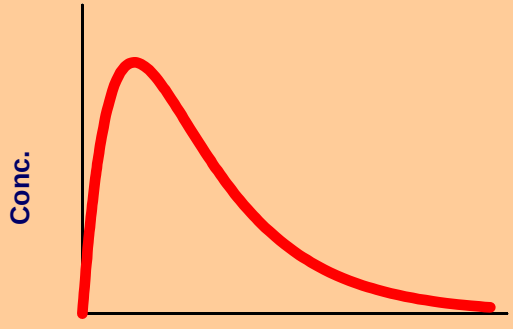


Central Paradigm of Clinical Pharmacology

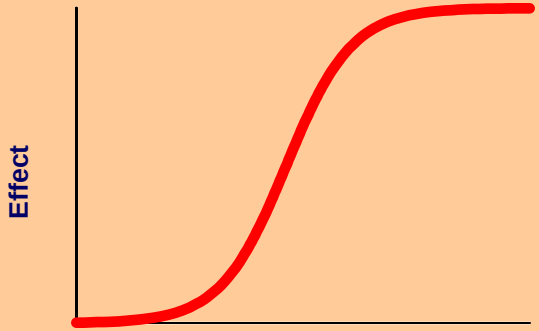


PK/PD-Modeling

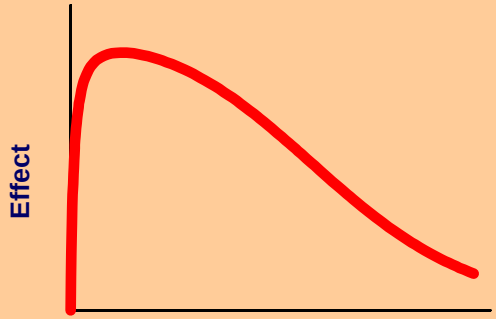
Pharmacokinetics
Concentration vs. Time



Pharmacodynamics
Concentration vs. Effect

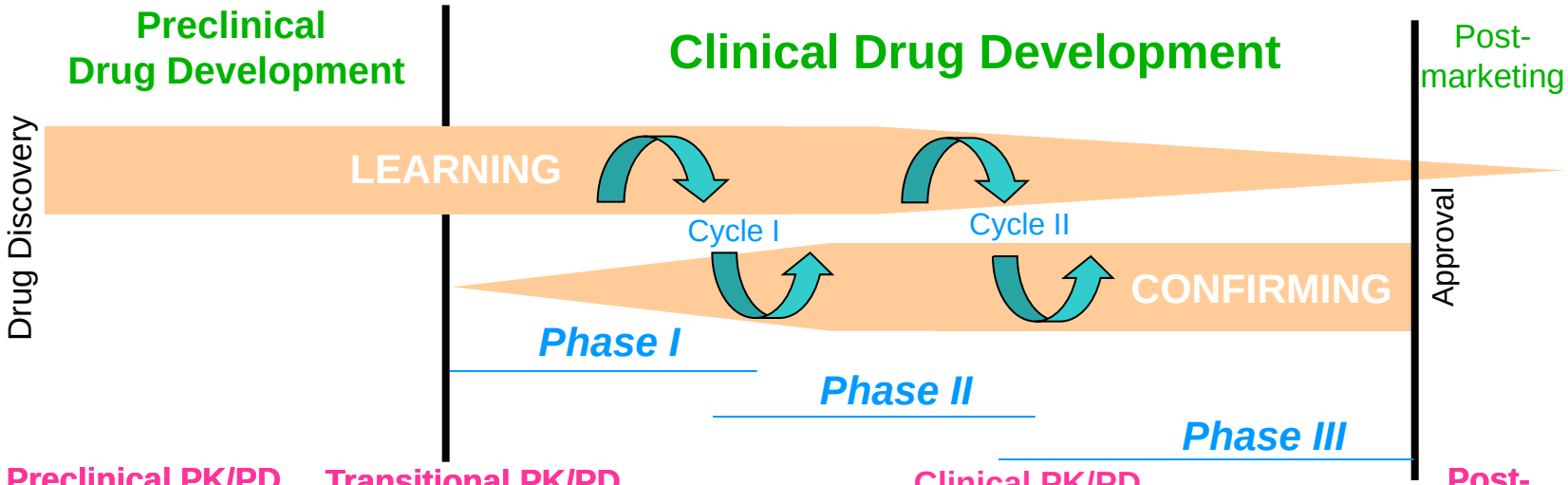


PK/PD
Effect vs. Time



Derendorf & Meibohm
Pharm Res 1999, 16, 176-85

PKPD in Drug Development



Preclinical PK/PD

- Development of mechanism-based models
- Evaluation of In vivo potency and intrinsic activity
- Evaluation of In vivo drug interactions
- Identification of surrogates and animal models for efficacy/toxicity
- Dosage form and dosage regimen optimization
- Integrated information supporting go/no go decision

Transitional PK/PD

- Extrapolation of preclinical data to humans
- Allometric scaling
- Dose selection/escalation

Clinical PK/PD

Analytical PK/PD

- Characterization of dose-concentration-effect relationship
- Evaluation of dosage forms and administration pathways
- Food effects
- Gender effects
- Special populations (children, elderly)
- In vivo evaluation of active metabolites
- Drug/Drug interactions
- Drug/Disease interactions
- Tolerance development
- Evaluation of drug analogues
- Population PK/PD
- Bridging studies

