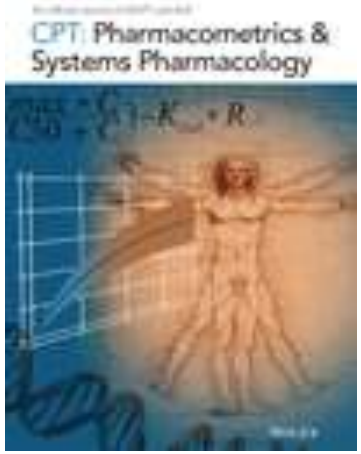
Basel, 04-04-16

Roche QSP Methodology Workshop

Piet van der Graaf

Editor-in-Chief
CPT: Pharmacometrics
Systems Pharmacology



Leiden Academic Centre for Drug Research (LACDR)
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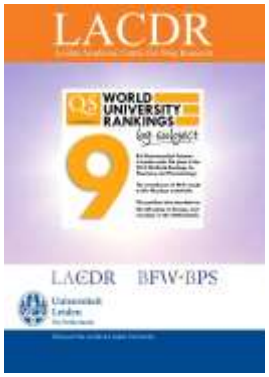

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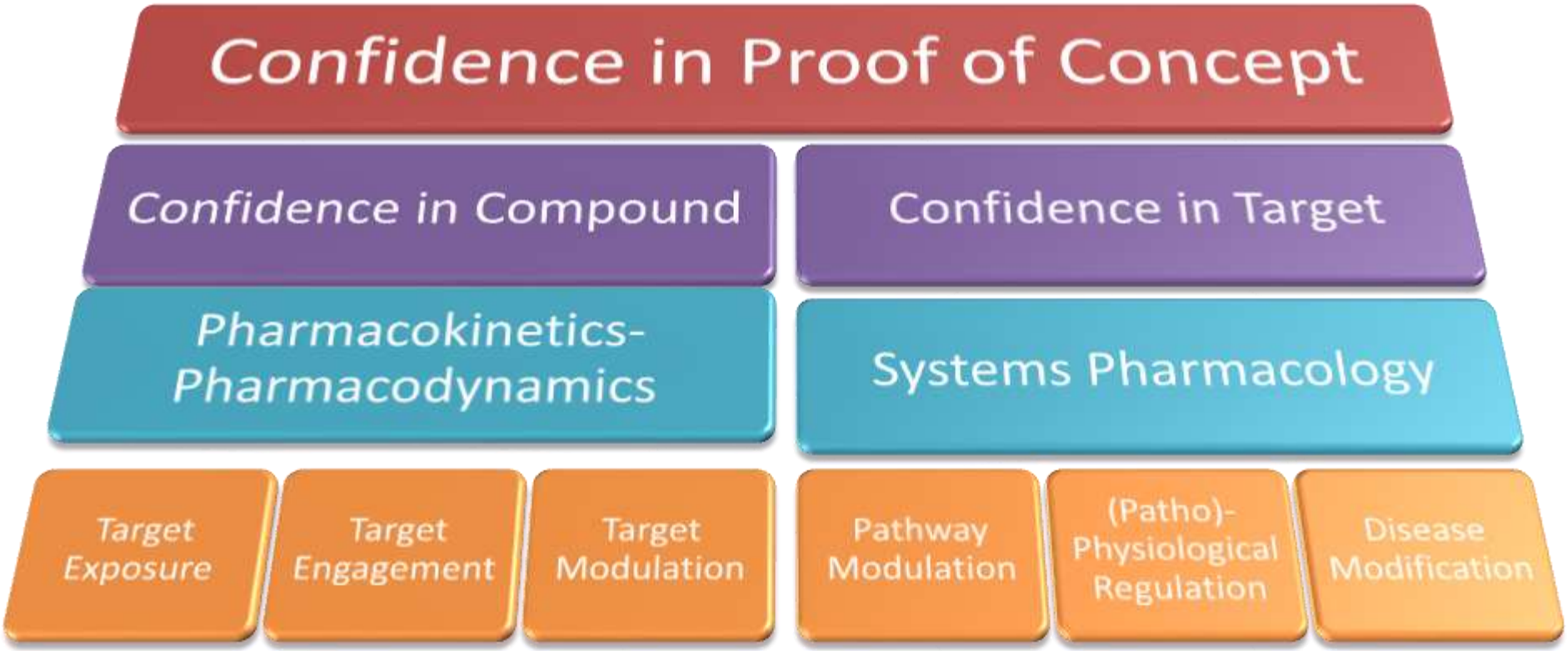
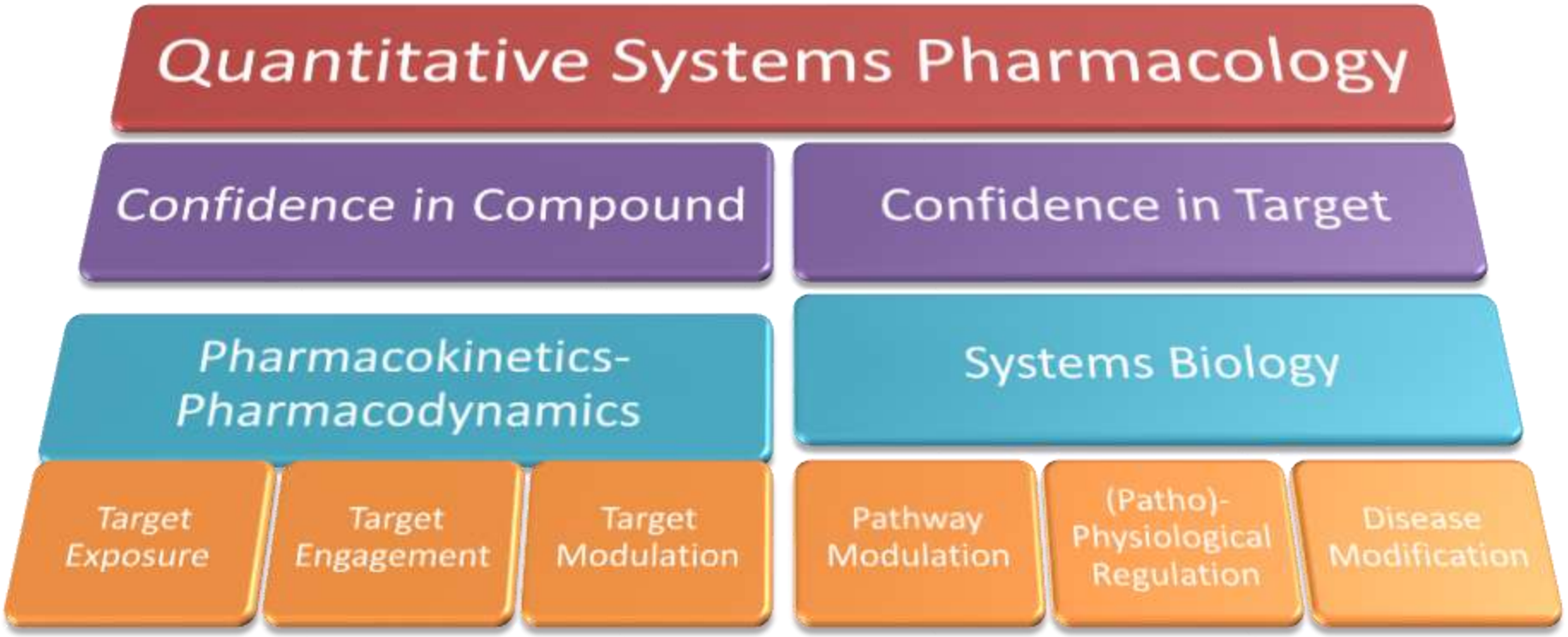
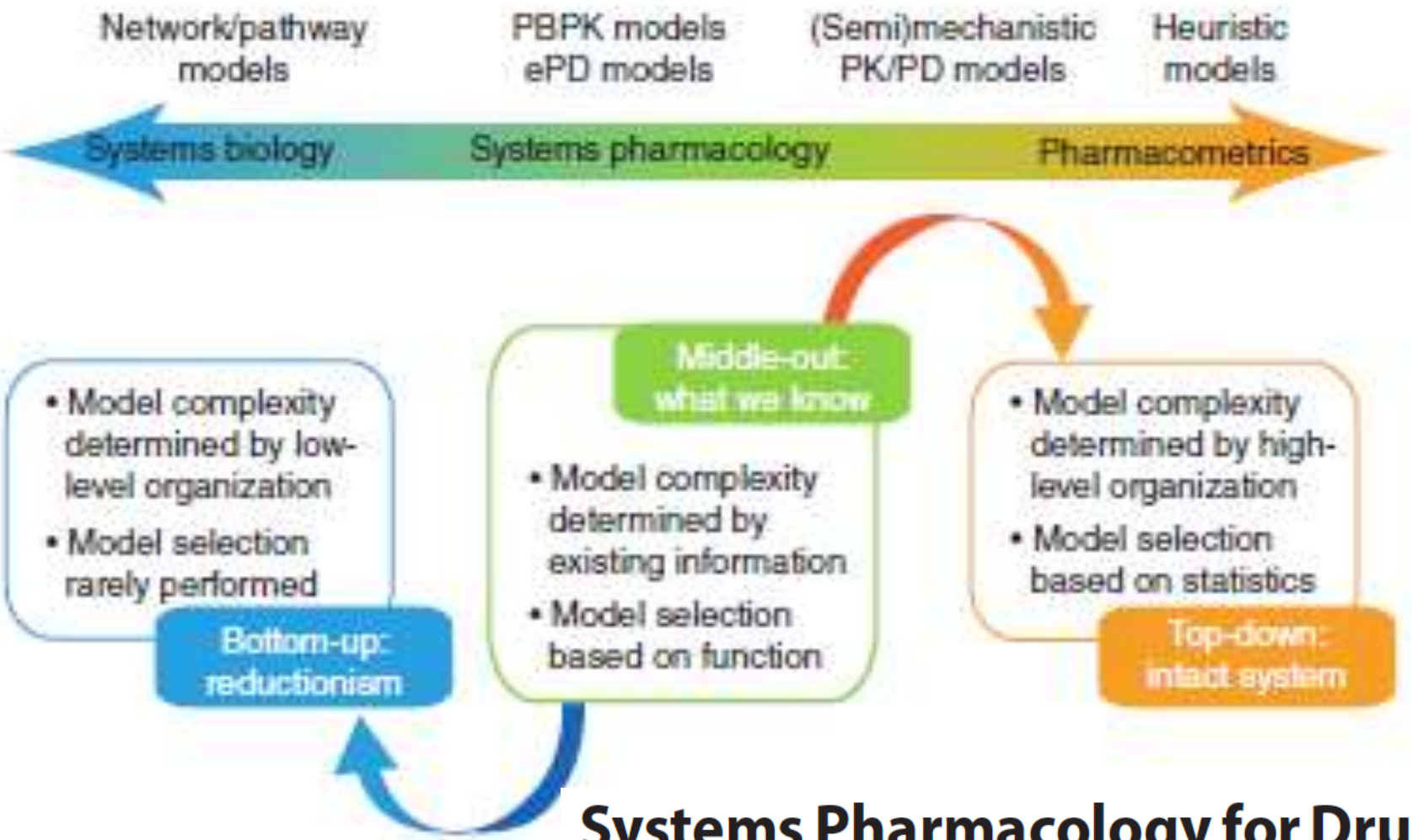
Quantitative Systems Pharmacology (QSP) to improve Phase 2 success



