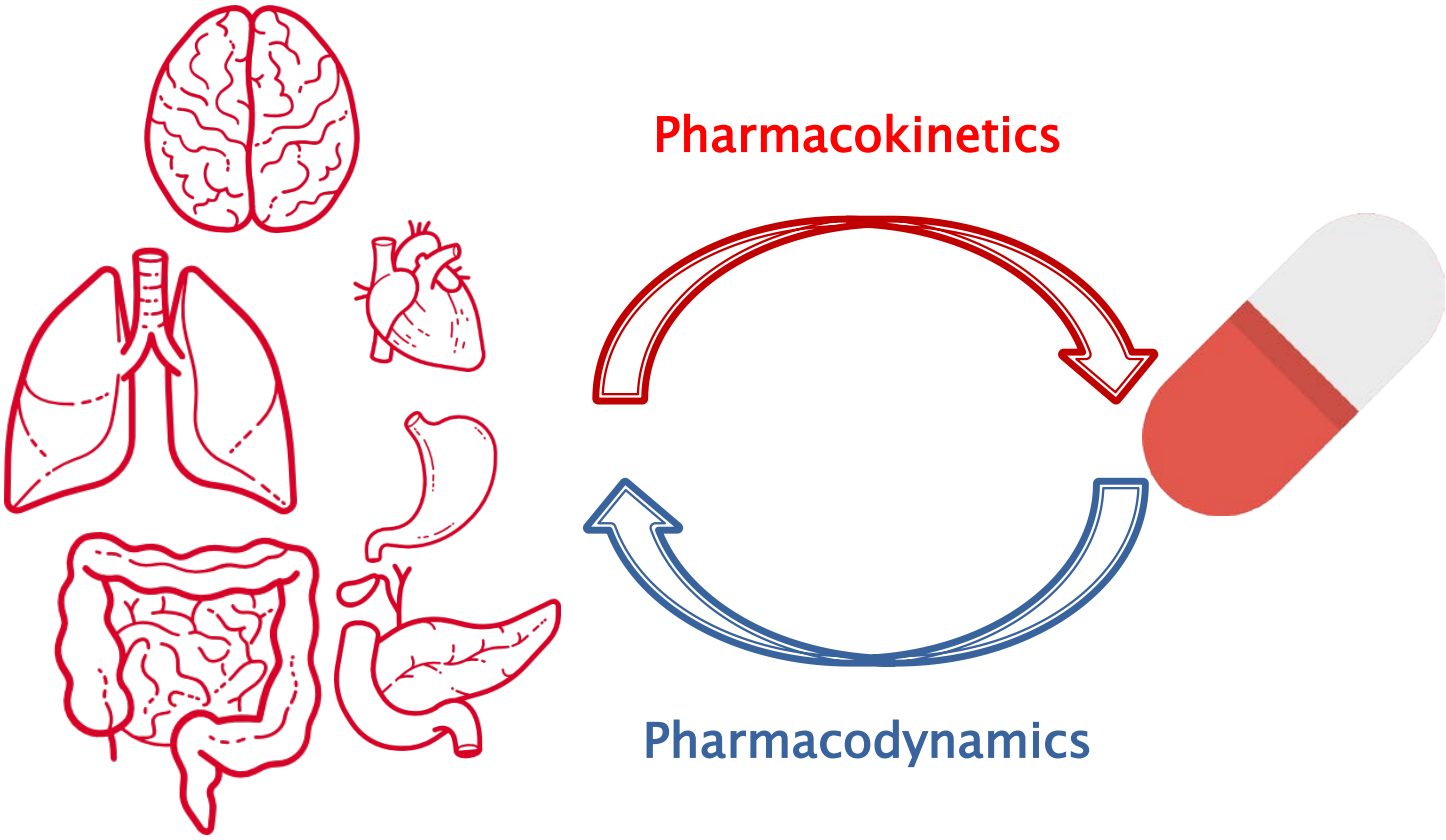
Clinical PK-PD Model:
Problems and Countermeasures