Predictive PK/PD

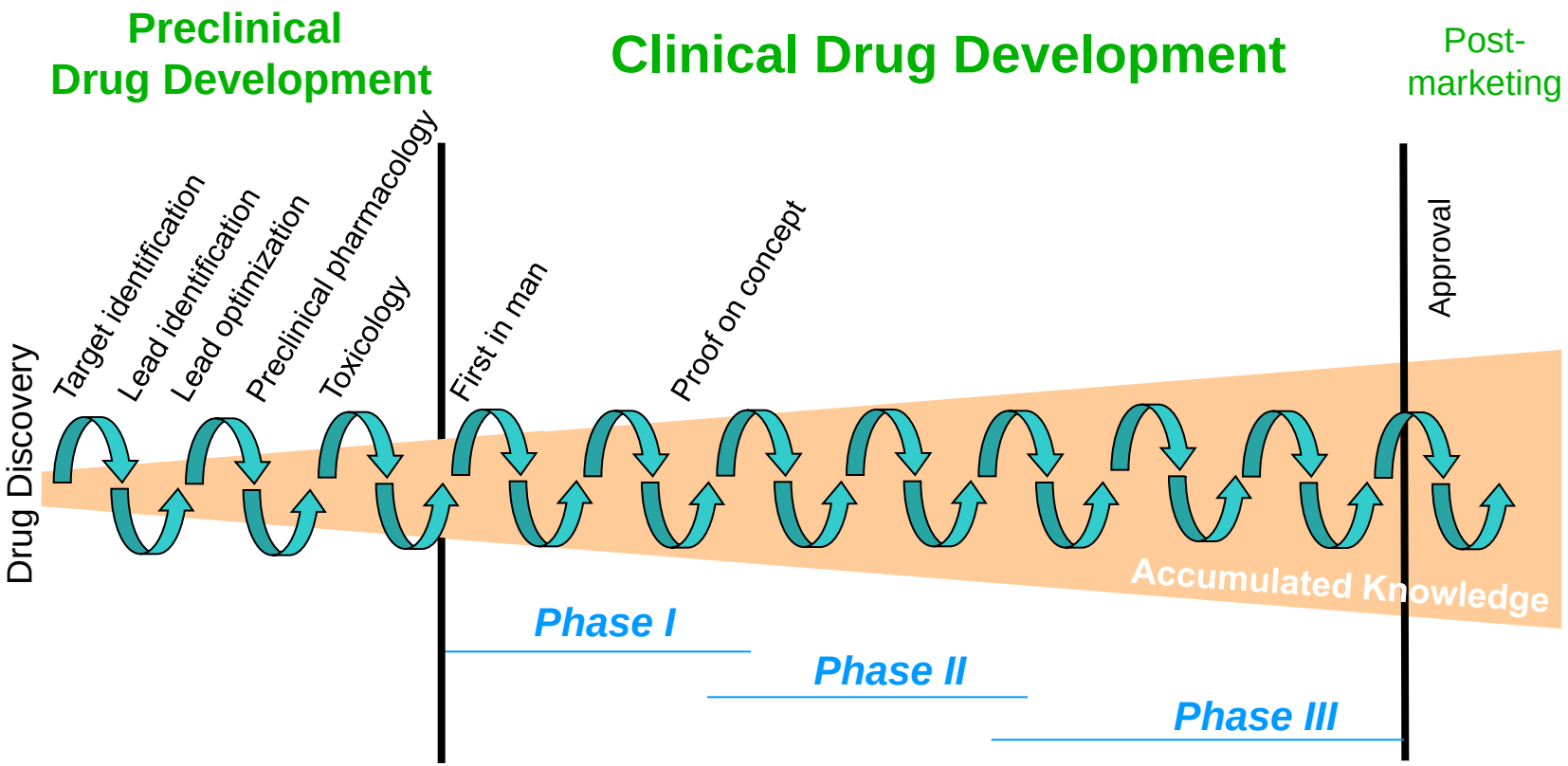
- Simulations
- Trial forecasting

Post-marketing PK/PD

- Post-marketing surveillance

Meibohm & Derendorf, J Pharm Sci 2002; 91:18-31

Model-Based Drug Development (I)



Learn-Confirm Cycle

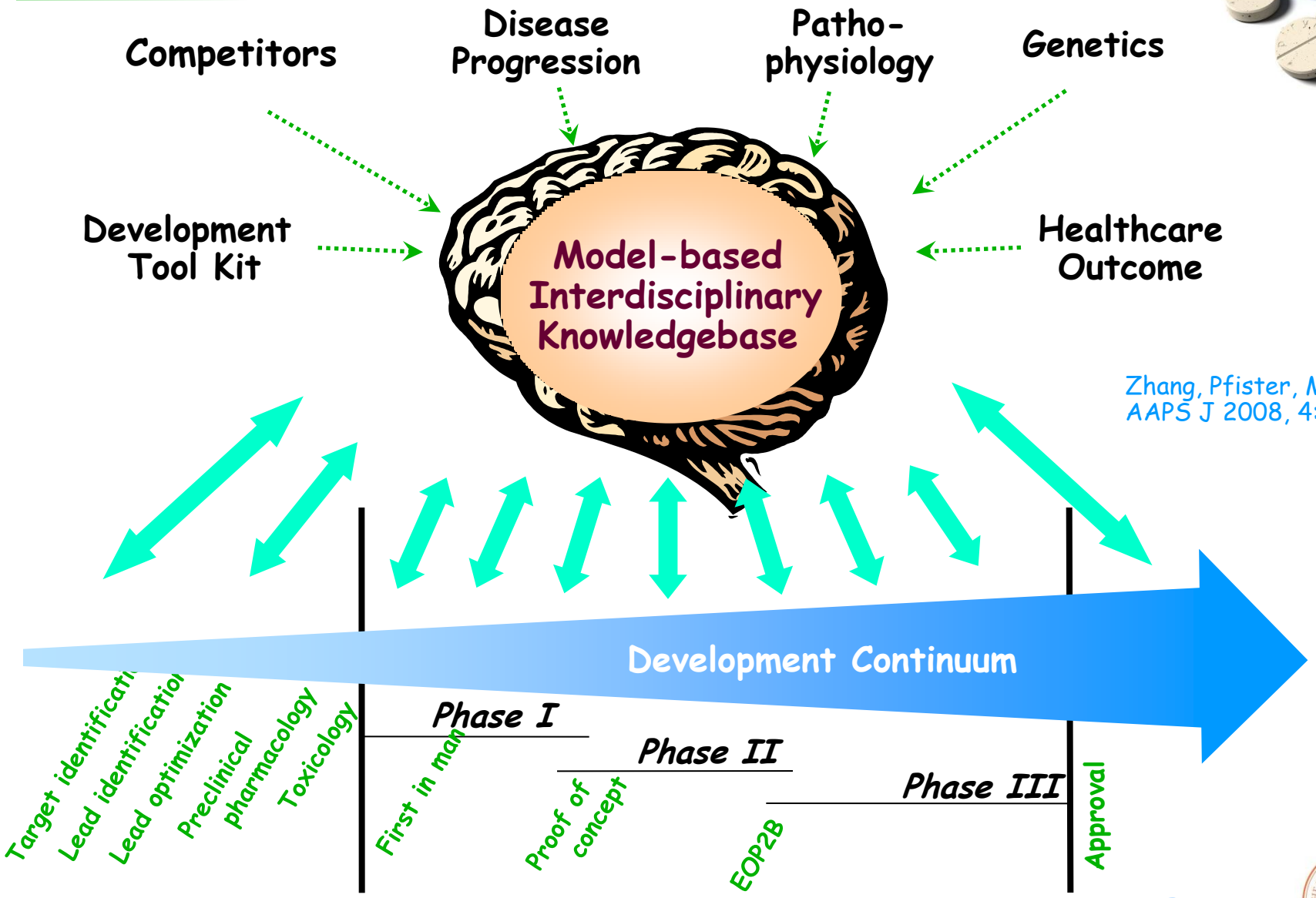
Suryawanshi, Zhang, Pfister & Meibohm, Expert Opin Drug Discov 2010; 5:311-21

Model-Based Drug Development (II)

A multi-disciplinary approach that integrates the relationships between diseases, drug characteristics, and individual variability

- ✓ A framework for synthesizing information and extrapolating beyond what is traditionally studied in RCTs
- ✓ A tool for rationale, critical decision making
- ✓ From drug discovery to post-marketing
- ✓ A mathematical explanation of the relationships needed to explain clinical outcomes over a timeframe of interest at its core
- ✓ Away from study centric approach: seamless data mining and knowledge management strategy that quantitatively integrates data across studies and development phases

