



Role of PKPD Modeling and Simulation in Influencing the Design of Early Clinical Studies

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Outline

- A Brief History of PK/PD and of its Environment
- Role of PK/PD Modeling and Simulation in Influencing the Design of Early Clinical Studies
 - Case Study 1: transitioning from preclinical to FIH
 - Case Study 2: assessment of an in-licensing candidate
- Future perspectives of PK/PD Modeling and Simulation

A Brief History of PK/PD

THE LATE 60'S: A PREMATURE BIRTH?



1968: The Birth of PK/PD

- Presence of a delay between norepinephrine concentration-time profiles and the kinetics of pharmacological response, i.e. blood pressure-time data.
- Gino Segre introduced the concept of a “hypothetical effect compartment” to account for this delay.
- This allowed an empirical description of time-dissociated kinetics.

Segre G. Kinetics of interaction between drugs and biological systems. *Farmaco Sci.* 1968 Oct;23(10):907-18.

1968: Was it a Premature Birth?

- NONLIN software only introduced in a year later by Carl Metzler.
- It was written in FORTRAN-66 programming language for mainframe computers.



- Long gap of PK/PD publications until 1979

CM Metzler. A Users Manual for NONLIN. Technical Report 7297 69 7292 005. Upjohn Co., Kalamazoo, Michigan (1969).

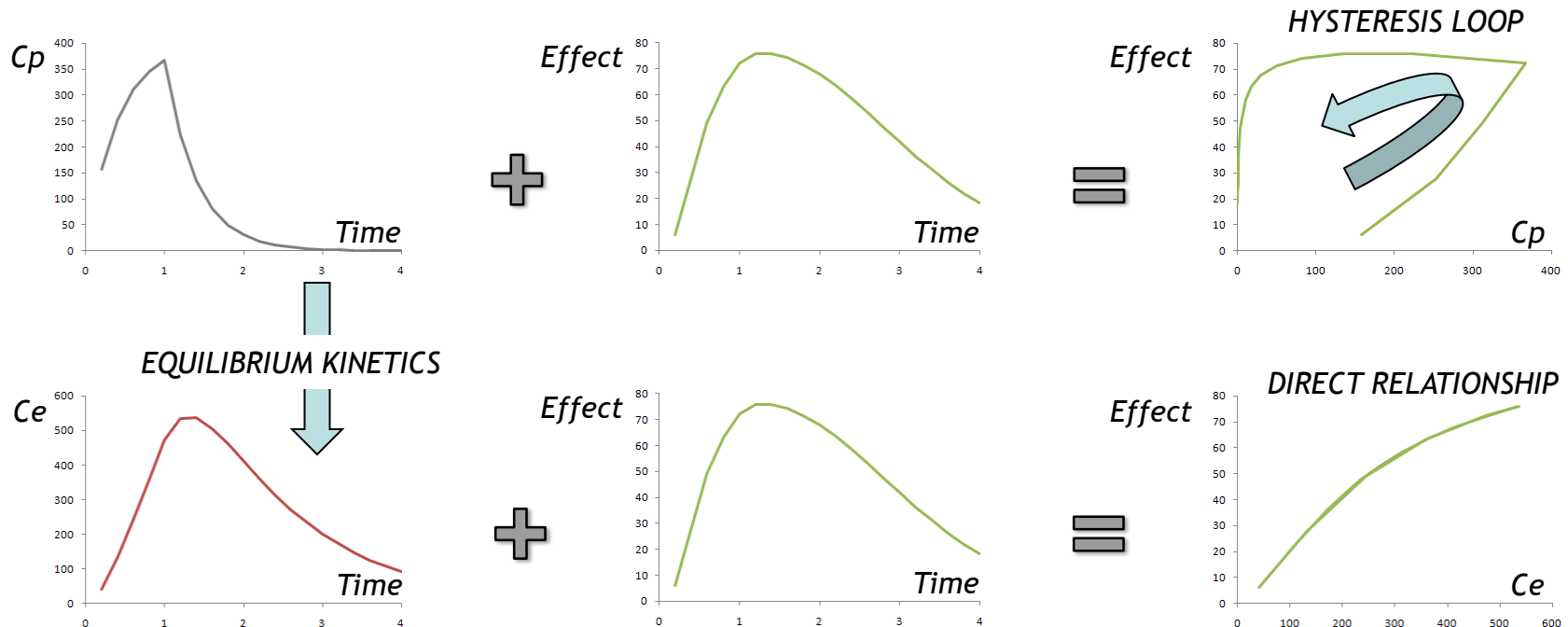
A Brief History of PK/PD

THE LATE 70'S: A REBIRTH



1979: A Rebirth

Lewis Sheiner and coworkers made Segre's model more popular. They were the first to formalize this concept into a model to describe hysteresis caused by distribution to the biophase. It was reborn as the "Link Model":

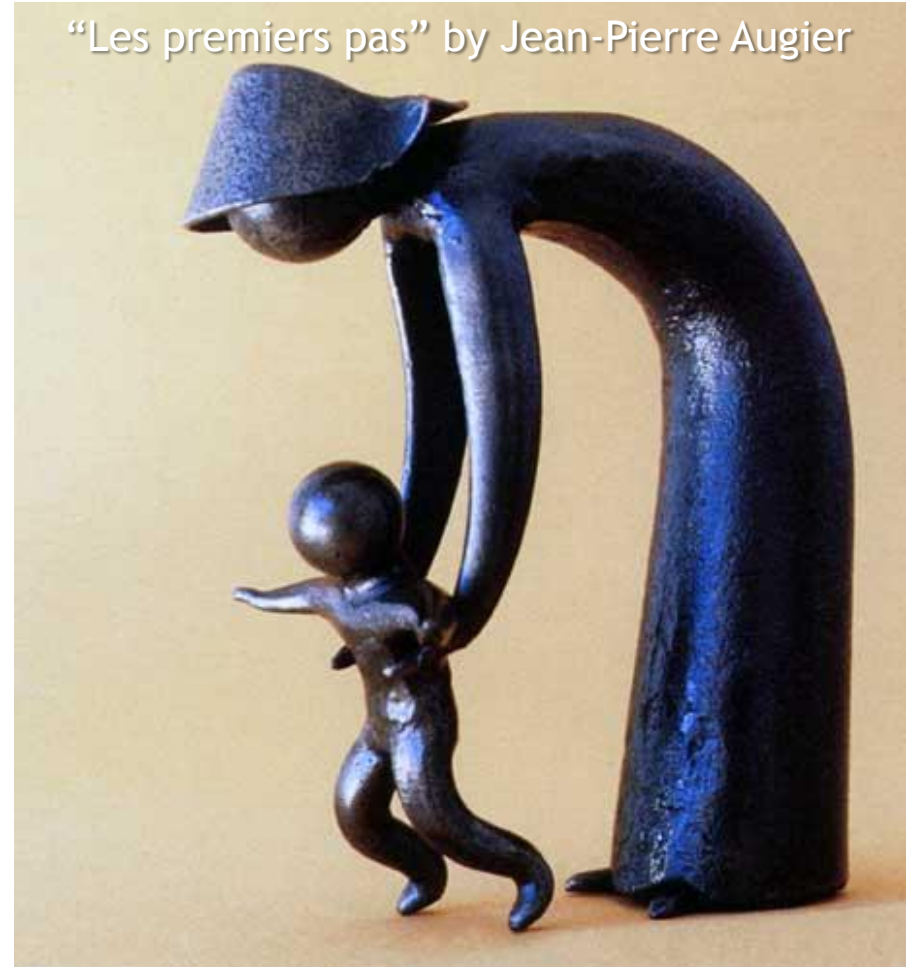


Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. Clin Pharmacol Ther. 1979 Mar;25(3):358-71.