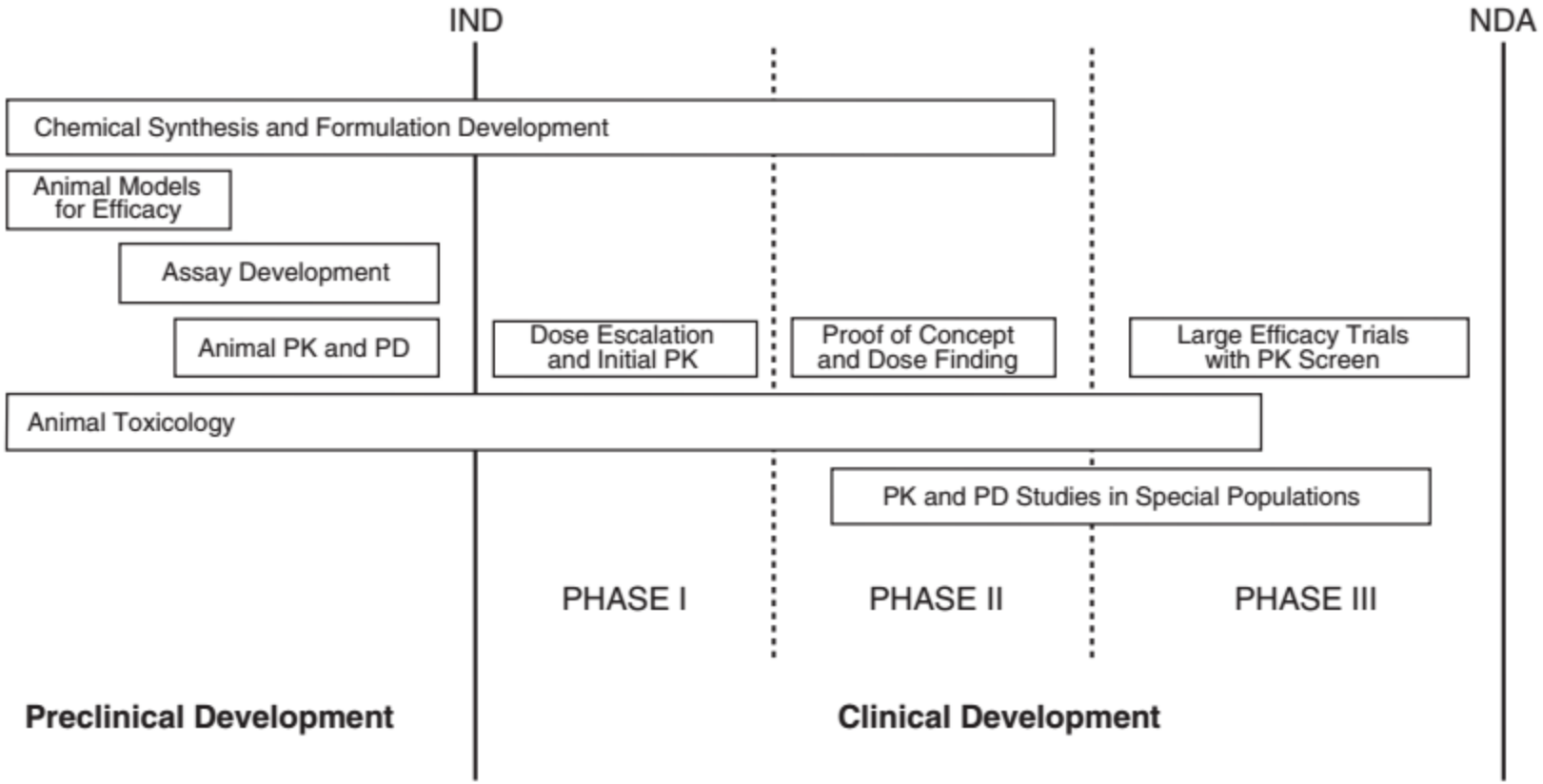
Wang Chen, Amgen

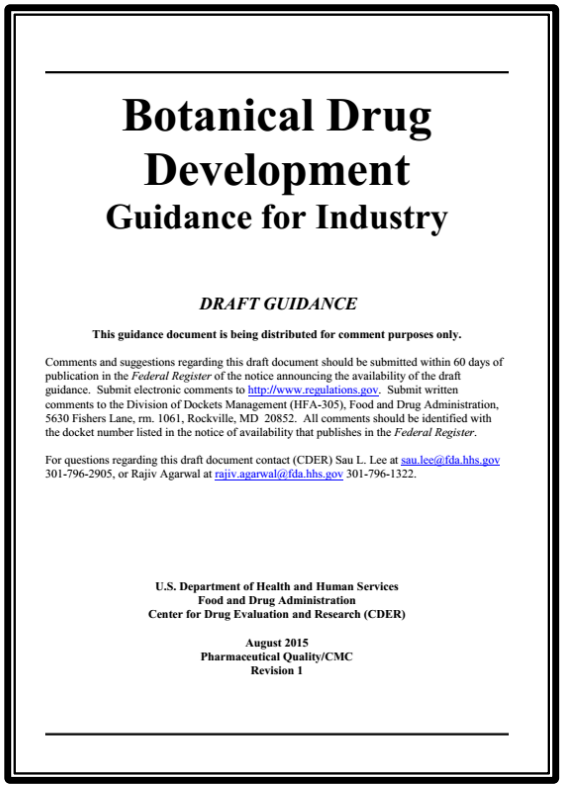
PharmaSUG China 2017

Section 1: Background

Pharmacokinetics & Pharmacodynamics




IND
NDA
Chemical Synthesis and Formulation Development
Animal Models for Efficacy
Assay Development
Animal PK and PD
Dose Escalation and Initial PK
Proof of Concept and Dose Finding
Large Efficacy Trials with PK Screen
Animal Toxicology
PK and PD Studies in Special Populations