Model-Based Drug Development (III)



Zhang, Pfister, Meibohm
AAPS J 2008, 4:552-9

MADD vs. MBDD

	"Model-aided" drug development	Quantitative model-based drug development
Nature	Models are largely empirical	Both empirical and mechanistic models are developed and applied given modeling objectives
	• Model function formats are driven by the observed trend in data	• Functions formats are elucidated by underlying drug, disease, and physiologic mechanisms
	• Difficulties in linking models across experiments, response types, developmental stage, and compounds	• Models include knowledge, data and scientific perspective from all relevant aspects and are constantly updated
	• Model quality is restricted by data quantity and quality	• Rich prior knowledge alleviates the dependence on data quantity and quality
	• Limited predictability for future studies	• Predictability is the key model performance requirement
Content	Models are mostly developed in pharmacokinetics and pharmacodynamics in late stage clinical development, and are mainly used for quantifying	Models are developed at various stages and in different disciplines in preclinical and clinical development. Models are used for characterizing
	• Response levels in exposure, biomarkers, and endpoints	• Candidate attributes
	• Sources of variation	• Disease mechanisms
	• Covariate effects	• Competitor information
		• Trial execution patterns
Impact	Models confirm decisions, in which they	Models facilitate quantitative decisions, in which they
	• Are used at the discretion of stakeholders	• Serve as instruments and aims of drug development
	• Focus on a few attributes separately	• Reflect all known attributes and call attention to important yet unknown attributes
	• Are developed by a few scientists with "modeling expertise" and viewed skeptically by other parties	• Are synergistic results from all relevant stakeholders
	• Are not timely to influence key decisions	• Are developed prospectively and are a necessity for decision making

Zhang, Pfister, Meibohm. AAPS J 2008, 4:552-9

'PKPD Reasoning' in Discovery DMPK

Drug Discovery Today • Volume 00, Number 00 • January 2009 REVIEWS

ELSEVIER

PKPD awareness is vital if we are to attempt to relate preclinical results to the acute and long term consequences in humans. The debate on whether preclinical findings can be translation to the human usage is still engaging scientists across industry, academia and regulatory bodies.

Foundation review:

Early integration of pharmacokinetic and dynamic reasoning is essential for optimal development of lead compounds: strategic considerations

Reviews • FOUNDATION REVIEW

Johan Gabrielsson[1], Hugues Dolgos[1], Per-Göran Gillberg[2], Ulf Bredberg[1], Bert Benthem[2] and Göran Duker[2]

[1] Discovery DMPK & BAC CVGI, AstraZeneca R&D Mölndal, S-431 83 Mölndal, Sweden
[2] Bioscience CVGI, AstraZeneca R&D Mölndal, S-431 83 Mölndal, Sweden

The aims of this report are firstly to raise awareness among kineticists and pharmacologists as to why pharmacokinetic–pharmacodynamic (PKPD) integration is essential for target validation (TV), optimizing development of lead compounds (lead generation [LG] and lead optimization [LO]) and scaling these to human. A related aim is to demonstrate strategic examples of PKPD collaborations that have improved the planning, execution and evaluation of experiments in primary and safety pharmacology. Examples include design of TV studies, design and data 'pruning' of PKPD studies in LO, analysis of data with marginal and substantial temporal (time) differences between exposure and response, design of safety pharmacology studies, assessment of safety margin and assessment of uncertainties in predictions of first dose in human.

DR JOHAN GABRIELSSON

Dr Johan Gabrielsson is a Senior Principal Scientist at AstraZeneca R&D Mölndal. He is author of the book 'Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications' 4th ed. (2006). He is academically affiliated with the Department of Pharmacology, Gothenburg University, Sweden. His research focuses on modeling different aspects of endogenous turnover, such as functional tolerance and rebound phenomena by means of feedback, physiological limits and target-mediated drug disposition in collaboration with Professor Lambertus A. Peletier at Department of Mathematics at Leiden University, the Netherlands. He has conducted numerous workshops on biological (PK/PD) data analysis within and outside the pharmaceutical industry.

'PKPD Reasoning' in Discovery DMPK

Compound	Species	f_u (%)	*F* (%)	CL (mL min^{-1})	$t_{1/2}$ (hours)	Comment
Felodipine	Rat	1.5		108[a]		
	Dog			1875[a]		
	Human	<1	<15	5000[a]	5[b]	EC_{u50} <10 nM
Omeprazole	Rat		<5	25	0.12	
	Dog		15	150	1	
	Human	3	60	4900	<1	$t_{1/2resp}$ 15–20 hours
Quetiapine	Rat	10	<10	41	0.35	
	Dog	10	<10	450	1.5	
	Human	17		1890	3.6	$t_{1/2resp}$ one to two weeks