Vicini & Van Der Graaf CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 93 NUMBER 5 | MAY 2013

Quantitative Systems Pharmacology (QSP) to improve Phase 2 success





Systems Pharmacology for Drug Discovery and Development: Paradigm Shift or Flash in the Pan?

P Vicini[1] and PH van der Graaf[2,3]

QSP IMPLEMENTATION: Some Points for discussion

1. Why, What & When:
   - Define the question and potential impact
   - Scope and Timing

2. How:
   - Training and Education
   - New data requirements
     - *Biomarkers*
     - *Biomeasures*
   - Model validation
   - (Precompetitive) collaboration
     - *Models*
     - *Databases*

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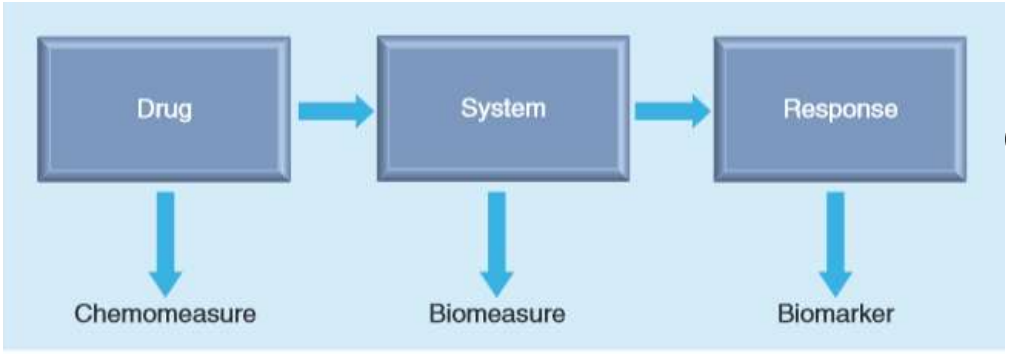


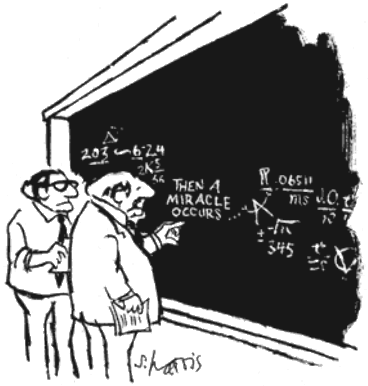
Figure 1. Three types of measures underpinning the development of

ration

Bioanalysis (2012) 4(10), 1143–1145

QSP IMPL "Validating" Systems Pharmacology Models? ssion

1. Why,
   - De
   - Sc



2. How:
   - Tra
   - Ne
   -
   - *Biomeasures*

Models are psychologically most appealing when they succeed, but logically strongest when they fail

After Yates (1978), *Am. J. Physiol.* 3, R159-160

…all models are wrong, but some are useful

Wrong models are most useful?

- Model validation
- (Precompetitive) collaboration
  - *Models*
  - *Databases*

PERSPECTIVE

Evaluating Systems Pharmacology Models Is Different From Evaluating Standard Pharmacokinetic–Pharmacodynamic Models

B Ageren'

Based on the author's recent experience, there appears to be some confusion regarding the steps required to qualify a systems pharmacology model as adequate for the intended purpose. This manuscript outlines the model evaluation approach used in the author's recent publication' on the systems pharmacology of a 5-lipoxygenase inhibitor and is an attempt to generate discussion on this topic within the pharmacometrics and systems pharmacology community.

CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e101; doi:10.1038/psp.2013.77; published online 19 February 2014

COMMENTARY

Negative Modeling Results: A Dime a Dozen or a Stepping Stone to Scientific Discovery?

B Hendrika'

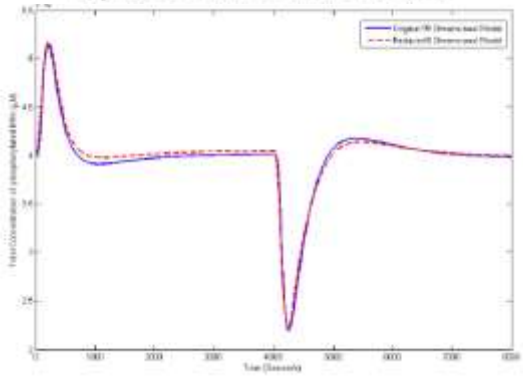
CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e48; doi:10.1038/psp.2013.28; advance online publication 12 June 2013

Systems pharmacology models, in general, tend to span multiple timescales bridging detailed mechanism with higher level responses or functional outputs. These features serve to put systems pharmacology models in a separate class that brings with it specific challenges, particularly in evaluating such work. When models are constructed on well-understood mechanisms but fail to match experimental data, in what cases should "negative modeling results" be considered scientific findings?

