Applying physiologically-based pharmacokinetic (PBPK) modeling & simulation to assist with pharmaceutical research and regulatory submissions

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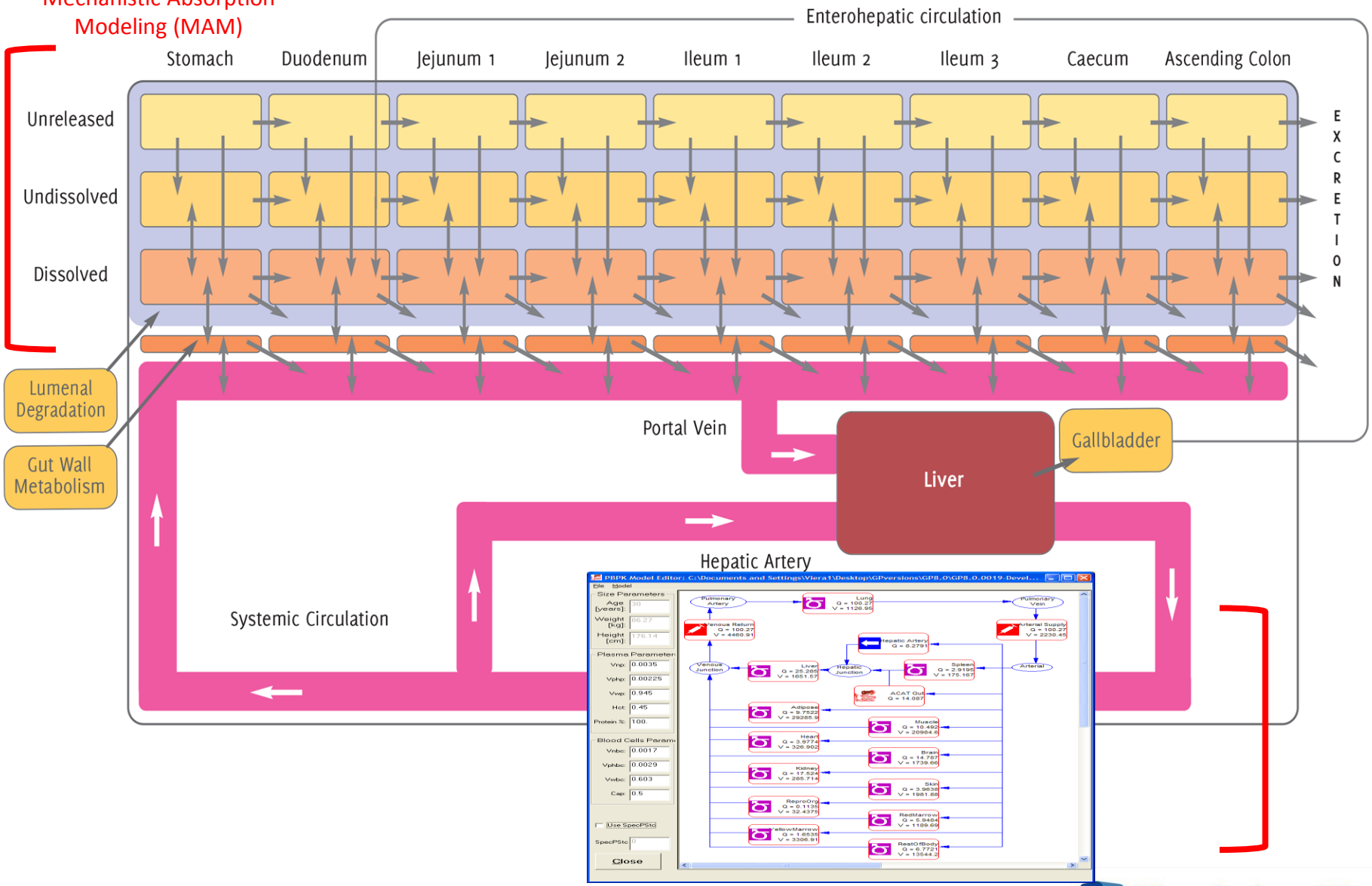
Outline

- GastroPlus™ PBPK models – the big picture
- PBPK M&S applications at the FDA
- Future directions

Advanced Compartmental Absorption and Transit Model (ACAT™)

Mechanistic Absorption Modeling (MAM)