PHASE I
PHASE II
PHASE III
Preclinical Development
Clinical Development



Botanical Drug Development
Guidance for Industry

DRAFT GUIDANCE

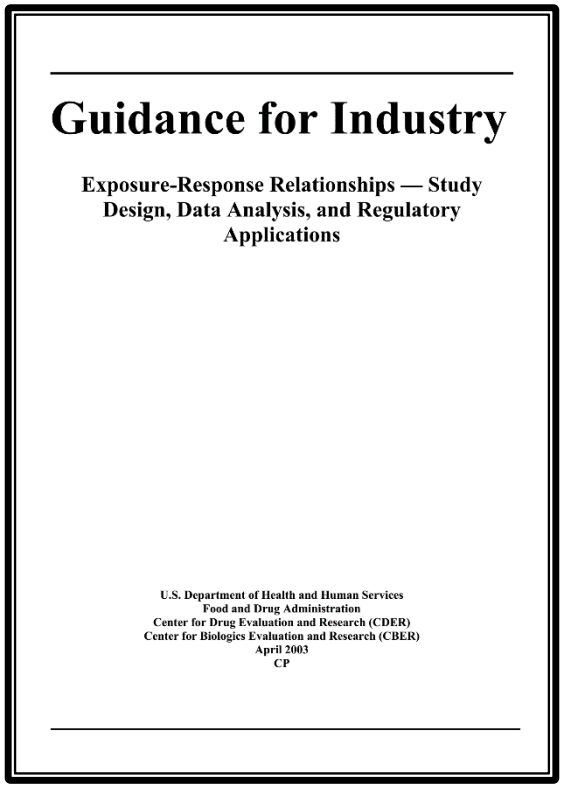
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Sau L. Lee at sau.lee@fda.hhs.gov 301-796-2905, or Rajiv Agarwal at rajiv.agarwal@fda.hhs.gov 301-796-1322.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2015
Pharmaceutical Quality/CMC
Revision 1