[a] Oral clearance.
[b] Effective half-life.
[c] *b.i.d.*

Gabrielsson et al.
Drug Discov Today 2009

Biomarkers for PK/PD-Modeling

Types of Biomarkers

Based on Application

Pathophysiologic Biomarkers

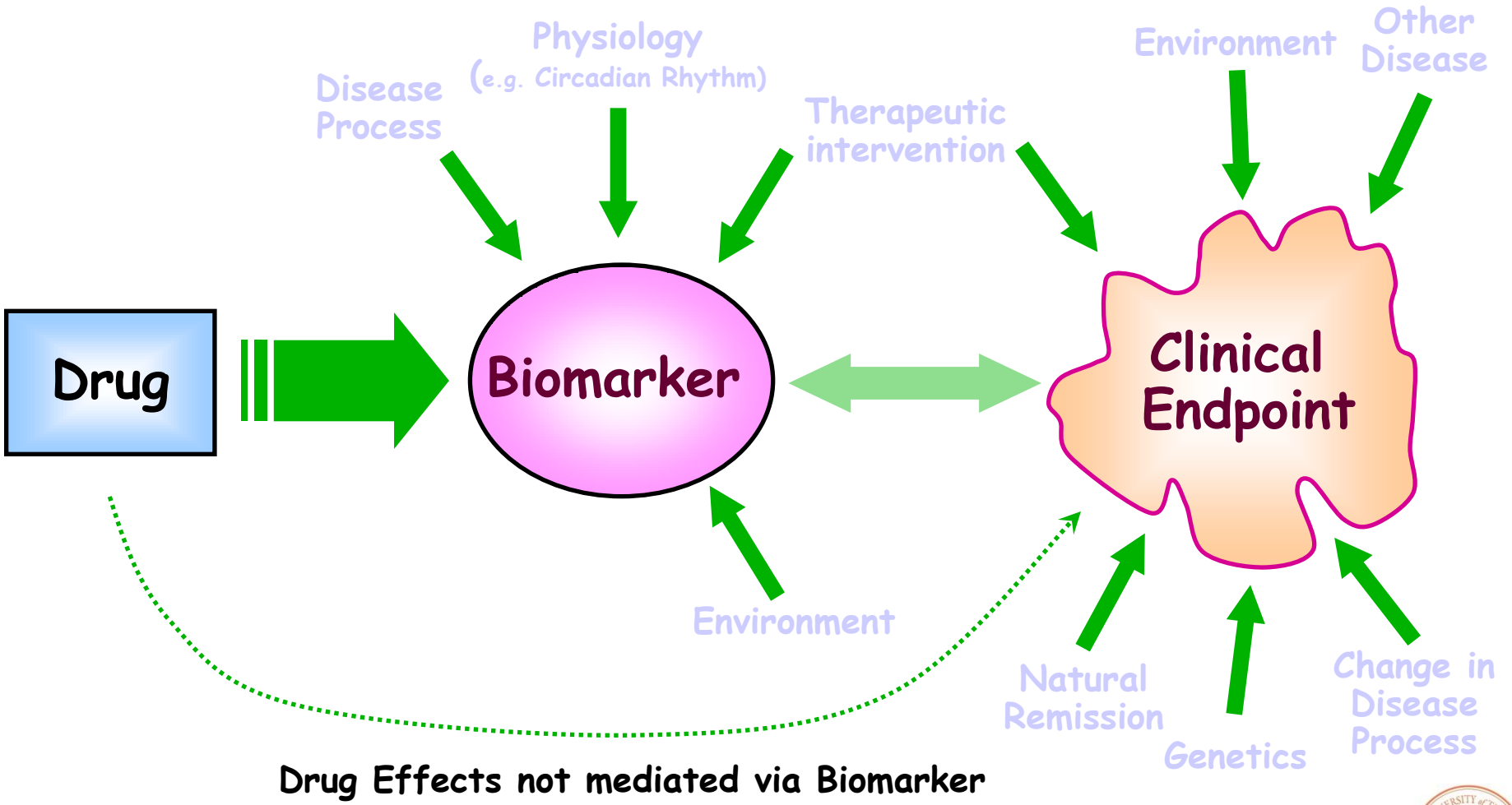
- **Disease Biomarker:** a biomarker than relates to a clinical outcome or measure of disease
- **Staging Biomarker:** a biomarker that distinguishes between different stages of a disorder
- **Predisposition Biomarker:** a biomarker that relates to the risk of developing a pathologic condition

Response Biomarkers: Measure response to therapeutic intervention

- **Toxicity Biomarker:** a biomarker that reports a toxicological effect of a drug
- **Stratification Biomarker:** a biomarker that is predictive for the presence/absence of drug response
- **Target Biomarker:** a biomarker that reports interaction of the drug with its target
- **Mechanism Biomarker:** a biomarker that reports a downstream effect of a drug

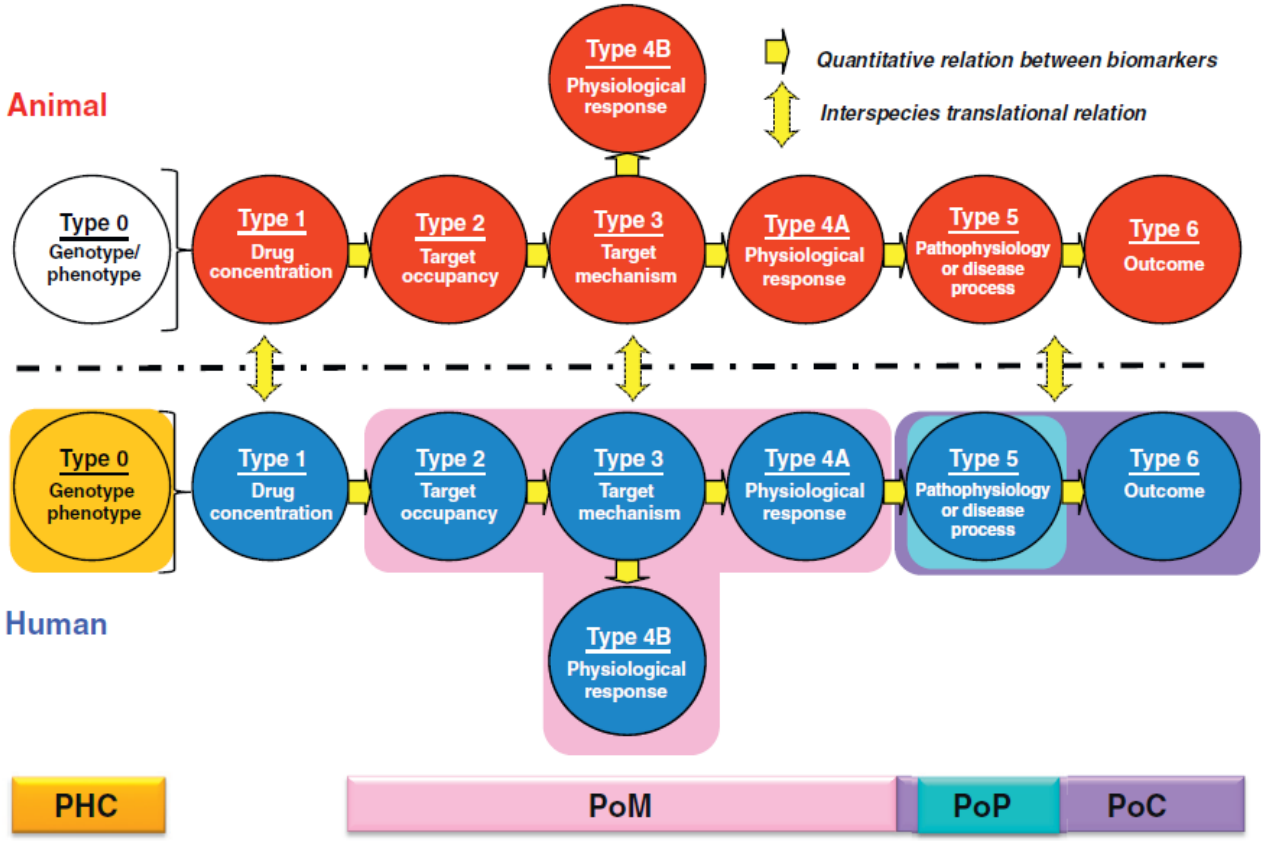
Biomarkers & Clinical Endpoints

Intermediate Measure of Drug Response



Biomarkers & Clinical Endpoints

Cascade of Intermediary Biomarkers



Type 0	Biomarker that determines the disease state or the potential for therapeutic response or patient stratification (e.g., genotype or phenotype)
Type 1	The PK of the compound; typically unbound plasma concentrations and/or target site exposure
Type 2	Target occupancy via a direct measurement of receptor binding.(e.g., PET, autoradiography)
Type 3	An immediate biochemical response as a result of the interaction with the target (e.g., measure of signal transduction or of an enzyme product)
Type 4A	A physiological or tissue response directly linked to the pathophysiology
Type 4B	Parallel pharmacology driven through the same target but not directly linked to the pathophysiology (e.g., different tissues, such as central versus peripheral)
Type 5	A biomarker of the pathophysiology (e.g. disease marker)
Type 6	Clinical measure of the outcome in a patient population approved by regulators (e.g., pain relief)