Physiologically based Pharmacokinetics (PBPK)

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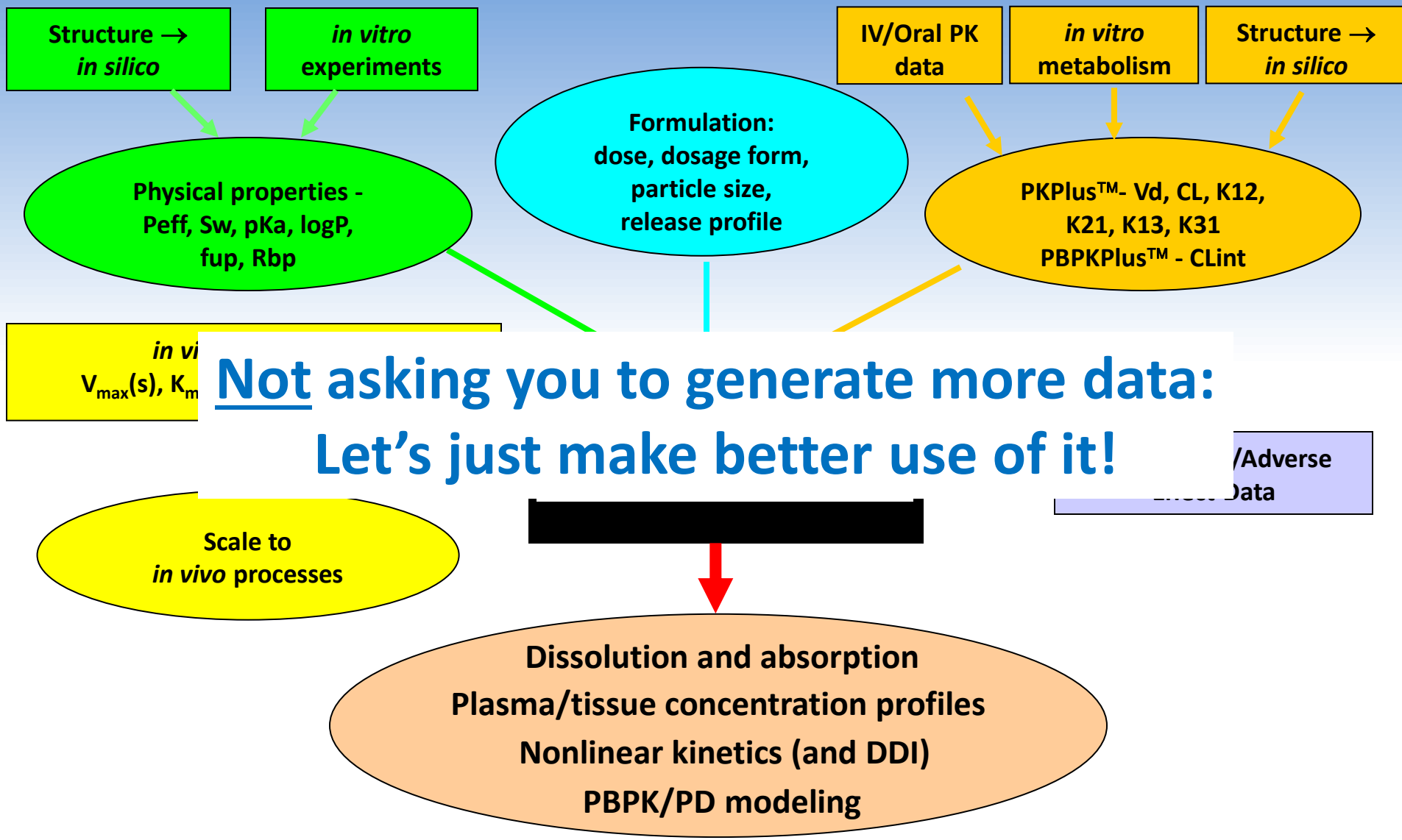
The Big Picture – Drug Inputs