Summary of PhD Research

Tom Snowden

Supervisors: PH van der Graaf & MJ Tindall



QSP IMPLEMENTATION

Need for (precompetitive) collaboration

MODELS

REVIEW

The impact of mathematical modeling on the understanding of diabetes and related complications

I Ajmera[1,2], M Swat[1], C Laibe[1], N Le Novère[1,3] and V Chelliah[1]

Diabetes is a chronic and complex multifactorial disease caused by persistent hyperglycemia and for which underlying pathogenesis is still not completely understood. The mathematical modeling of glucose homeostasis, diabetic condition, and its associated complications is rapidly growing and provides new insights into the underlying mechanisms involved. Here, we discuss contributions to the diabetes modeling field over the past five decades, highlighting the areas where more focused research is required.

CPT: Pharmacometrics & Systems Pharmacology (2013) **2**, e54; doi:10.1038/psp.2013.30; advance online publication 10 July 2013

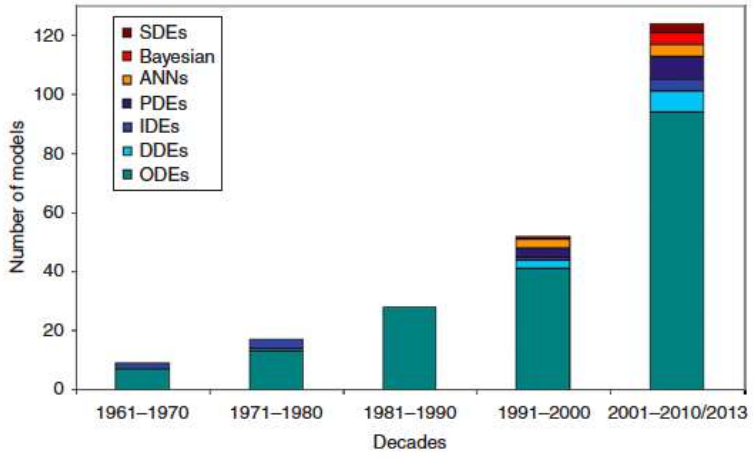


Figure 2 Modeling approaches vs. the number of models in relation to diabetes and associated complications, over the past five decades. There has been a significant increase in the number of models, as well as in the diversity of the modeling approaches applied toward addressing diabetes. ANNs, artificial neural networks; DDEs, delay differential equations; IDEs, integro-differential equations; ODEs, ordinary differential equations; PDEs, partial differential equations; SDEs, stochastic differential equations.

DATABASES

CPT: Pharmacometrics & Systems Pharmacology
An Official Journal of ASCPT and ISoP
Open Access

Database -

A New Article Type in *CPT: Pharmacometrics & Systems Pharmacology*

Lang Li[1] and Piet H. van der Graaf[2]

[1]Associate Editor
Center for Computational Biology and Bioinformatics, Department of Medical and Molecular Genetics, School of Medicine, Indiana University, Indianapolis, 46202, U.S.A.
lali@iu.edu

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CPT: Pharmacometrics & Systems Pharmacology
An Official Journal of ASCPT and ISoP
Open Access

Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 00, 00; doi:10.1002/psp4.55

DATABASE

Organ Impairment—Drug–Drug Interaction Database: A Tool for Evaluating the Impact of Renal or Hepatic Impairment and Pharmacologic Inhibition on the Systemic Exposure of Drugs

CK Yeung[1,2], K Yoshida[3], M Kusama[4], H Zhang[3], I Ragueneau-Majlessi[3]*, S Argon[3], L Li[3], P Chang[3], CD Le[3], P Zhao[3], L Zhang[3], Y Sugiyama[4] and S-M Huang[3]*

The organ impairment and drug–drug interaction (OI-DDI) database is the first rigorously assembled database of pharmacokinetic drug exposure data from publicly available renal and hepatic impairment studies presented together with the maximum change in drug exposure from drug interaction inhibition studies. The database was used to conduct a systematic comparison of the effect of renal/hepatic impairment and pharmacologic inhibition on drug exposure. Additional applications are feasible with the public availability of this database.

CPT Pharmacometrics Syst. Pharmacol. (2015) **00**, 00; doi:10.1002/psp4.55; published online on 0 Month 2015.