Visser et al., Drug Discov Today 2013, 18:764-75

Biomarkers & Clinical Endpoints

Cascade of Intermediary Biomarkers

- Biomarkers are usually more closely related to the drug's mechanism of action than clinical endpoints
- Biomarkers are usually more precisely measured with validated assays compared to clinical outcome
- Biomarkers usually have a larger dynamic range compared to clinical endpoints.
- Variations in biomarker signal(s) are usually more causally related to drug effect than variations in clinical endpoints
- Biomarker may be useful even if not validated as surrogate endpoint predictive for clinical endpoints

➔ **Biomarkers may be superior to clinical endpoints for the characterization of exposure/response relationships**

Application of PKPD M&S Strategies in Drug Development

1. Exploring and optimizing study designs and treatment options
2. Integrating data over multiple studies and development phases
3. Confirmatory evidence for regulatory approval

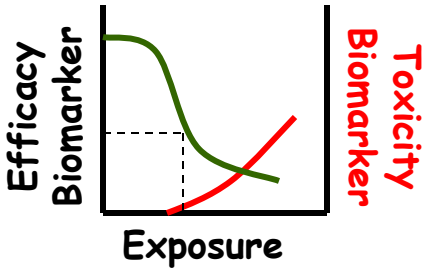
Clinical Trial Simulation (I)

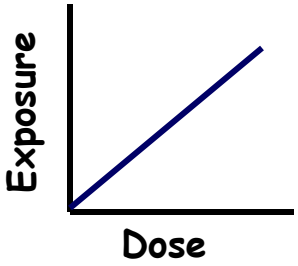
- Simulation *in silico* how a trial performs based on prior knowledge and assumptions for underlying distributions and mechanisms
  - ✓Study design: inclusion/exclusion criteria, setup, dosing regimens, measurements and interventions
  - ✓Structural dose-concentration-response/toxicity relationship (PK-PD-model)
  - ✓Between and within patient variability in PK and PD parameters
  - ✓Effect of patient characteristics (covariates) on PK and PD
  - ✓Natural progression of the disease
  - ✓Adherence, drop-out rate, enrollment limitations

- Simulation execution
  - ✓Monte-Carlo simulation
  - ✓Hundreds to thousands of replicates
  - ✓Analysis of each study according to predefined analysis plan for primary/secondary outcomes
    - o e.g. ANOVA between treatment arms for efficacy outcome parameters

Clinical Trial Simulation (II)

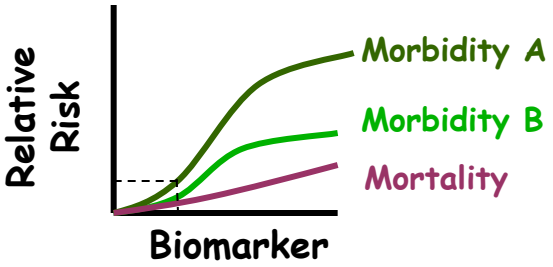
Exposure-Response Model (PK/PD)

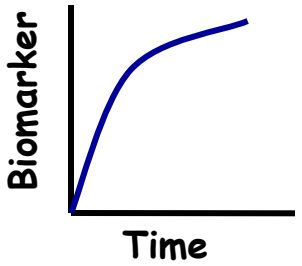




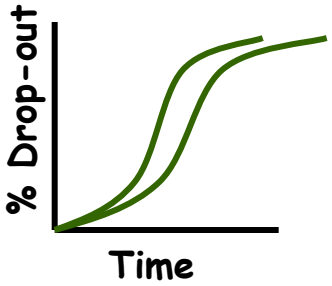
In silico Clinical Trial

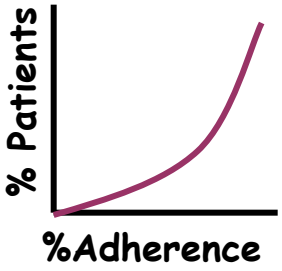
Disease Progression & Placebo Model

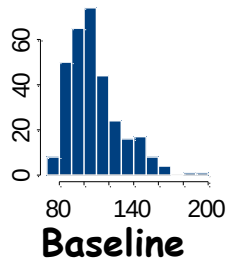


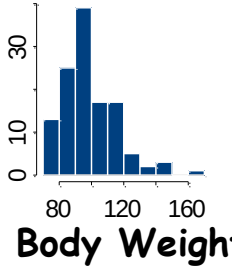


Trail Execution model



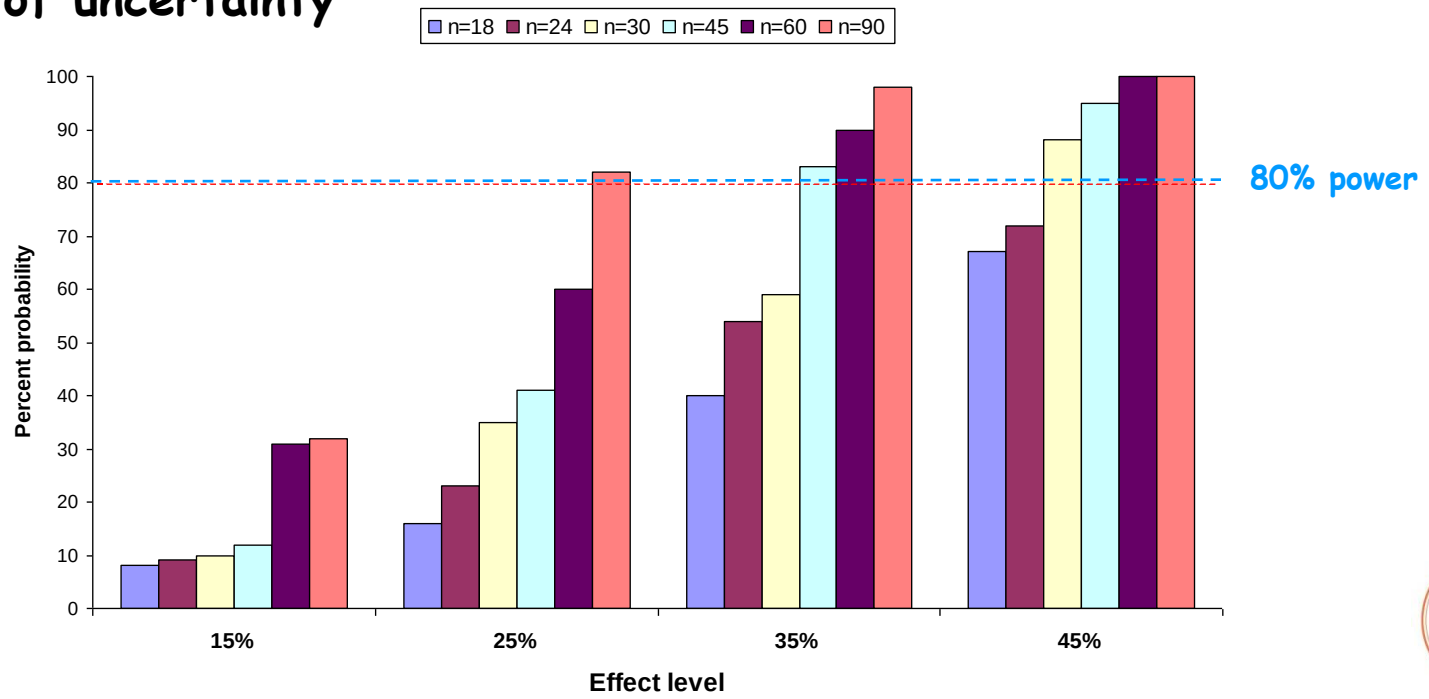






Clinical Trial Simulation (III)