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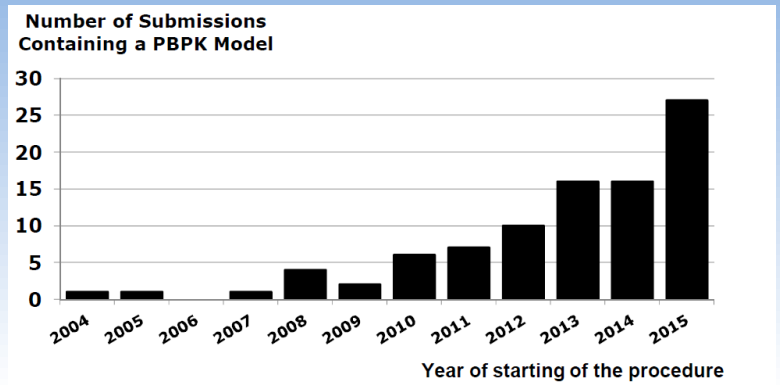
Recent PBPK Modeling Trends: Regulatory Information

Modeling and Simulation of Biopharmaceutical Performance

X Zhang[1] and R A Lionberger[1]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 95 NUMBER 5 | MAY 2014

"there is great potential for absorption modeling and simulation to identify clinically relevant dissolution and particle size specifications and support waivers of in vivo BE studies. However there is a need for confidence-building steps that include case studies or pilots"



Preliminary analysis
Eliza Luzon- EMA

Courtesy of Sue Cole MHRA

Presented at JPAG Meeting; The use of in silico modelling in drug development

Thursday 17th March 2016, Royal Society of Chemistry.

FARYDAK (panobinostat) capsules 10mg/15mg/20mg

Farydak from Novartis an example where ADAM/ACAT has been used by FDA reviewer for food effect and PPI effect assessment.

FDA's Office of New Drug Products Places Order for 50 Additional Licenses to GastroPlus™

Additional Licenses Required to Meet Increasing Number of Submissions Utilizing GastroPlus

LANCASTER, Calif.--(BUSINESS WIRE)-- Simulations Plus, Inc. (NASDAQ: SLP), the leading provider of consulting services and software for pharmaceutical discovery and development, today announced that the U.S. Food and Drug Administration's (FDA) Office of New Drug Products, Division of Biopharmaceutics has placed an order for 50 additional licenses to the Company's GastroPlus™ software. This brings to 70 the total number of GastroPlus licenses in use at the FDA. The licenses are spread across various divisions, including the Office of Generic Drugs, Center for

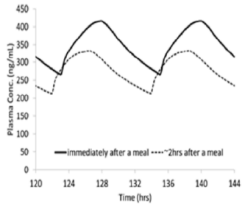
ALECENSA alectinib 150 mg capsules — Roche — **Now Approved**

PBPK Model

The Applicant developed a PBPK model for alectinib using GastroPlus™ to support recommendations for the relative time of an alectinib dose with respect to a meal. The applicant

Figure 11. Model Simulations of the Effect of Dosing Time relative to Meal Administration following administration of Alectinib at a Dose of 600 mg Twice Daily