Guidance for Industry

Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

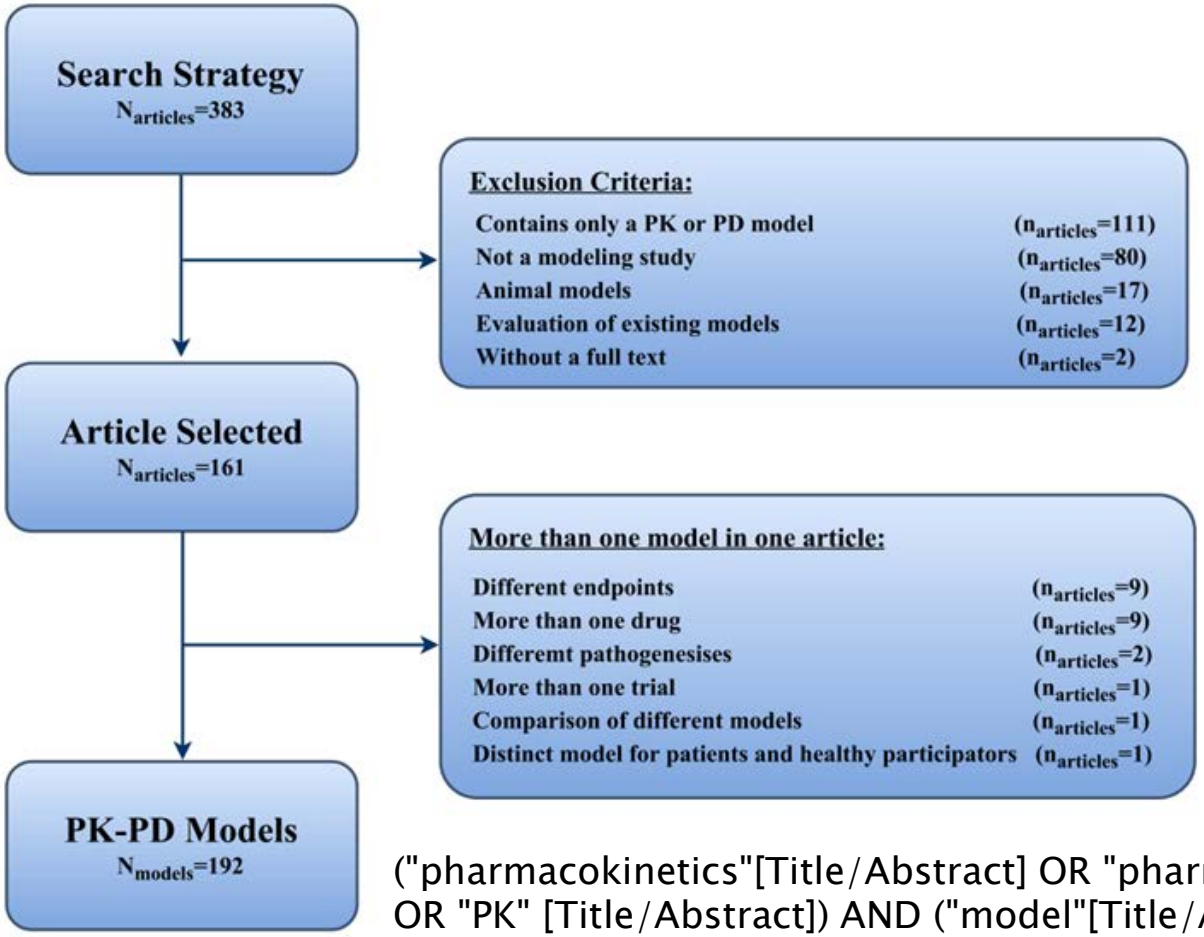
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
April 2003
CP

BACKGROUND

Drug	Value of Pharmacometrics
Toradol® *Analgesic (1991)*	• The final approved dosing was derived based on modeling and simulation, and was not directly studied in clinical trials (see Doblin RE).
Remifentanil® *Analgesic (1996)*	• One of the early examples of model-based drug development. The final approved dosing was derived based on modeling and simulation, and was not directly studied in clinical trials (see Egan TD et al).
Netrecor® *Treatment of CHF (2001)*	• Dosing for the final registration trial was derived using exposure-response modeling and simulation to balance benefit-risk. The drug is currently approved (see Bhattaram et al).
Neurontin® *Treatment of post herpectic neuralgia (2002)*	• Exposure-response modeling provided confirmatory evidence of effectiveness and alleviated the need for additional registration trials (see Lalonde et al).
Trileptal® *Anti-epileptic (mono-therapy in pediatrics) (2003)*	• Mono-therapy in pediatrics (4 years and older) was approved without additional clinical trials. Exposure-response modeling of the adjunct therapy trials in adults and pediatrics provided the evidence of effectiveness for mono-therapy (see Bhattaram et al).
Enbrel® *Treatment of rheumatoid arthritis (2003)*	• Modeling and simulation of prior clinical trial data alleviated the need for a longer safety assessment for the 50 mg once a week regimen (see Lee H et al).
CellCept® *Treatment of acute organ rejection (1998)*	• One of the early full-fledged clinical trial simulation conducted to design a registration trial based on early trial data (see Hale et al).
Firmagon® *Treatment of prostate cancer (2008)*	• The first drug development program to avail the End-of-Phase 2A meeting to select the loading and maintenance doses for the registration trial. The drug is currently approved (see Firmagon's approval history).