- Outcome metric of simulation
  - ✓Probability distribution rather than p-value
  - ✓Fraction of simulated studies that meet predefined outcome
    - What is the likelihood of a given trial design to achieve a certain outcome
    - How sensitive is the trial outcome the underlying assumptions (e.g. efficacy, variability, adherence etc.)
- Provides insights into trial performance and thus offers a rational basis for making decisions about a clinical study given different areas of uncertainty



Evaluation of Dose Intensification

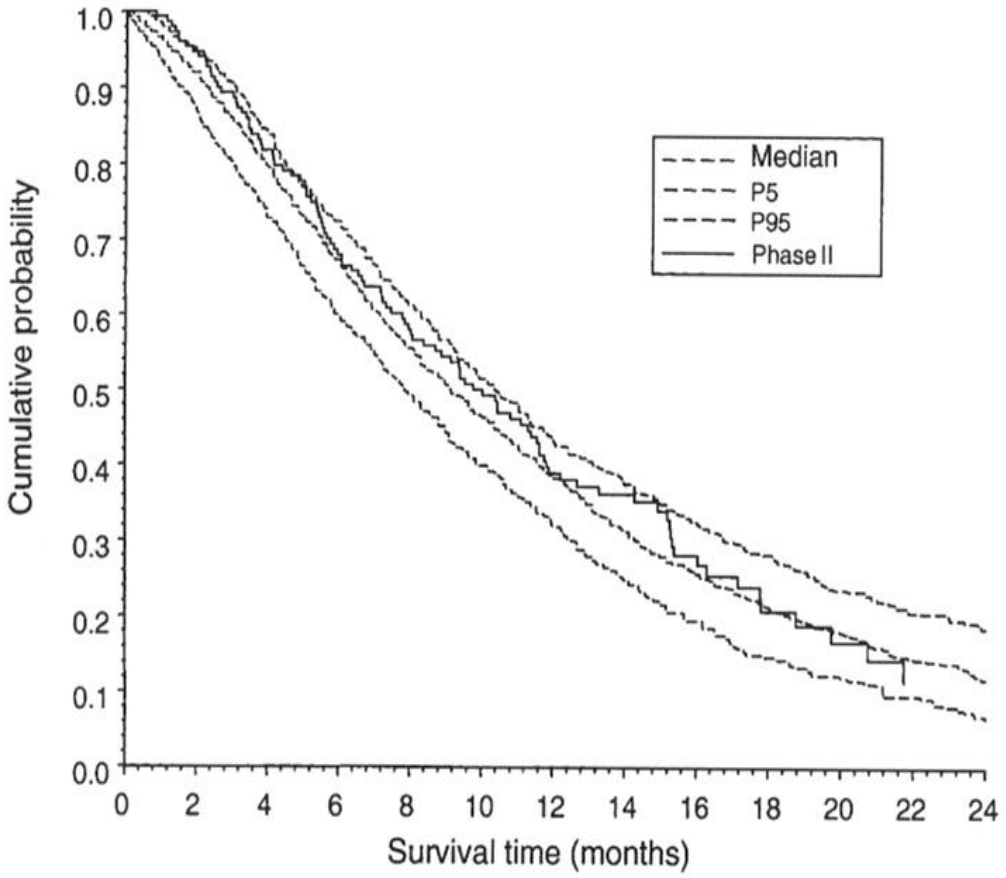
Docetaxel Phase III Study

- Population PK/PD analysis of Phase II data:
  - ✓ NSCLC patients with increased AAG have shorter TTP and survival
  - ✓ AAG as docetaxel binding protein may alter distribution processes
- Do patients with increased AAG benefit from dose intensification ?
- Clinical trial simulation of Phase III study to evaluate whether this question can be addressed

Veyrat-Follet *et al.*, Clin. Pharmacol. Ther. 2000; 68:677-87

Evaluation of Dose Intensification

Docetaxel Phase III Study



Model validation:

- Simulation of Phase II study that was used for model development
- 100 studies in 151 patients

	Actual	Simulated
No. of deaths	105	111(102-119)
Median survival [months]	10(8.6-11.6)	9.1(7.8-10.4)
1 year [%]	39	38(32-43)

Veyrat-Follet *et al.*, Clin. Pharmacol. Ther. 2000; 68:677-87

Evaluation of Dose Intensification

Docetaxel Phase III Study

- Simulation of 100 studies with 200 NSCLC patients with increased AAG

	100 mg/m²	125 mg/m²	Power [%]
TTP [weeks]	9.1 (8.0-10.5)	9.5 (8.4-10.8)	11
Survival [months]	5.3 (4.7-5.8)	5.5 (4.8-6.2)	6
1 year survival [%]	14 (11-18)	15 (10-20)	

- The simulations indicated a low power to detect a difference in survival due to dose intensification in the simulated study design.
- **Based on these simulations, it was decided not to perform the trial.**
- M & S provided key information for decision making in docetaxel development

Veyrat-Follet *et al.*, Clin. Pharmacol. Ther. 2000; 68:677-87

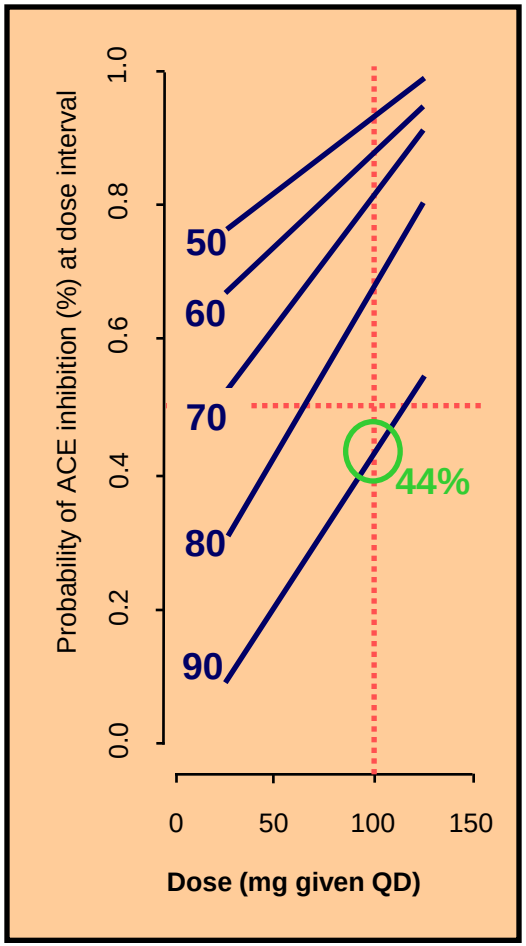
Application of PKPD M&S Strategies in Drug Development