This work was used in the NDA filing with FDA



Food effect extrapolated

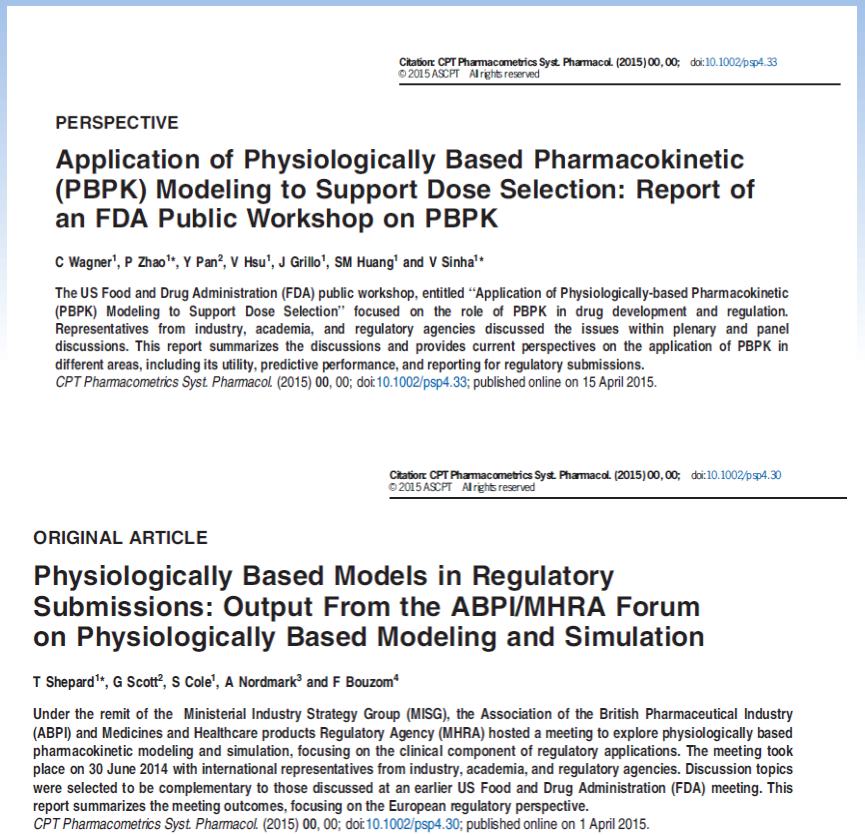
PPI absorption lack of DDI explained

(Table 17). Similarly, simulations performed using GastroPlus™ predicted no impact of esomeprazole on alectinib exposures (report no. 1064595). The Applicant postulated that gastric pH changes did not affect alectinib exposure, because alectinib does not undergo relevant

Cole et al., 2016 JPAG Meeting

Parrott et al., 2015 AAPS Annual Meeting

PBPK Modeling: Encouragement from Regulatory Agencies



Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 00, 00; doi:10.1002/psp4.33

PERSPECTIVE

Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK

C Wagner[1], P Zhao[1]*, Y Pan[2], V Hsu[1], J Grillo[1], SM Huang[1] and V Sinha[1]*

The US Food and Drug Administration (FDA) public workshop, entitled "Application of Physiologically-based Pharmacokinetic (PBPK) Modeling to Support Dose Selection" focused on the role of PBPK in drug development and regulation. Representatives from industry, academia, and regulatory agencies discussed the issues within plenary and panel discussions. This report summarizes the discussions and provides current perspectives on the application of PBPK in different areas, including its utility, predictive performance, and reporting for regulatory submissions.
CPT Pharmacometrics Syst. Pharmacol. (2015) **00**, 00; doi:10.1002/psp4.33; published online on 15 April 2015.

Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 00, 00; doi:10.1002/psp4.30

ORIGINAL ARTICLE

Physiologically Based Models in Regulatory Submissions: Output From the ABPI/MHRA Forum on Physiologically Based Modeling and Simulation

T Shepard[1]*, G Scott[2], S Cole[1], A Nordmark[3] and F Bouzom[4]

Under the remit of the Ministerial Industry Strategy Group (MISG), the Association of the British Pharmaceutical Industry (ABPI) and Medicines and Healthcare products Regulatory Agency (MHRA) hosted a meeting to explore physiologically based pharmacokinetic modeling and simulation, focusing on the clinical component of regulatory applications. The meeting took place on 30 June 2014 with international representatives from industry, academia, and regulatory agencies. Discussion topics were selected to be complementary to those discussed at an earlier US Food and Drug Administration (FDA) meeting. This report summarizes the meeting outcomes, focusing on the European regulatory perspective.
CPT Pharmacometrics Syst. Pharmacol. (2015) **00**, 00; doi:10.1002/psp4.30; published online on 1 April 2015.

- Both FDA and MHRA/EMA hosted PBPK workshops in 2014
  - Additional workshops in 2016
- Discussed areas where PBPK modeling is helpful:
  - Dose selection & First-in-Human (FIH) predictions
  - Drug-drug interactions (DDIs)
  - Pediatric & special populations
  - Absorption/virtual bioequivalence
  - Food effects (not yet applicable)
- First PBPK guidance developed in 2016 by FDA and EMA
  - EMA focused on qualification of models
  - FDA focused on submission reporting

Shepard et al., (2015) CPT 4:221-225
Wagner et al., (2015) CPT 4:226-230

FDA Office of Generic Drugs: Publications

RESEARCH ARTICLE – *Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism*

Application of Physiologically Based Absorption Modeling for Amphetamine Salts Drug Products in Generic Drug Evaluation

ANDREW H. BABISKIN, XINYUAN ZHANG

Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland 20993

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rary.com). DOI 10.1002/jps.24474

se (ER) drug products are widely used for the treatment of attention deficit absorption models for mixed AMP salts ER capsules and dextroamphetamine g generic drug postmarketing surveillance and bioequivalence (BE) guidance ets. Virtual BE simulations were conducted to assess BE in various populations herally conducted for approval. The models were also used to predict phar- lution profiles falling within specification after the development of *in vitro–in* dels to test sensitivity of PK metrics to the changes in formulation variables. is in the public domain in the USA J Pharm Sci

e; bioavailability; clinical trial simulation; modified release

Using M&S to predict virtual BE and assess dissolution specifications

(Babiskin et al., 2015)