A Brief History of PK/PD

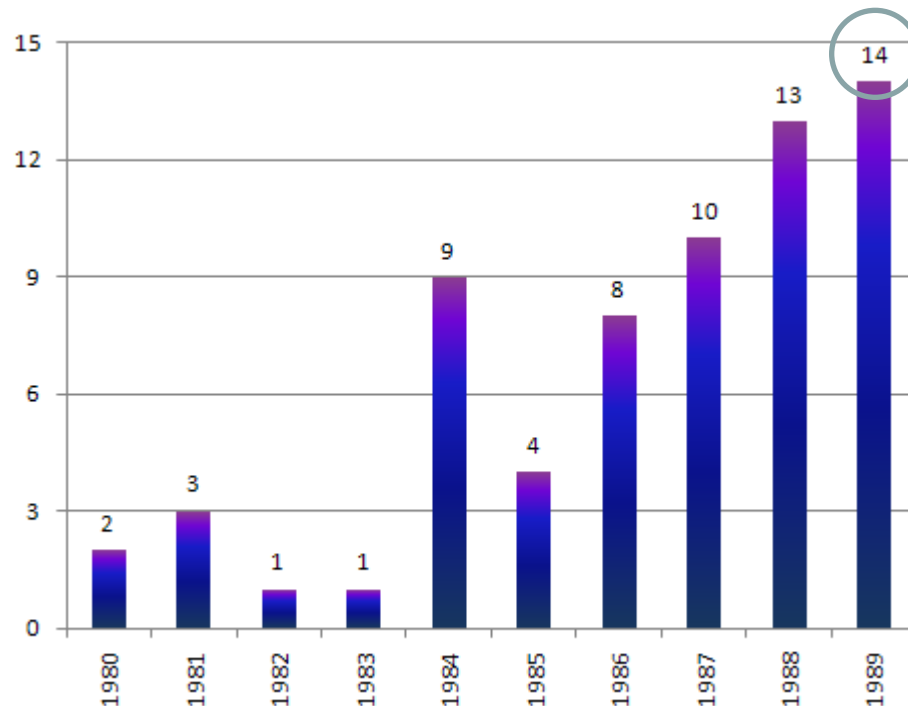
THE 80'S: TODDLING

“Les premiers pas” by Jean-Pierre Augier



80's: Toddling

Growing use of PK/PD modeling, with applications to diverse therapeutic areas (mainly cardiovascular)



Source: Pubmed search on March 29th, 2011 (Key-words: “pharmacodynamic AND modeling”)

80's: Toddling

1982
MS-DOS 1.0

NEC APC
\$5,000



Apr. 1980
NONMEM

IBM-specific
magnetic tapes

NONLIN84

```

MODEL
COMMANDS
NFUN 2
NCON 7
REMA NUMBER OF DOSES, DOSE, BW, DOSING TIMES
CONS      4, 5000, 58.4, 0, 24, 48, 72
NPAR 7
PNames Primary Parameters names
INIT 2 0.007 0.6 0.04 10 2 0.1
LOWER 0 0 0 0 0 0 0
UPPER 500 50 10 1 100 100 5
NSEC 25
SNames Secondary Parameters names
XNUM 1
YNUM 2
FNUM 3
METHOD 1
ITER 5000
END
EOM
TITLE
Title for the model
DATA Path and filename for the data
REWEIGHT -2
BEGIN
FINISH
    
```

1989
NONMEM III

First NONMEM course

MicroVAX II



1986
PCNONLIN

1985
Sharp PC-7000
\$1,800



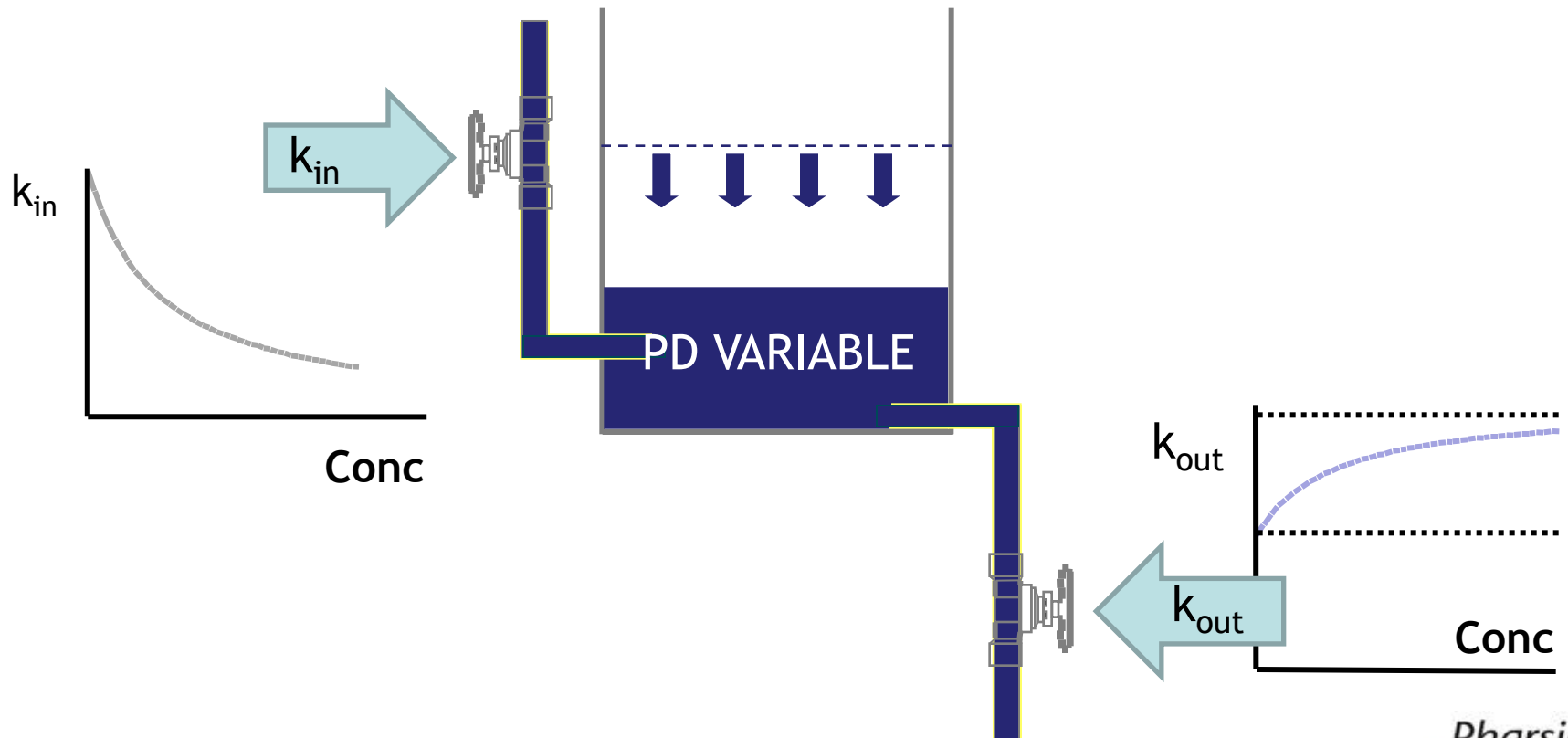


A Brief History of PK/PD

THE 90'S: A STEEP LEARNING CURVE

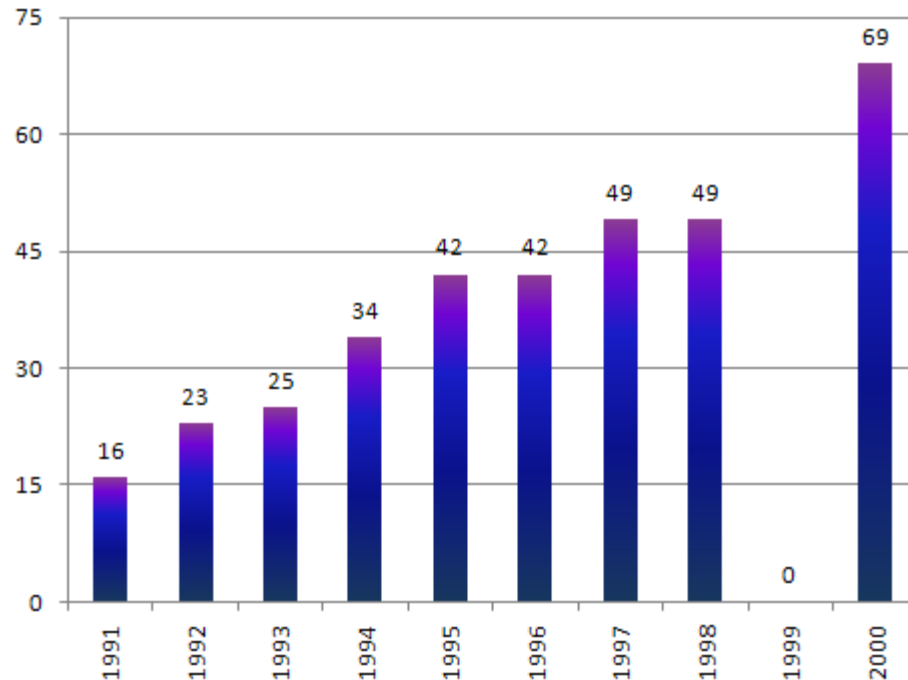
90's: The Advent of Mechanism-Based PK/PD

In so-called “Indirect Physiological Response (IPR) models”, the drug concentration is no longer related to the PD variable itself. Instead, it is assumed to modulate upstream and/ or downstream regulation mechanisms.