1. Exploring and optimizing study designs and treatment options
2. **Integrating data over multiple studies and development phases**
3. Confirmatory evidence for regulatory approval

Evaluation of Dosing Frequency

Dosing Frequency of MDL100,173

- **Indication:** Treatment of hypertension, heart failure and renoprotection
- **Mechanism of action:** Vasopeptidase inhibitor: dual inhibition of angiotensin-converting enzyme (ACE) and neutral endopeptidase 24.11 (NEP)
- **Mechanism biomarker:** % Plasma ACE inhibition
- **Study design:**
  - ✓ Four phase I/II studies with multiple dose levels where MDL100,173 was given orally as thioester prodrug M100240
  - ✓ Healthy subjects (n=62) and hypertensive patients (n=189)
  - ✓ Combined population PK/PD analysis with ACE inhibition directly linked to the plasma concentration via an E_{max} model with a circadian rhythm for ACE activity
- **Study objective:**
  - Evaluate whether once daily administration is feasible for efficacious dosing regimens

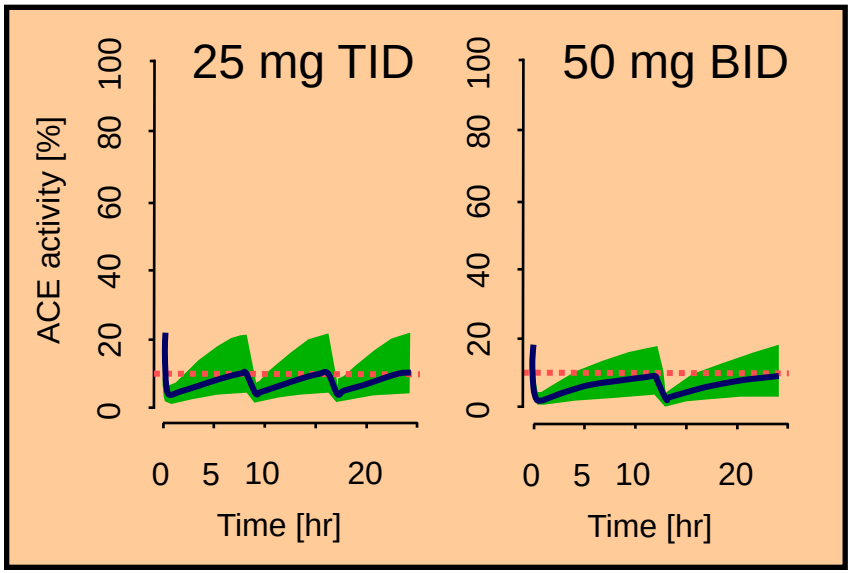


Pfister et al., J Clin Pharmacol 2004, 44, 621-31

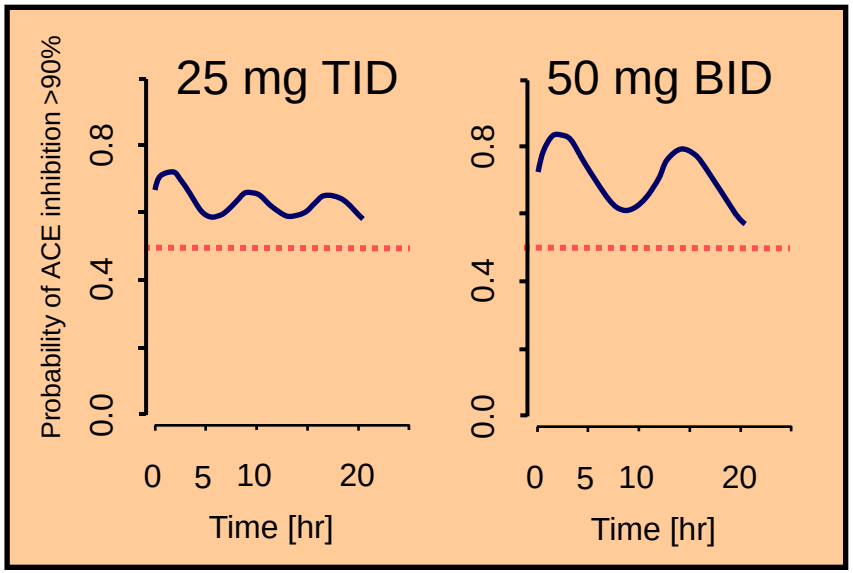
Evaluation of Dosing Frequency

Dosing Frequency of MDL100,173

ACE Activity Profiles
(median, 10-90th percentile)



Probability of ACE inhibition >90%
(Target: 50% of the population)



- **Target:** 90% ACE inhibition over 24 hours in at least 50% of patients
- **Conclusion:** Higher and/or more frequent doses are necessary to achieve target, e.g. 25 mg TID or 50 mg BID.

Pfister et al., J Clin Pharmacol 2004, 44, 621-31

Application of PKPD M&S Strategies in Drug Development

1. Exploring and optimizing study designs and treatment options
2. Integrating data over multiple studies and development phases
3. **Confirmatory evidence for regulatory approval**

Simulation for Regulatory Approval

Gabapentin sNDA for neuropathic pain

- Gabapentin approved 1993 as adjunctive therapy in the treatment of partial seizures in epilepsia
- Postmarketing, anecdotal evidence of efficacy in post herpectic neuralgia ⇨ supplemental NDA
- Two randomized placebo controlled trials, but different dose levels:

Study	Study Duration	Gabapentin (mg/day)[a] Target Dose	Patients Receiving Gabapentin	Patients Receiving Placebo
1	8 weeks	3600	113	116
2	7 weeks	1800, 2400	223	111
		Total	336	227

[a] Given in 3 divided doses (TID)

- Regulatory concern:
  - ✓No replication of efficacy at tested doses
  - ✓Exposure-response for gabapentin complicated by saturable absorption, leading to less than proportional increases in exposure with increasing dose