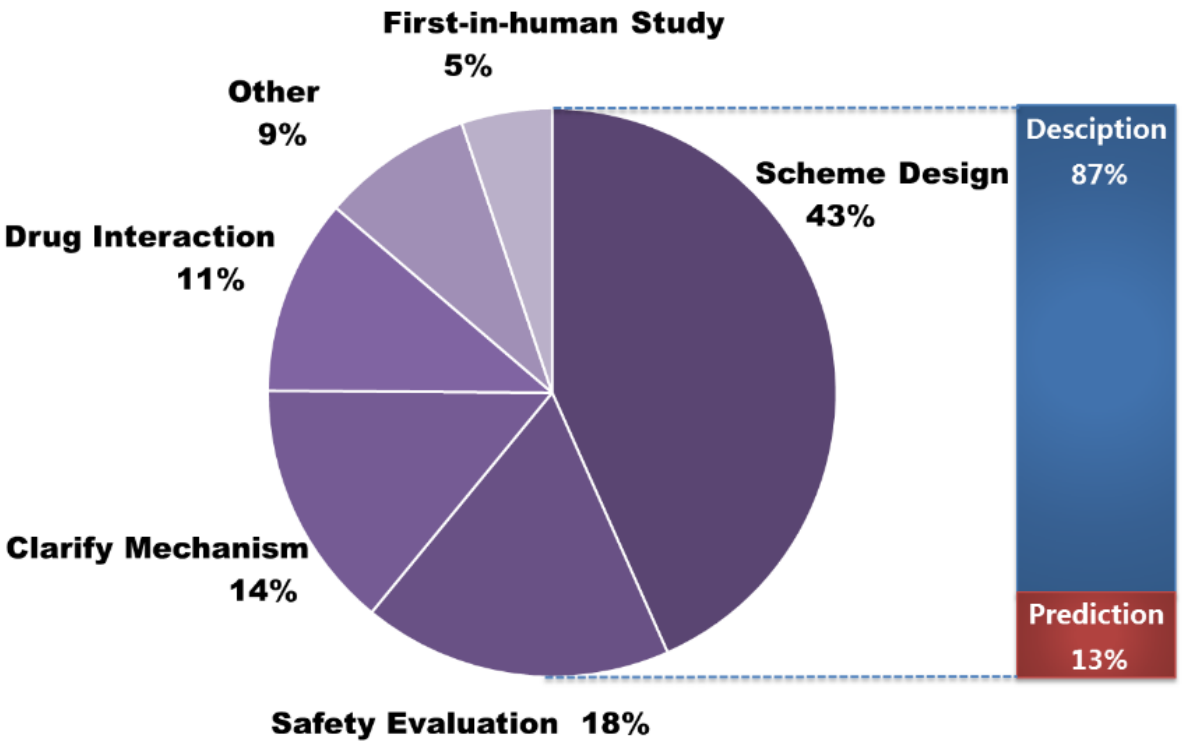
Section 2: Problem

SCREENING PROCESS



("pharmacokinetics"[Title/Abstract] OR "pharmacokinetic"[Title/Abstract] OR "PK" [Title/Abstract]) AND ("model"[Title/Abstract] OR "modeling"[Title/Abstract]) AND (Clinical Trial [ptyp] AND English [lang]) AND ("2007/08/20"[PDat]: "2014/08/20" [PDat])