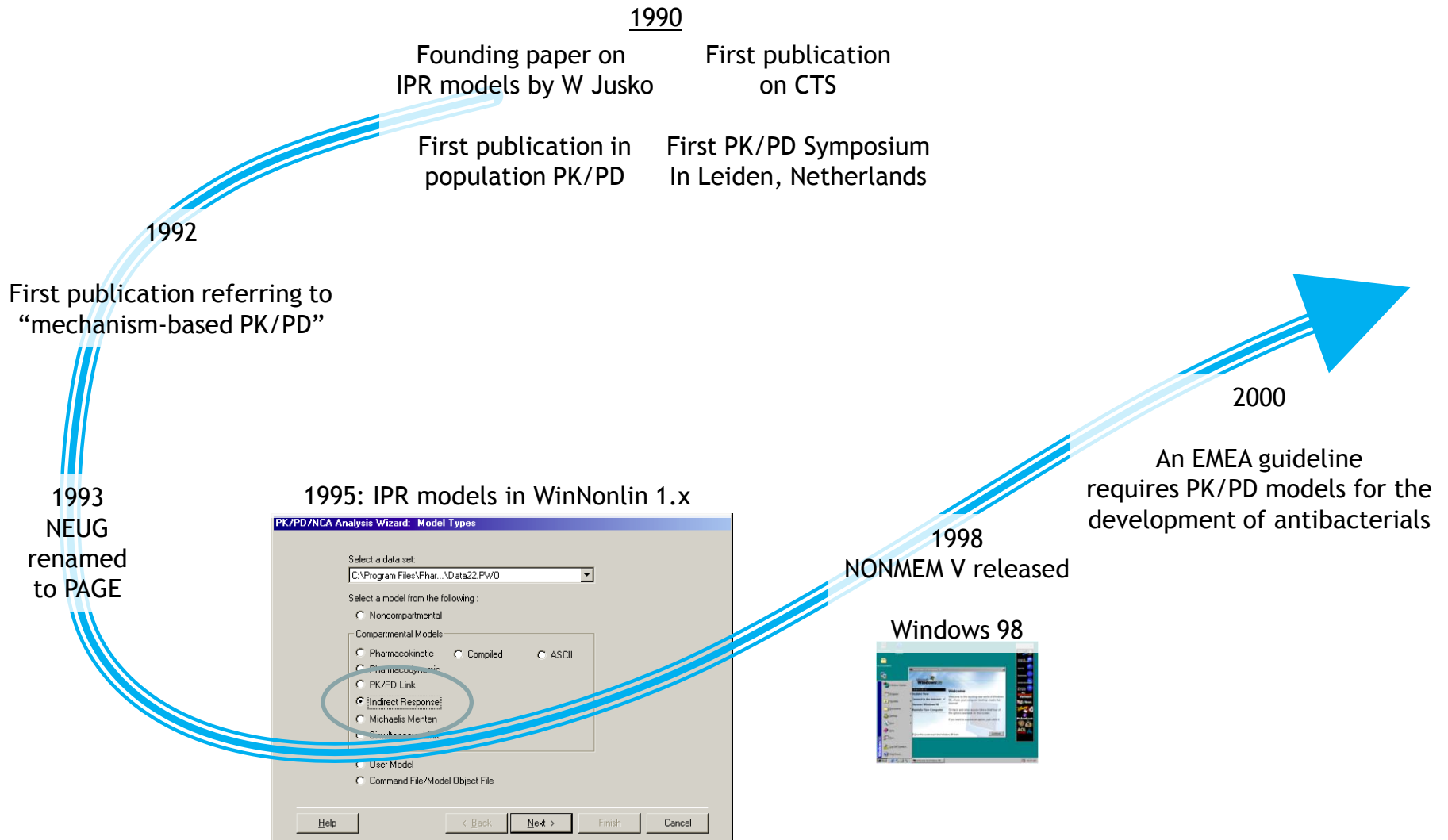
90's: The Advent of Mechanism-Based PK/PD

Significant increase in the number of publications.
Predominantly theoretical until 1993. Growing number of increasingly complex applications afterwards.



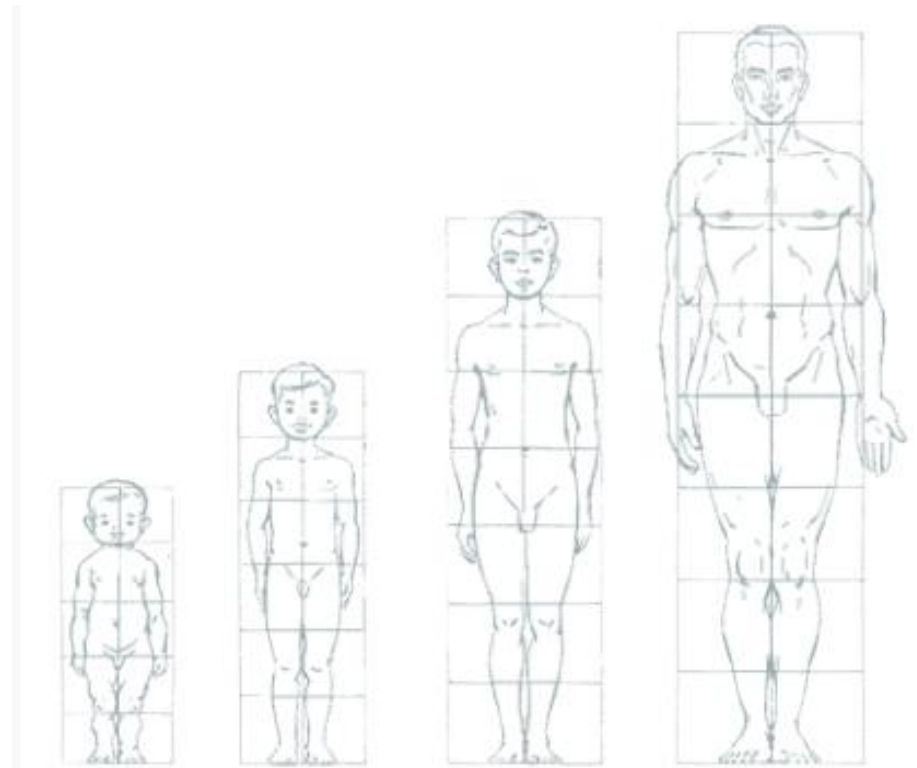
Source: Pubmed search on March 29th, 2011 (Key-words: “pharmacodynamic AND modeling”)