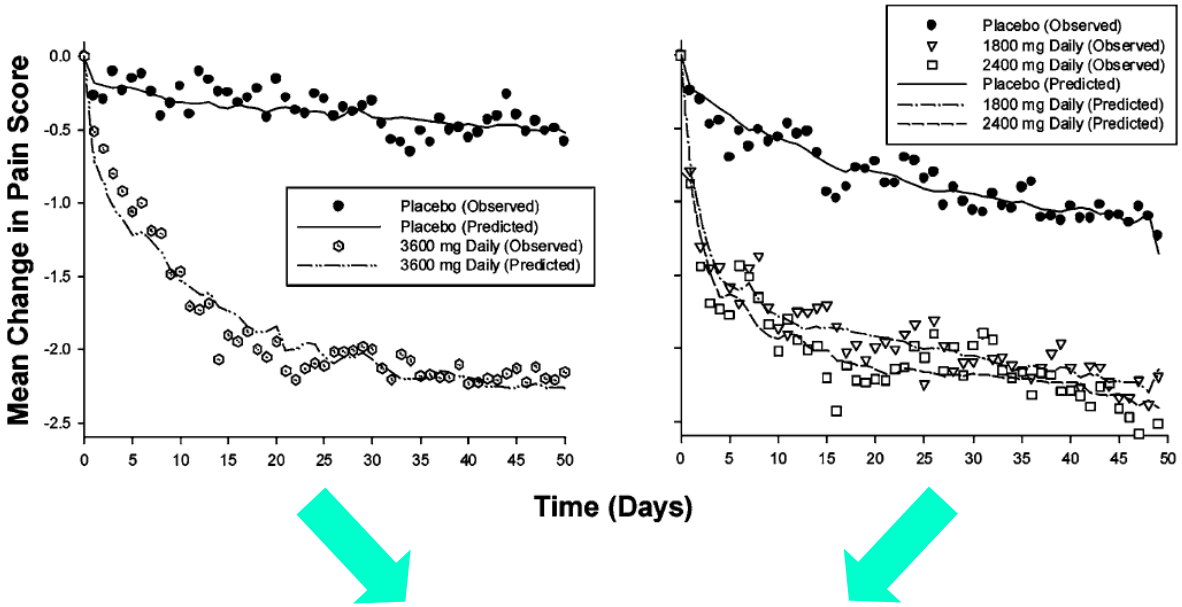
Simulation for Regulatory Approval

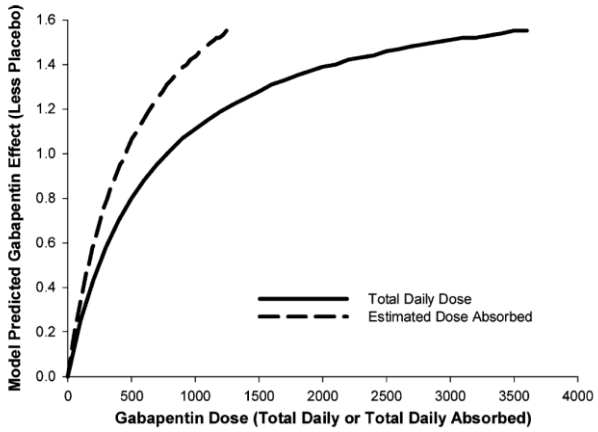
FDAMA 1997

- At least two adequate and well controlled clinical investigations (pivotal Phase III trials) required to confirm effectiveness
- Food & Drug Administration Modernization Act 1997 opens MBDD application for approval
  - ✓ FDAMA SEC. 115. CLINICAL INVESTIGATIONS.
    (a) Clarification of the Number of Required Clinical Investigations for Approval. Section 505(d) (21 U.S.C. 355(d)) is amended by adding at the end the following:
    "If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.''
- FDAMA: one pivotal trail combined with confirmatory evidence (such as M&S based exposure-response data) may be sufficient to confirm effectiveness

Simulation for Regulatory Approval

Gabapentin sNDA for neuropathic pain





- M&S based exposure-response information used to link the two pivotal trials
  - ✓Population PK/PD analyses quantifying exposure-dependent decreases in daily pain score with correction of estimated bioavailability and time-dependent placebo effect

Miller *et al.*,
J Pharmacokinet Pharmacodyn 32, 185-197

Simulation for Regulatory Approval

Gabapentin sNDA for neuropathic pain

- PK/PD analysis needed to withstand the same qualitative and quantitative review that data from a pivotal trial would:
  - ✓Analysis tested and reviewed by FDA
  - ✓Using data from additional 3 randomized, placebo-controlled phase II studies
  - ✓Longitudinal analysis of all data simultaneously
  - ✓By considering patient demographics, dose, baseline, treatment, and placebo effects, pain scores could be predicted with confidence based on information from either the four other studies or from the comparative pivotal study
  - ⇨Both pivotal clinical studies would have the same pain relief outcomes if doses were the same ⇨ cross-confirming
  - ⇨Confirmation of efficacy across the three studied doses
- Package insert/prescribing information: *"PK/PD modeling provided confirmatory evidence of efficacy across all doses"*

PKPD M&S in Drug Development

Conclusions

- M&S and MBDD are multi-disciplinary approaches that integrate the relationships between disease, drug characteristics and individual variability in drug response.
- M&S is already established in multiple areas of drug development, with a high likelihood of further expansion.
- M&S provides a quantitative, data-driven framework that enables rational, scientifically–based choices at critical decisions points in drug development.
- M&S allows for a more efficient drug development process through more informed go/no-go decisions and optimized resource allocation.

www.PKPDofProteinTherapeutics.com

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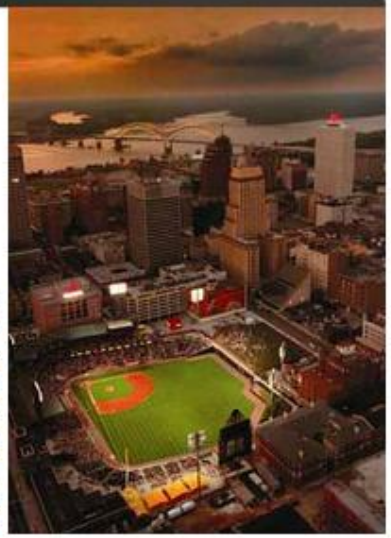
6th *Introductory Pharmacometric Training Course*

Pharmacokinetics & Pharmacodynamics of Protein Therapeutics

- Concepts and Hands-On Modeling and Simulation -



Course Directors:
Bernd Meibohm, University of Tennessee
Johan Gabrielsson, Swedish University of Agricultural Sciences

The 5-day course will introduce participants to basic principles in the pharmacokinetic and pharmacodynamic evaluation of novel protein therapeutics and provide opportunities for hands-on PK and PK/PD modeling and simulation examples relevant for protein drugs. Topics include target-mediated drug disposition, tissue and tumor penetration, interspecies scaling, first-in human dose selection, immunogenicity, model-based drug development, disease progression modeling, and drug-drug interactions. Hands-on data analysis will be performed individually and in small groups using several software packages.

Location: **University of Tennessee College of Pharmacy, Memphis, TN, USA**

Time: April 11-15, 2016

Last updated: May 30, 2012

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Participants of the 2nd 'PKPD of Protein Therapeutics' pharmacometric training course, April 2012

April 11-15, 2016

sity of Tennessee