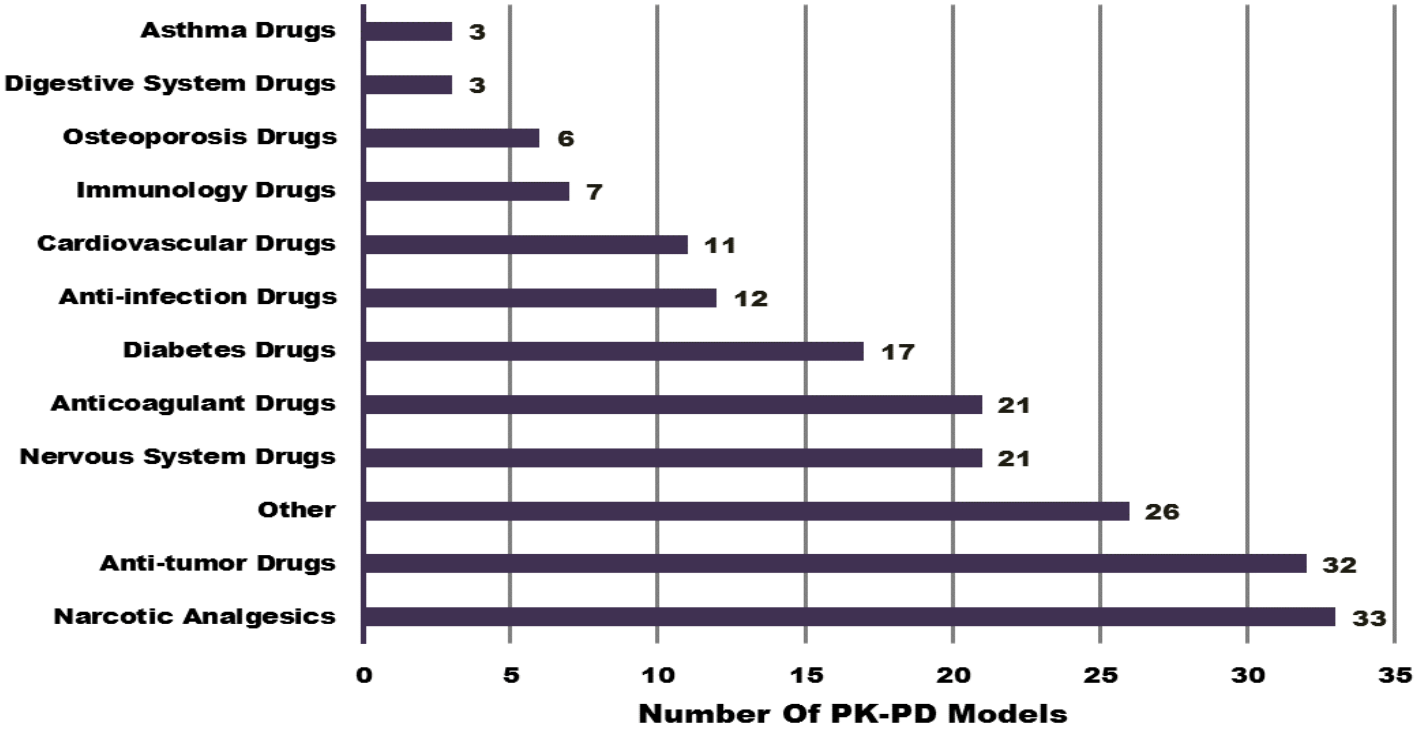
APPLICATION OF PD/PD MODEL



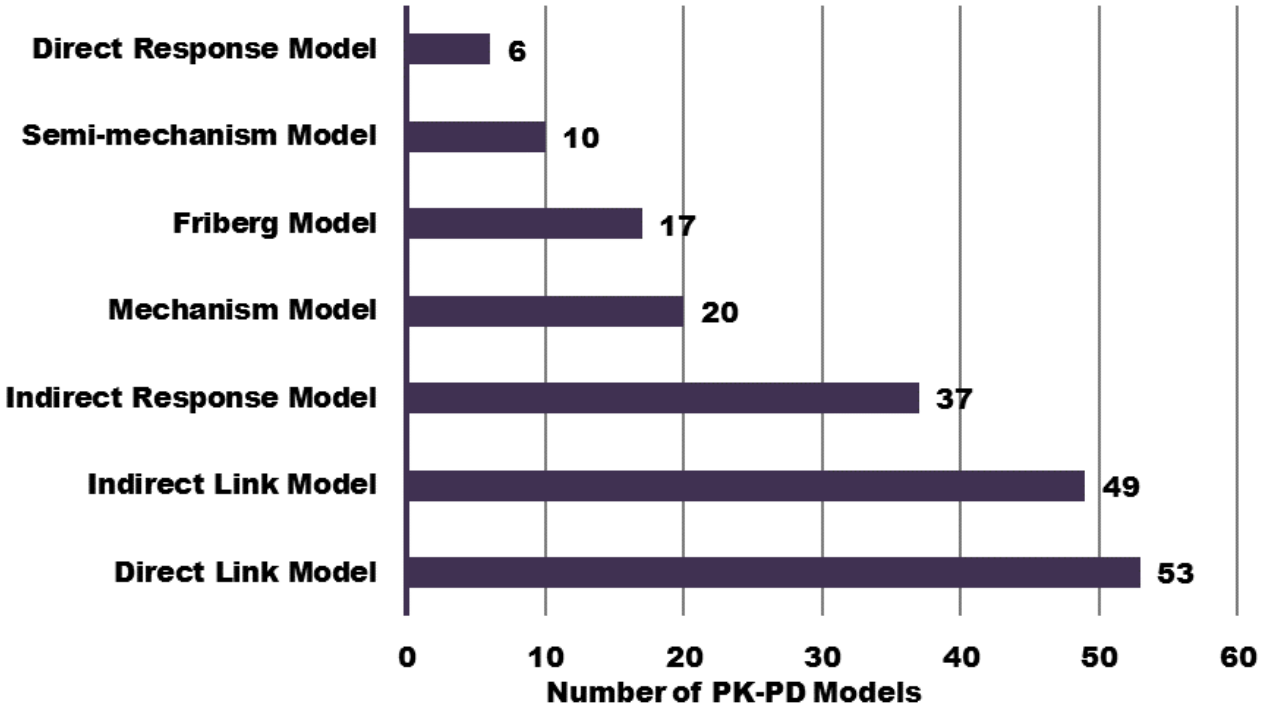
Problem:

- Most for description
- Limit use of safety evaluation

TREATMENT FIELD



MODEL CLASSIFICATION

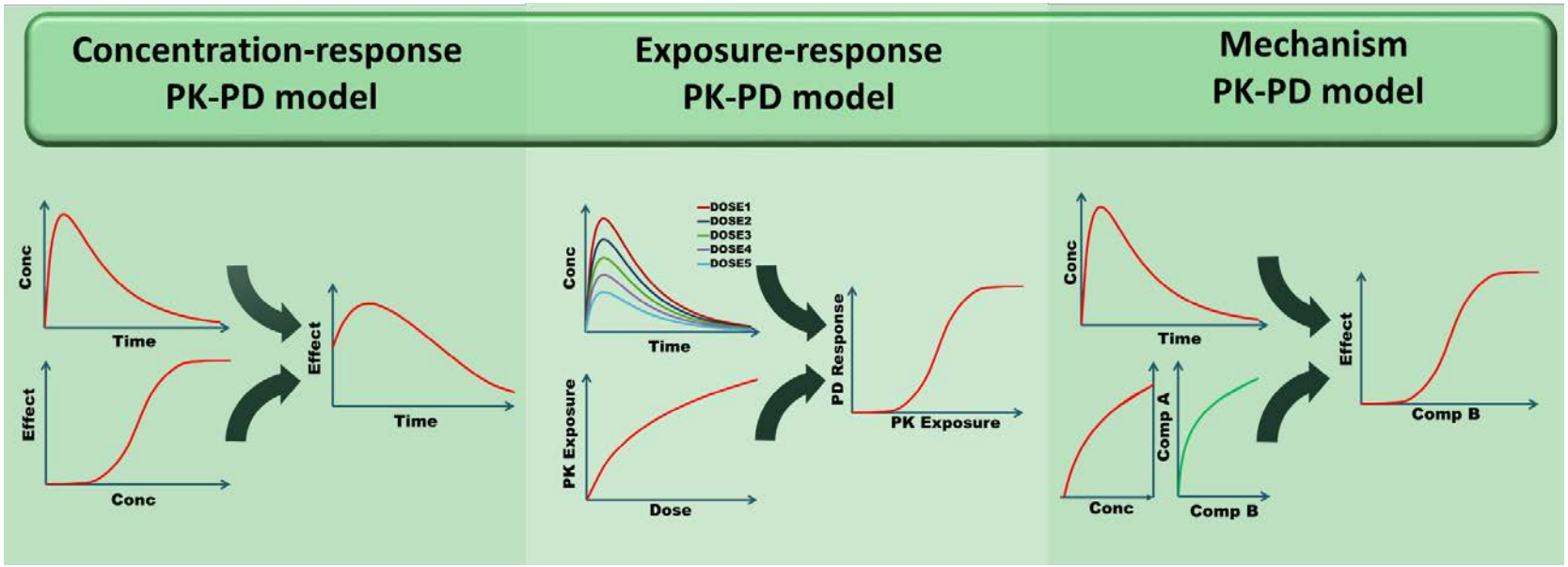


PROBLEMS

- Classical modeling method has some defects which limited the applying of PK-PD approach. Classical PK-PD modeling establishes the relationship between an instant concentration and its effect, but such data is difficult to observe for most drugs;
- The current classification of PK-PD models is complicated which greatly enhanced the difficulties during the modeling process;
- The design and specific research method of existing PK-PD studies also has some deficiencies which produces limits.