90's: The Advent of Mechanism-Based PK/PD



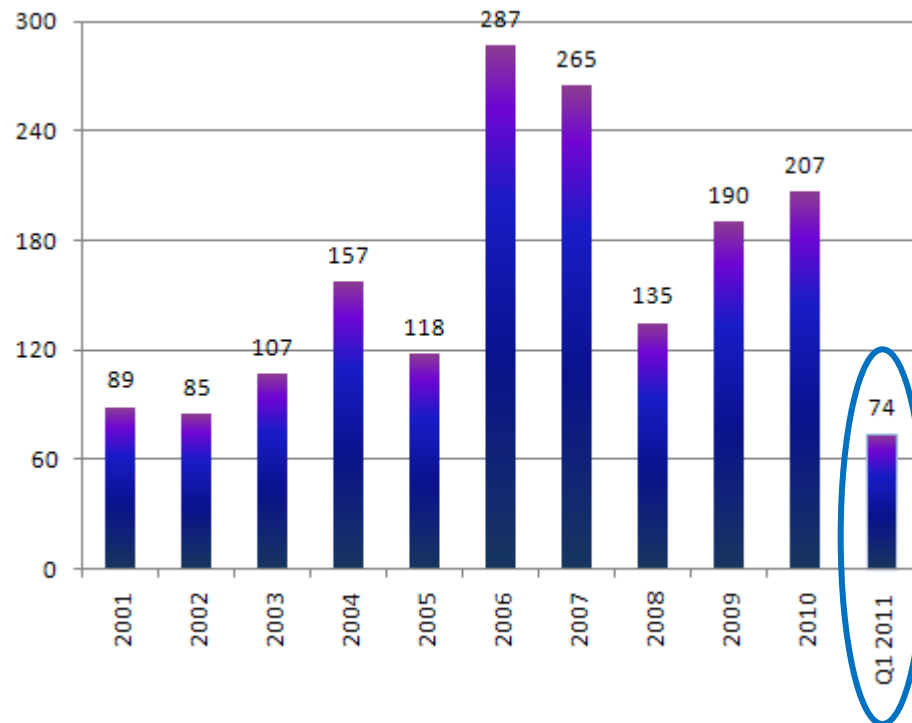
A Brief History of PK/PD

PK/PD TODAY: A MATURE DISCIPLINE



PK/PD Today: a Mature Discipline

Since 2000, the number of published PK/PD models has increased dramatically, with slightly more papers in Q1 this year than in the whole year 2000.



Source: Pubmed search on March 29th, 2011 (Key-words: “pharmacodynamic AND modeling”)

PK/PD has Matured Technically...

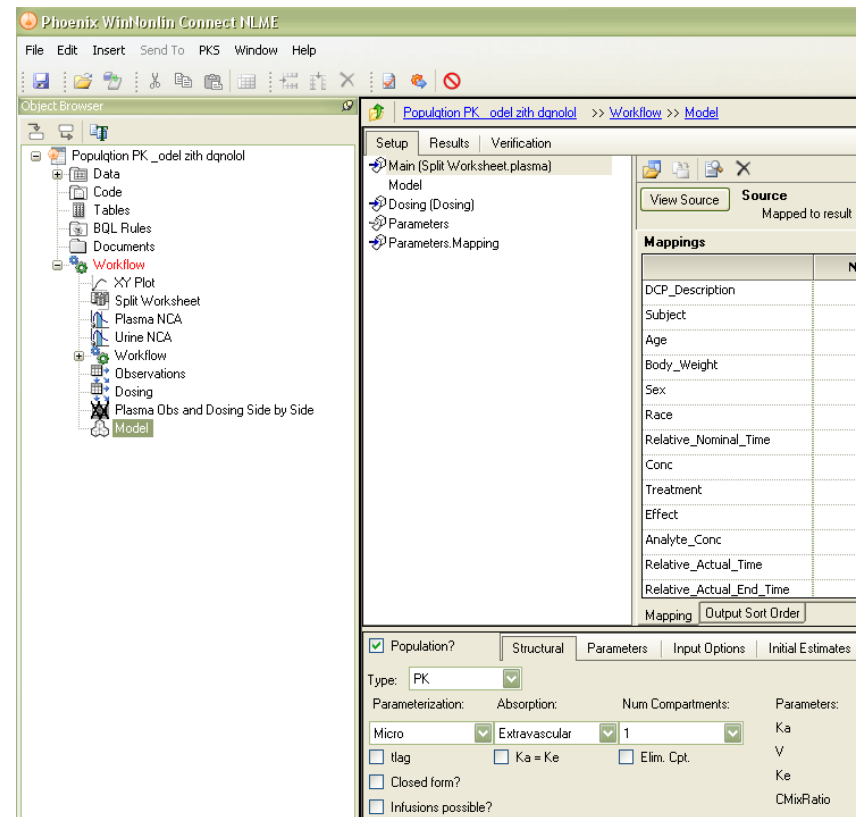
- Types of PD variables:

- Continuous
- Categorical
- Binary
- Time to event

- Types of models:

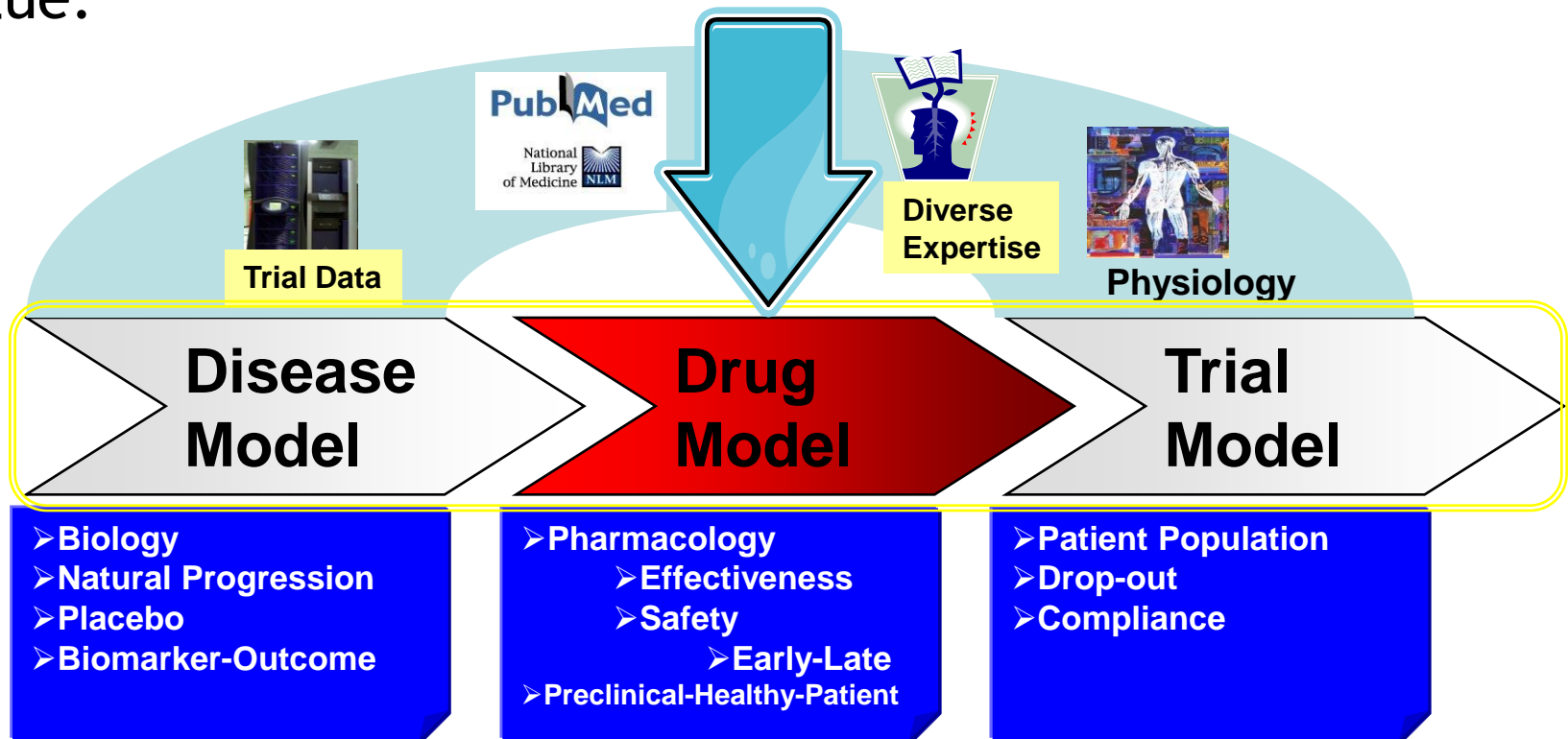
- Direct or link models
- Indirect response models
- PD Drug interaction models
- Closed-loop dynamic systems
- Mechanistic models, e.g. TMDD
- Baselines with complex patterns
- Linkage to decision analytic and economic models

- Phoenix® NLME: a Dedicated Technology Platform



... and Strategically

Application of integrated drug-disease-trial models to optimize clinical development programs with respect to therapeutic potential, R&D productivity and commercial value.