Research Article

Utility of Physiologically Based Absorption Modeling in Implementing Quality by Design in Drug Development

Xinyuan Zhang,[1] Robert A. Lionberger,[1,2] Barbara M. Davit,[1] and Lawrence X. Yu[1]

Received 16 September 2010; accepted 14 December 2010; published online 5 January 2011

Abstract. To implement Quality by Design (QbD) in drug development, scientists need tools that link drug products properties to *in vivo* performance. Physiologically based absorption models are potentially useful tools; yet, their utility of QbD implementation has not been discussed or explored much in the literature. We simulated pharmacokinetics (PK) of carbamazepine (CBZ) after administration of four oral formulations, immediate-release (IR) suspension, IR tablet, extended-release (XR) tablet and capsule, under fasted and fed conditions and presented a general diagram of a modeling and simulation strategy integrated with pharmaceutical development. We obtained PK parameters and absorption scale factors (ASFs) by deconvo validated for other PK pr explored three key areas w used to help identify optim critical formulations variab for the IR tablet that show decreased. Finally, virtual t Virtual bioequivalence stu test may be a more sensitiv predictive model is a poten

KEY WORDS: advanced release (MR); quality by design (QbD).

Incorporating M&S to assist with Quality by Design (QbD)

(Zhang et al., 2011)

RESEARCH PAPER

Use of *In Vitro–In Vivo* Correlation to Predict the Pharmacokinetics of Several Products Containing a BCS Class I Drug in Extended Release Matrices

Tahseen Mirza • Srikant A. Bykadi • Christopher D. Ellison • Yongheng Yang • Barbara M. Davit • Mansoor A. Khan

Received: 28 February 2012 / Accepted: 9 August 2012

ABSTRACT

Purpose To determine if an IVIVC model can predict PK profiles of varying formulations of a BCS Class I drug that is a salt of a weak base.

Method An IVIVC model (Level A) was created by correlating deconvoluted *in vivo* absorption data obtained from oral administration of 50 mg, 100 mg, and 200 mg fast and slow extended release formulations with *in vitro* percent dissolved using residual regression analysis. The model was then used to predict the *in vivo* profile of five test products that varied in formulation characteristics.

Results The model passed internal validation for predicted Cmax and AUC. For external validation, *in vitro* data of five different test formulations was utilized. The model passed external validation for two test formulations that were different but belonging to the same release mechanism as that of the reference formulation. Three formulations failed external validation because they belonged to either a mixed or different release mechanism. The model and results were further confirmed

ABBREVIATIONS

AUC	area under the curve
BCS	biopharmaceutics classification system
C_{max}	maximum drug concentration observed in the blood plasma profile
FRA	fraction of drug absorbed into the body
FRD	fraction of drug dissolved during *in vitro* experimentation
IVIVC	*in vitro–in vivo* correlation
k_e	constant of elimination
MAPE	mean absolute percentage error
rpm	revolutions per minute
SUPAC-MR	scale up post approval changes modified release
V_d	volume of distribution
$\%PE_{AUC}$	percent error of AUC prediction
$\%PE_{Cmax}$	percent error of C_{max} prediction

UCTION

in correlation (IVIVC) has been defined by the ites Pharmacopeia (USP) Subcommittee on Bio- tics as "the establishment of a rational rela- between a biological property, or parameter on a biological property produced by a dosage a physicochemical property or characteristic of dosage form" (1). The Food and Drug Admin- defines IVIVC as "A predictive mathematical scribing the relationship between an *in vitro* of an extended release dosage form (usually the rate or extent of drug dissolution or release) and a rele- vant *in vivo* response, e.g., plasma drug concentration or amount of drug absorbed" (2). In most cases, the *in vitro* property is the rate or extent of drug dissolution or release while the *in vivo* response is the plasma drug concentration

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Published online: 22 August 2012

Generating mechanistic IVIVCs to predict test formulations

(Mirza et al., 2012)

International Journal of Pharmaceutics 418 (2011) 151–160

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The role of predictive biopharmaceutical modeling and simulation in drug development and regulatory evaluation☆