QSP IMPLEMENTATION

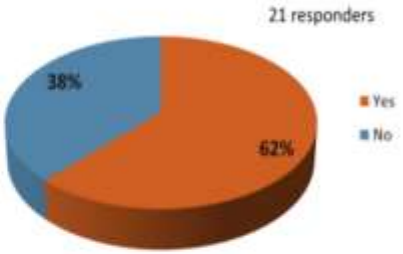
Need for (precompetitive) collaboration

Status of Quantitative Systems Pharmacology Modeling in the Pharmaceutical Industry: A Consortium Survey of the What, When and How

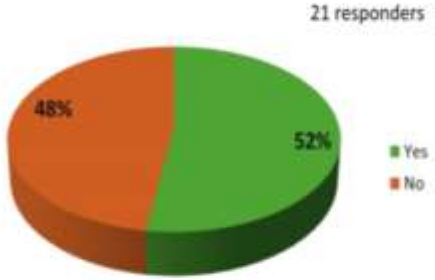
Mohamad Shebley[1], Marjoleen Nijsen[1], Masoud Jamei[2] and Amin Rostami-Hodjegan [2,3]

[1] Translational Modeling & Simulations, DMPK-Bioanalysis, AbbVie Inc. North Chicago IL U.S.A.; [2] Simcyp Limited (a Certara Company), Blades Enterprise Centre, Sheffield S2 4SU, UK; [3] Centre for Applied Pharmacokinetic Research, Manchester Pharmacy School, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT, UK

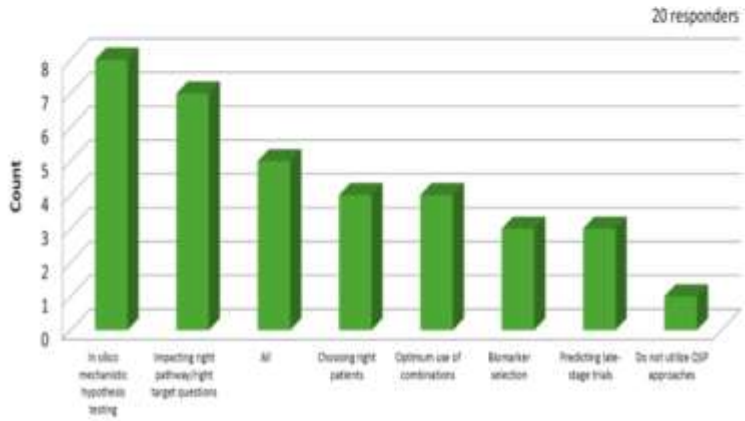
Question 1.
Is QSP modeling a part of your company's modeling & simulations tool box?



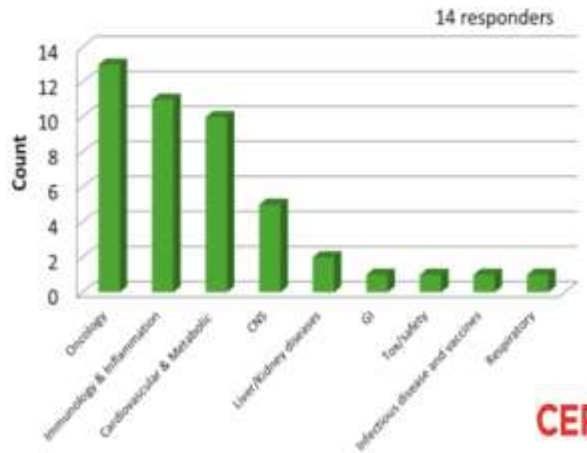
If so, do you have dedicated QSP modellers within your company?



Question 4.
What applications does your company mostly utilize/plan to utilize QSP approaches for?



Question 5.
Is your company interested in developing pre-competitive QSP disease models? If so, which therapeutic areas or indications?



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Protecting and Promoting Public Health
www.fda.gov

Clinical Pharmacology Review of Natpara® (BLA 125511)

Endocrinologic and Metabolic Drugs Advisory Committee
Advisory Committee Meeting, September 12, 2014

Manoj Khurana, PhD
Immo Zadezensky, PhD
Nitin Mehrotra, PhD
Office of Clinical Pharmacology

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Natpara

Natpara is recombinant human parathyroid hormone (PTH) identical in primary sequence to the full-length human endogenous hormone (i.e., 84 amino acids)

Indication sought:

- *Natpara for injection is a replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism*

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling

Mark C. Peterson [a,*,1], Matthew M. Riggs [b]