Graphic provided courtesy of Dr. Joga Gobburu, OCP/FDA.

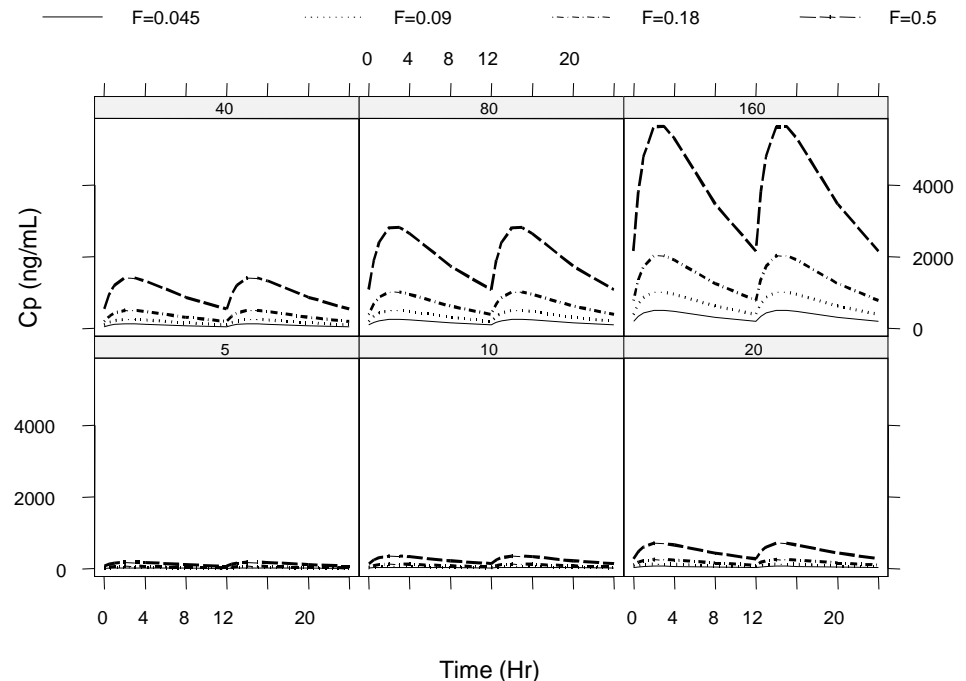
ROLE OF PK/PD MODELING AND SIMULATION IN INFLUENCING THE DESIGN OF EARLY CLINICAL STUDIES

Case Study 1: Transitioning from Preclinical to FIH

Allometric scaling was used to predict human pharmacokinetics of CS-3030, an oral, direct Factor Xa inhibitor. A combination of daily doses (10 to 320mg), regimens (QD and BID), and bioavailability ranges (4.5 to 50%) was chosen to compensate for any misspecification due to projection method or underlying assumptions.

Parameter	Monkey	Projected Human
Ka	0.75 h ⁻¹	0.75 h ⁻¹
V/F	7.6 L	151 L
CL/F	0.5 L/h/kg	18.2 L/h

Assumes F = 0.09



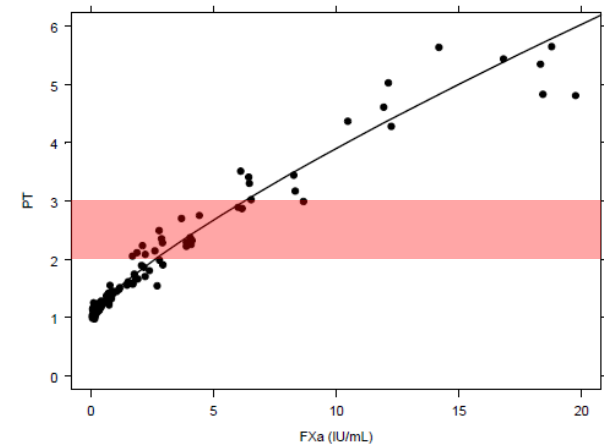
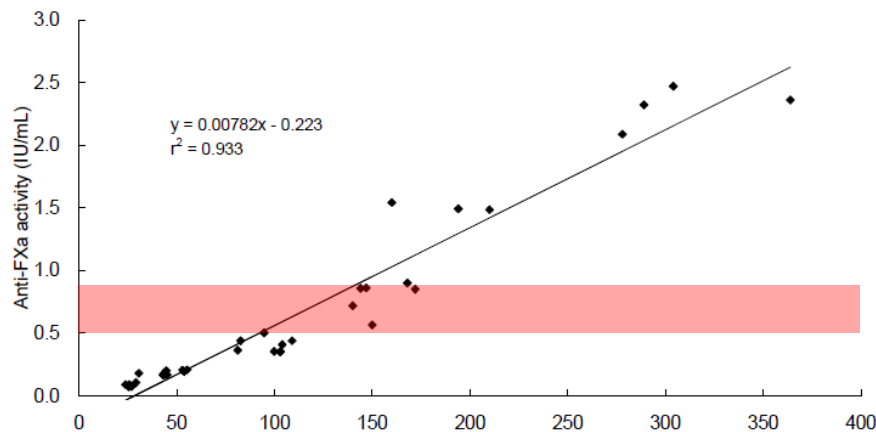
S Rohatagi et al., Model based development of a direct Factor Xa inhibitor, ACoP Meeting, Tucson AZ, Mar 2008

Case Study 1: Transitioning from Preclinical to FIH

Preclinical PK/PD data from cynomolgous monkey, relative potency information and literature data were used for simulation. Similar biomarker models were assumed in monkey and human.

$$\text{Anti-FXa} = 0.008 \cdot C_p - 0.2$$

$$\text{PT} = 1 + 0.47 \cdot (\text{Anti-FXa})^{0.8}$$



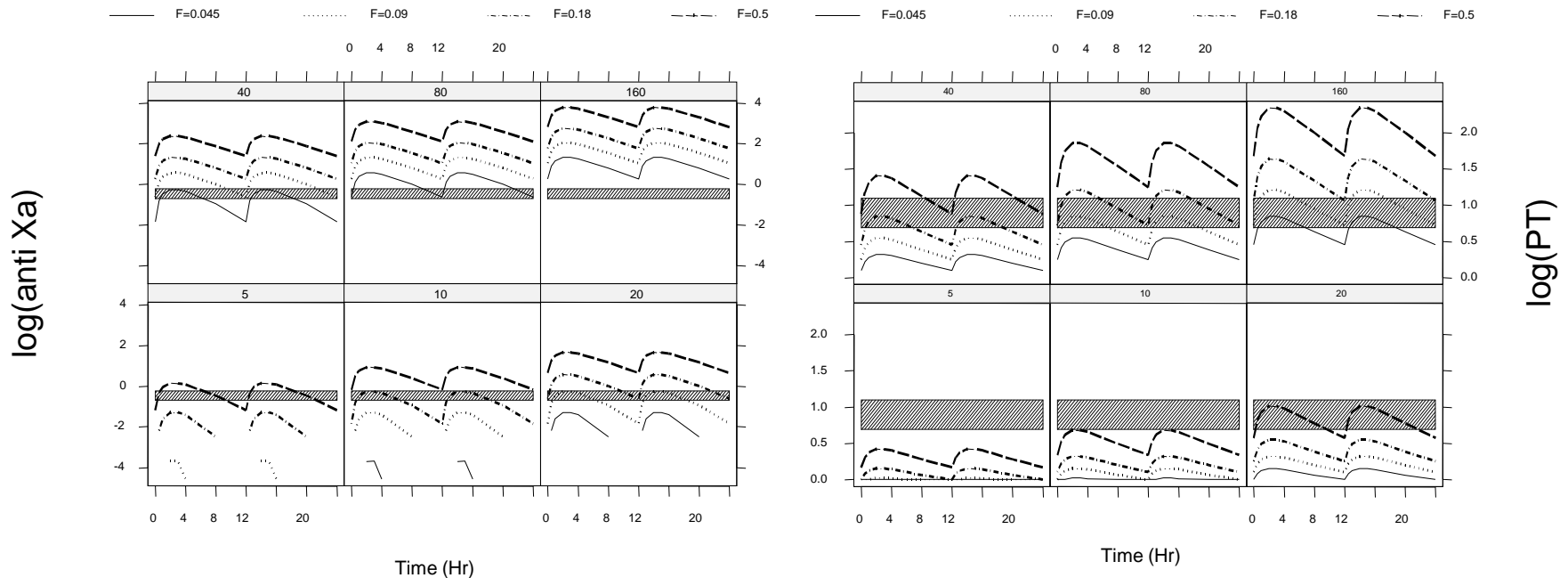
The following criteria to determine the target dose range:

- anti-FXa activity within 0.5-0.8 IU/mL range (based on enoxaparin)
- 2- to 3-fold increase in PT (based on warfarin)

S Rohatagi et al., Model based development of a direct Factor Xa inhibitor, ACoP Meeting, Tucson AZ, Mar 2008

Case Study 1: Transitioning from Preclinical to FIH

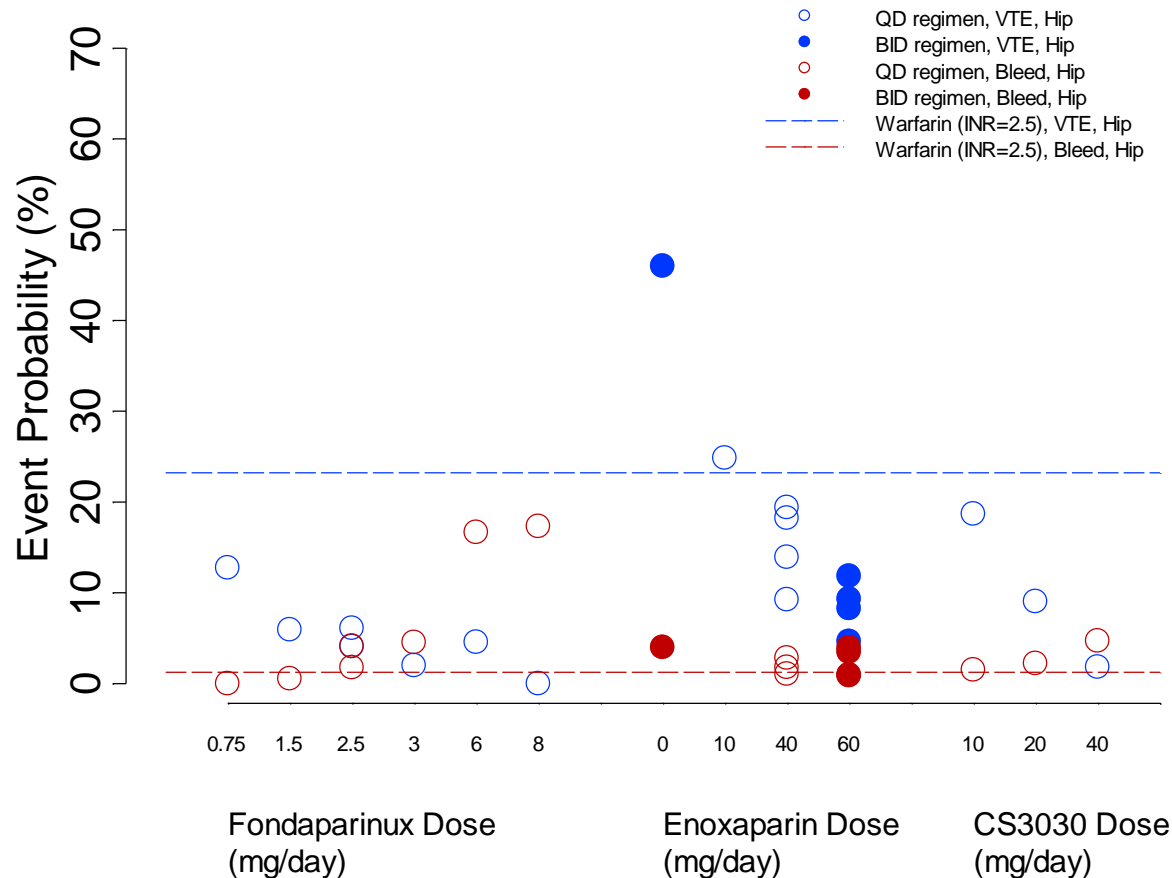
Time-courses of anti-FXa activity and PT were derived:



S Rohatagi et al., Model based development of a direct Factor Xa inhibitor, ACoP Meeting, Tucson AZ, Mar 2008

Case Study 1: Transitioning from Preclinical to FIH

Comparison across drugs showed favorable projected response profile for CS-3030, comparable to observed responses for comparator drugs.



S Rohatagi et al., Model based development of a direct Factor Xa inhibitor, ACoP Meeting, Tucson AZ, Mar 2008

Case Study 1: Transitioning from Preclinical to FIH

- None of the doses met the dual criteria of anti-FXa activity and PT response.
- Target achievement was consistently larger for BID as compared to QD regimens.
- If a single criterion was used, e.g. anti-FXa activity only, then a dose of 40 mg provided 50% time within the target range.
- Human projections from animal FXa activity suggest doses up to 40mg/day CS-3030 may provide similar efficacy (prevention of deep vein thrombosis) and safety (risk of bleeding) profiles to that of enoxaparin following hip and knees surgeries.

Case Study 1: Transitioning from Preclinical to FIH

- Integration of animal data and public literature allowed human PK-PD to be projected under certain plausible assumptions and scenarios.
- Human projections for CS-3030 identified dosing regimens which provided similar efficacy and safety profiles to that of comparators
- This example illustrates the application of M&S to guide drug development and inform the design of clinical trials.

Case Study 2: Should We In-License This Compound?

Client

- Specialty pharma focused on diabetes, obesity and metabolic disease
- Building portfolio through in-licensing clinical stage of drug candidates

Critical Issue

- Looking to get VCs to fund in-licensing for development of a PPAR- γ agonist for treatment of Type 2 diabetes
- Objective: need quantitative support for potential of efficacy and safety vs. currently marketed treatments (rosiglitazone, pioglitazone monotherapy)
 - Limited data available (1 Ph IIa study, 4 weeks, placebo + 2 doses, 75 subjects)
 - Analysis must be for similar patient populations and adjusting for the effects of baseline and other covariates of response