Wenlei Jiang, Stephanie Kim, Xinyuan Zhang, Robert A. Lionberger*, Barbara M. Davit, Dale P. Conner, Lawrence X. Yu

Office of Generic Drugs, Food and Drug Administration, United States

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Bioequivalence
In vitro–in vivo correlation
Drug development and review

ABSTRACT

Advances in predicting *in vivo* performance o ucts are developed and reviewed. Modeling drug product development and regulatory dr the development of biorelevant specification release products with rapid therapeutic onse framework, and prediction of food effect. As better application of biopharmaceutical mod bioequivalence demonstration of complex dr modeling and simulation approaches. A collaborative effort among academia, government and industry in modeling and simulation will result in improved safe and effective new/generic drugs to the American public.

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Role of M&S in drug development and regulatory evaluation

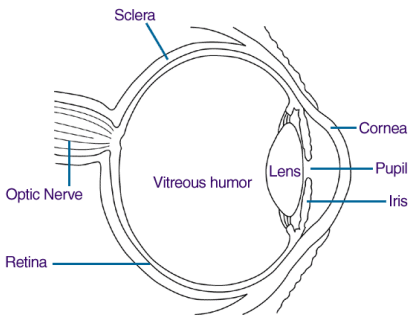
(Jiang et al., 2011)

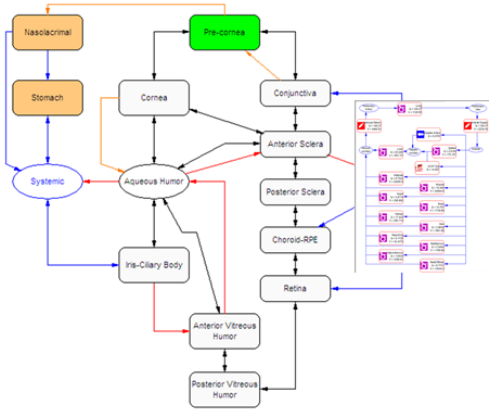
Collaboration Agreement with FDA (2014-19)

- 5-year collaborative project with the FDA Office of Testing and Research on the utility of GastroPlus **Mechanistic Absorption Modeling (MAM) and IVIVCs** to predict complex absorption characteristics
  - Goal is to facilitate drug product development by <u>decreasing regulatory burden</u> through modeling & simulation

Ocular Grant with the FDA (2014-16)

- 3-year ***<u>funded</u>*** collaborative project with the FDA Office of Generic Drugs to improve mechanistic Ocular models
- Grant members: FDA, Alcon, Santen, GSK





LAI Grant with the FDA (2014-16)

- 3-year ***<u>funded</u>*** collaborative project with the FDA Office of Generic Drugs to develop mechanistic Long Acting Injectable models
- Grant members: FDA, Amgen, Teva, Dr. Reddy's, GSK, Merck, and Novartis

Advancing the Science – Together

- Open communication between regulatory agencies, pharmaceutical companies, universities, and software providers will help identify new M&S applications:
  - Food effect modeling
  - Disease state populations
  - Oral/non-oral delivery of drug products – virtual BE
- FDA is increasing funding to scientists **from across the world** to ensure that the regulatory review of new chemical entities (NCEs) and generic drugs is based on the best available science
  - Will other regulatory agencies follow?
- FDA and EMA have developed first guidance documents for the application of PBPK simulation in submissions.

QUESTIONS FOR DISCUSSION

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Action BG2, Day 2, Q6

- What parameter fitting (and what deviation from experimental data) is acceptable? E.g. if in vivo solubility is optimized, what deviation from experimental solubility is acceptable? Same about permeability? How to know whether the optimized parameters are haphazardly adjusted?

Action BG2, Day 2, Q7

- For biowaiver/IVIVC applications, should the criteria outlined in the IVIVC guidance be used for model qualification?

Action BG2, Day 2, Q8

- In analogy to IVIVC principles, should model build up be done on an individual or average basis? Given that individual physiology information is almost never not available (although one could generate individual virtual populations), is average acceptable?

Action BG2, Day 2, Q9

- Dissolution is a key input in models especially for QbD/biowaiver type of applications – what are acceptable ways to link in vitro and in vivo dissolution for the model setup (mechanistic approach vs. empirical IVIVC?)