Section 3: Solutions

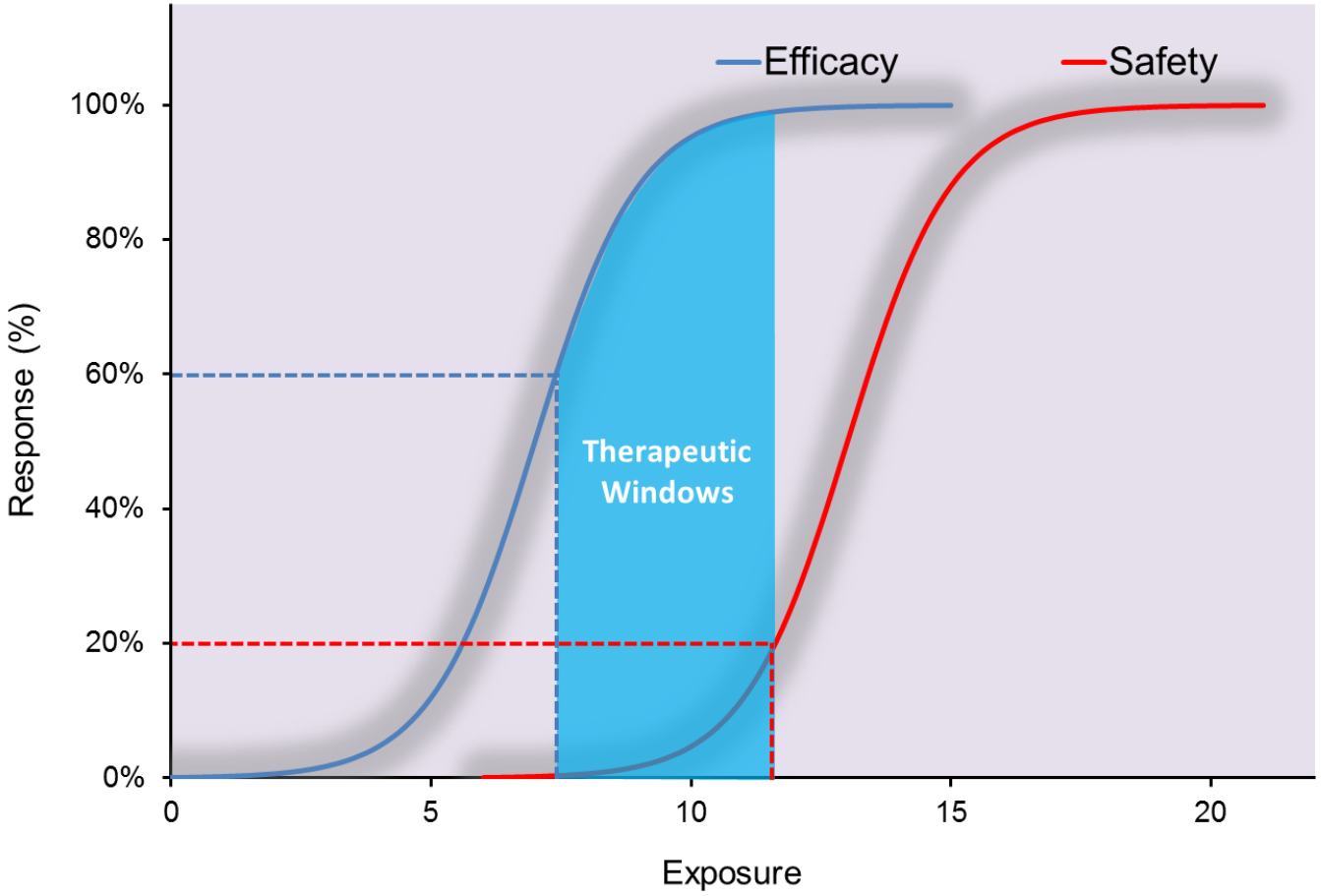
New Classification



PROPOSAL OF NEW PK–PD CLASSIFICATION

Trial and data	Modeling and simulation
Classical PK-PD Model ❑ suitable for data of instant concentration vs. its effect ❑ small sample size in trial ❑ a few doses design for trial ❑ time of sampling is limited with short space	❑ modeling relationship between instant concentration and its effect which is difficult to observe for most drugs ❑ with many concepts and hypothesizes which may be confused ❑ a lot of time-consuming ❑ without covariates in the model
Mechanism PK-PD Model ❑ small sample size in trial ❑ time of sampling is limited with short space ❑ strictly designed to get necessary data of intermediate products	❑ highly effective in prediction ❑ with too much parameters which is complex and hard to understand ❑ generally described by a flow chart ❑ a lot of time-consuming ❑ without covariates in the model
Parameterized PK-PD Model ❑ suitable for data of PK parameters vs. PD response ❑ large sample size in trial ❑ multiple-doses design for trial ❑ time of sampling is not limited	❑ modeling the relationship between PK exposure and PD response which is much easier to observe ❑ offering information which is at the heart of any determination of safety and effectiveness of drugs ❑ relative easy in modeling ❑ with covariates in the model ❑ a widely use of population approach

USE OF BOTH EFFICACY AND SAFETY



Name: Wang Chen
Organization: Amgen Asia R&D
Address: 13, Building , Jinchuang Building, 4560 Jinke Road
City, State ZIP: Shanghai 01210 P. R. China
Work Phone: 189 1832 9098
E-mail: c0101@amgen.com