Motivating Factors

- Tight timeframe (3 weeks)
- CEO-level referral

Case Study 2 – Step 1: Model Diabetes Treatment Landscape

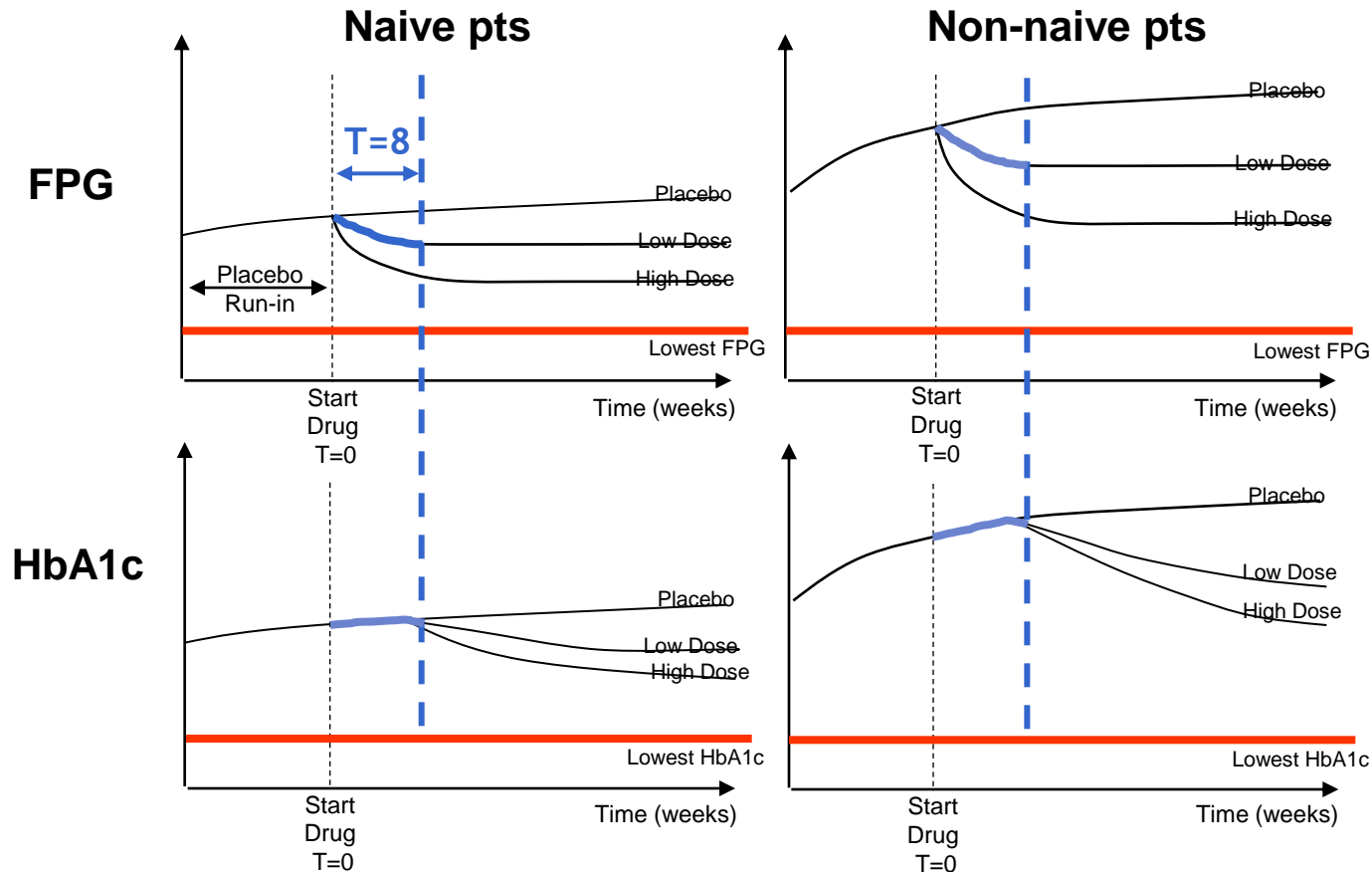
Build dose-response models for main efficacy and safety endpoints from NIDDM meta-database. Extracted summary level trial-data from literature.

Disease State/Indication			Version
Type II diabetes mellitus (NIDDM)			4.1
Time Period	Abstracts Reviewed	Studies Included	Literature Databases
1988-2006	750	106	PubMed, Medline, FDA Summary Basis of Approval (SBA)
Drug Classes	Endpoints	Comparative Treatments	
Sulfonylureas (first generation)	fasting plasma glucose, HbA1c, body weight	Chlorpropamide, Tolazamide	
Sulfonylureas (second generation)	fasting plasma glucose, glucose, HbA1c, lipids (total cholesterol, LDL, HDL, triglycerides), body weight, BMI, SBP, DBP, AIRg, Apo A1, Apo B, c-peptide, FFA, fructosamine, insulin, ISI, lactate, pyruvate, waist circ	Glyburide (Glibenclamide), Glipizide, Glimepiride	
Biguanides	fasting plasma glucose, HbA1c, lipids, body weight, BMI, SBP, DPB, adiponectin, ALP, ALT, AST, Apo A1, Apo B, c-peptide, CRP, AIRg, FFA, fructosamine, lactate, pyruvate, hematocrit, hemoglobin, insulin, ISI, waist circ. Waist to hip ratio	Metformin	
Fixed combinations	fasting plasma glucose, HbA1c, lipids, body weight, AIRg, Apo A1, Apo B, BMI, c-peptide, SBP, DBP, FFA, fructosamine, insulin, ISI, lactate, pyruvate, waist circ.	Metformin/glyburide, Metformin/rosiglitazone	
Thiazolidinediones	fasting plasma glucose, HbA1c, lipids, body weight, adiponectin, Apo B, BMI, c-peptide, CRP, SBP, DBP, FFA, hematocrit, hemoglobin, insulin, waist circ.	Rosiglitazone; Pioglitazone; Troglitazone	
Dipeptidyl peptidase 4 inhibitors	blood glucose, HbA1c, body weight, Apo B, BMI, c-peptide, SBP, DBP, DPP-4 act., GLP-1, glucagon, insulin, ISI, TC, TG	Sitagliptin, Vildagliptin	
GLP-1	fasting plasma glucose, HbA1c, body weight, BMI	Exenatide, Liraglutide	
PPAR alpha/gamma	Apo B, body weight, c-peptide, FFA, glucose, HbA1c, HDL, LDL, TC, TG	Muraglitazar	

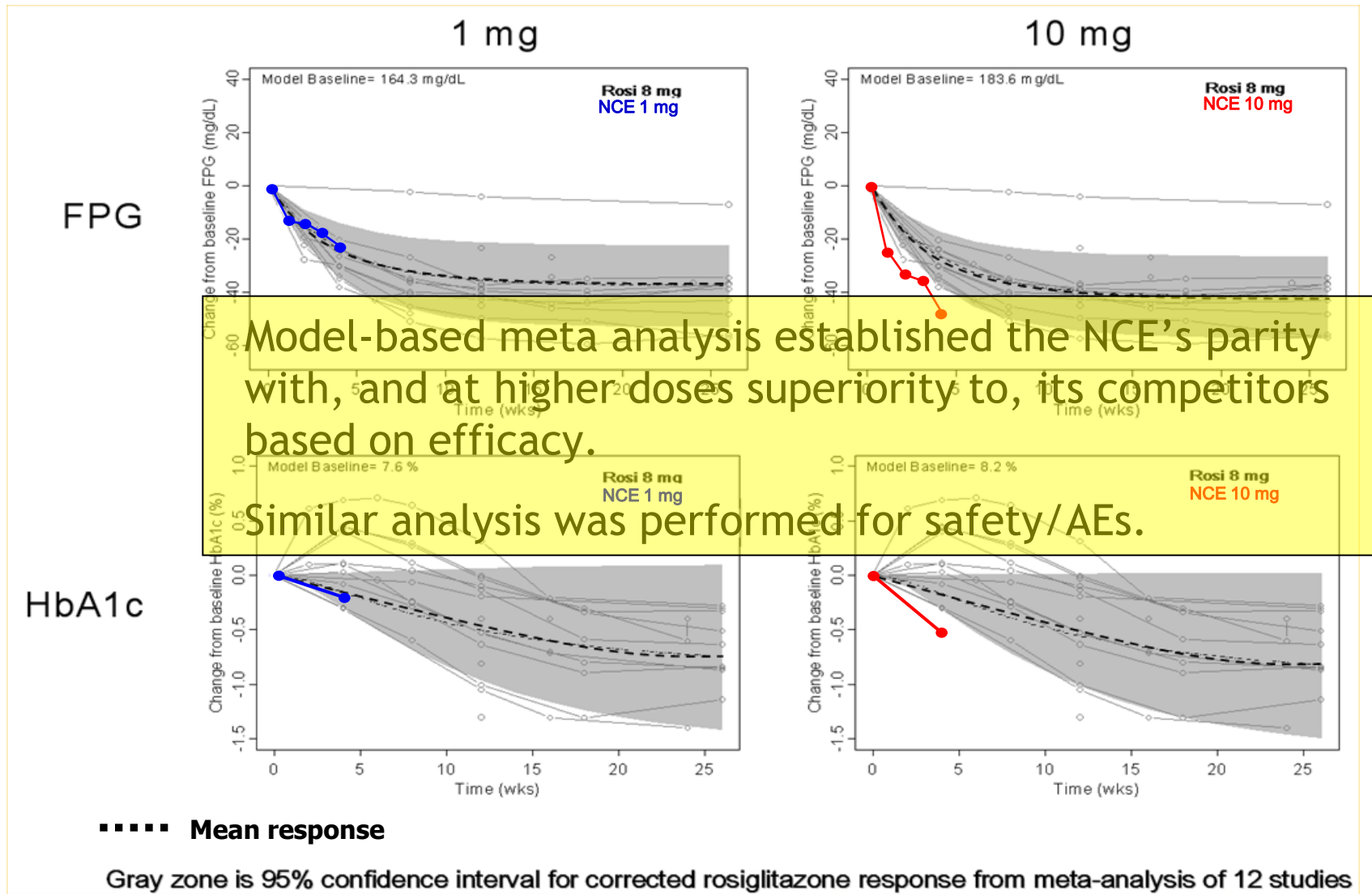
Case Study 2 – Step 2:

Simulate competitor trial arms that match the NCE data

Enables comparison across populations and studies, accounting for unique combinations of dose, baseline values, percent of naïve patients, run-in length.



Case Study 2 – Step 3: Match entry criteria for NCE and compare untested doses *versus* competitor simulations



Model-based meta analysis established the NCE's parity with, and at higher doses superiority to, its competitors based on efficacy.

Similar analysis was performed for safety/AEs.

Case Study 2: Value Delivered

Impact

- Modeling strategy provided sponsor timely and compelling support for positive efficacy signal of in-licensing candidate, helping to secure \$23 million financing round and advance compound to Phase IIb

Extensions

- Potential for models to be combined with Phase IIb data to support downstream trial design and program strategy decisions (e.g., making predictions about steady-state HbA1c)

PERSPECTIVES

Perspectives

- Growing use of drug-disease-trial Modeling & Simulation will influence drug development decisions ...

Portfolio

- Which indications should we pursue?
- At what level of investment?

Program

- What trials should we conduct, and when?
- When should we stop development?

Trial

- Which endpoints should we study?
- Which doses and what arm sizes?

Perspectives

- ... as well as regulatory decisions about labeling and approval

Pharmacometrics 2020

Jogarao V. S. Gobburu, PhD

This special issue of the Journal of Clinical Pharmacology is dedicated to pharmacometrics, covering topics related to methodological research, application to decisions, standardization, PhRMA survey, and growth strategy. Innovative methodological and technological advances in analyzing disease, drug, and trial data have equipped pharmacometricians with the know-how to influence high-level decisions, which in turn creates more pharmacometric opportunities. Pharmacometrics is revolutionizing drug development and regulatory decision making. To sustain the success and growth of this field, we need to up the ante. Strategic goals for pharmacometric groups

in industry, regulatory agencies, and academia are proposed in this report. These goals should be of significance to all stakeholders who have a vested interest in drug development and therapeutics. The future of pharmacometrics depends on how well we all can deliver on the strategic goals.

Keywords: *Clinical pharmacology; clinical trials; pharmaceutical research and development; regulatory/scientific affairs; pharmacodynamics.*
Journal of Clinical Pharmacology, 2010;50:151S-157S
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Pharmacometrics is the science of quantifying disease, drug, and trial characteristics with the goal of influencing drug development and regulatory and therapeutic decisions. Figure 1 depicts a macroscopic view of the evolution of pharmacometrics. The field started out (prior to 1960) with quantifying time courses of drug concentrations in biofluids (pharmacokinetics, or PK) from laboratory experiments.¹ Scientists then developed methods to link drug exposures to steady-state responses (pharmacodynamics),

“pharmacokinetic screening,” where sparse PK information is to be collected from registration trials to understand the sources of variability. Later, the FDA issued guidances for industry on population analyses in 1999 and on exposure–response relationships in 2003. By this time, labeling statements pertaining to intrinsic and extrinsic factors were being supported by pharmacometric analyses.

FDA's Vision for Modeling and Simulation ... Our Vision Too

- Develop Pharmacometricians' Core Expertise

“[...] master several fundamental PK, clinical pharmacology, and statistical concepts and develop the tools to implement these concepts”

- Technical Track

“Develop in-depth skills and knowledge of [various forms of] modeling.”

- Disease Track

“Advanced knowledge of particular disease areas”

- Drug Development Track

“Advanced knowledge of drug development – specifically how decisions are made”

- Develop Data and Analysis Standards for 15 Indications

“ [...] availability of efficient tools to create and manage knowledge”

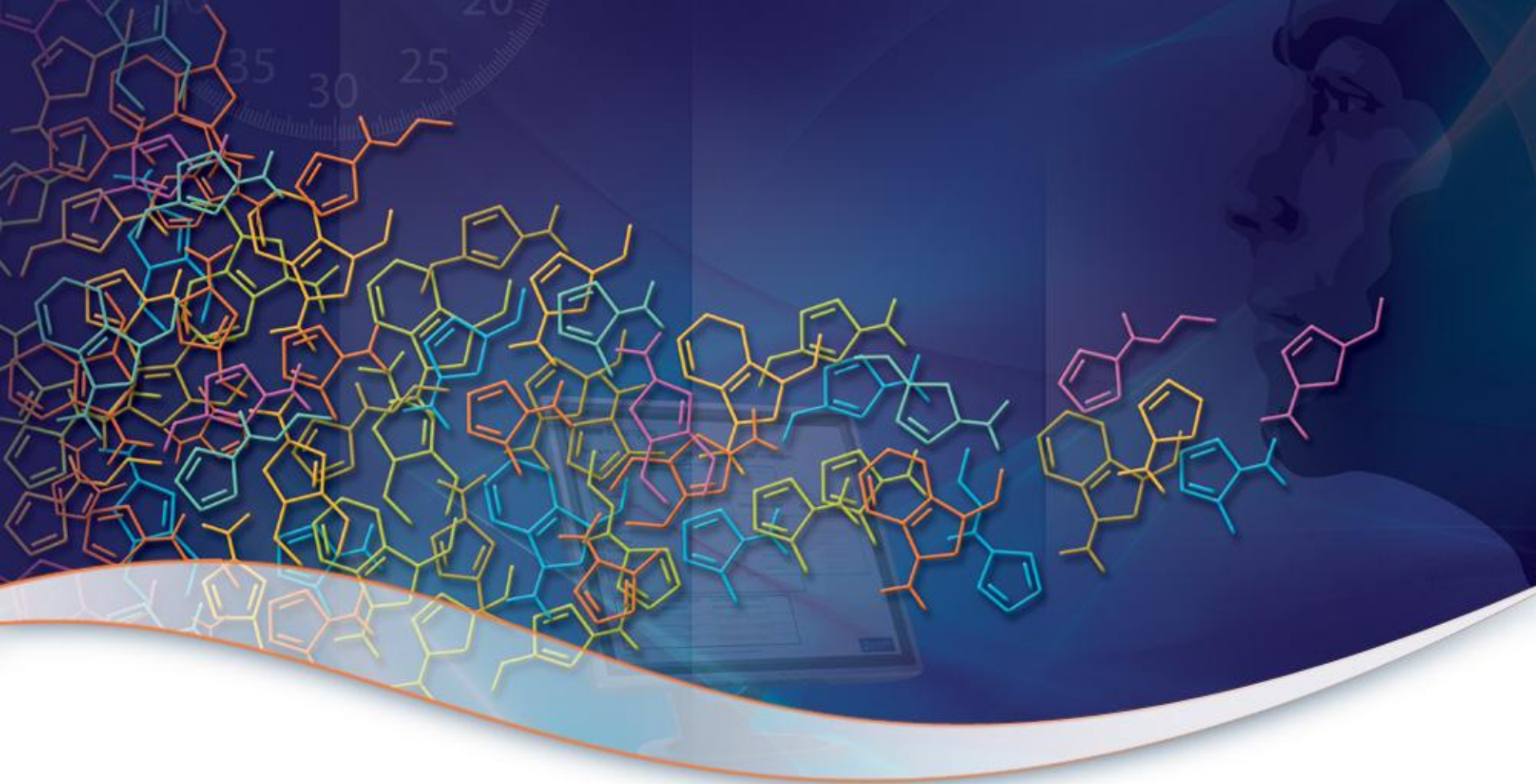
“ Development of more integrated software is critical to industrialize pharmacometric projects”

Gobburu JVS, Clin Pharmacol Ther 2010, 50:151S-157S.



Acknowledgements

- Pharsight colleagues
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