



FDA Public Workshop



Application of Physiologically-based Pharmacokinetic (PBPK) Modeling to Support Dose Selection

Docket Number FDA-2014-N-0129

Building 31, Great Room B/C (Note room change)

March 10, 2014

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

Agenda

8:00-8:30 am	Registration
8:30-8:35 am	Welcome and Logistics Vikram Sinha, PhD, Director, DPM/OCP/OTS/CDER/FDA
8:35-8:45 am	Opening Remarks Janet Woodcock, MD, Director, CDER/FDA
8:45-9:05 am	Introduction and Objectives of the Workshop Vikram Sinha, PhD, Director, DPM/OCP/OTS/CDER/FDA
9:05-9:30 am	FDA Presentation: Current Status of PBPK Applications in Clinical Pharmacology Reviews Ping Zhao, PhD, PBPK Lead, DPM/OCP/OTS/CDER/FDA
9:30-9:55 am	Industry Presentation: Industry PBPK Working Group White Paper Report Neil Parrott, PhD, Hoffmann-La Roche Ltd, Basel, Switzerland
9:55-10:20 am	PBPK: Where Are We Now, and Where Might We Like to Be in the Future Malcolm Rowland, PhD, Professor, University of Manchester, UK
10:20-10:35 am	Break
10:35 am-Noon	Panel Session 1: Applications of PBPK

The goal of this session is to discuss potential applications of PBPK in drug evaluation, and to determine which areas relevant to drug development and review are currently amenable to the use of PBPK.

A. Drug-drug interactions

1. Under what circumstances, can and should PBPK models be used to predict the effect of concomitant medications on the pharmacokinetics of an investigational drug via modulation of CYP-mediated metabolism? How should we use such models to design studies and inform drug labeling?
2. What are current knowledge (data, model) and confidence in using PBPK to predict the effect of an investigational drug on CYP-mediated metabolism? How should we use such models to design studies and inform drug labeling?
3. What is the current knowledge (data, model) and confidence in using PBPK to predict drug-drug interactions related to drug transporters systems? How should we use such models to design studies and inform drug labeling?

B. Pharmacokinetic prediction in human: First in Human (FIH)

Under what circumstances, should PBPK be used to predict PK prior to a FIH? Comment on its utility versus other methods (e.g. allometry) and predicting PK for biologics.

C. Other specific populations and scenarios

1. Is there sufficient knowledge to use PBPK to predict pharmacokinetics for the following :

- a. Organ impairment (hepatic or renal)
- b. Age (pediatric or geriatric)

For pediatrics, what is the utility of using a PBPK approach in humans older than 2 years?

- c. Different ethnicity/race groups
- d. Pregnancy
- e. Concomitant food intake and new formulations
- f. Intracellular concentrations

2. For the above mentioned areas, if the knowledge base and predictive performance have not been clearly established, what additional research would you suggest?
3. For scenarios where a clinical trial is not feasible or ethical, what model based approaches should be used to support dosing recommendations?
4. What kind and level of model based results should be included in drug labels?

Noon-1:00 pm

Lunch (on your own)

1:00-1:30 pm	Audience questions and comments to Panel Session 1
1:30-1:40 pm	FDA Presentation: Requirement for Regulatory Submissions of PBPK Modeling and Simulations
1:40-2:55 pm	<p>Panel Session 2: PBPK Model Verification and Reporting in Regulatory Submissions</p> <p>The objective of this session is to discuss assessment of model fidelity and best practices in reporting. There is heterogeneity in the level of detail on PBPK models included in submissions to the FDA. FDA would like to establish basic requirements for a PBPK-related regulatory submission to ensure completeness, consistency, and efficiency in the review process.</p> <p>1. What would be the critical elements for each of the following categories within a PBPK study report? Comment on the following:</p> <ul style="list-style-type: none"> - Purpose - Summary input parameters and assumptions - Necessary sensitivity analysis - Model verification process - Model application - Simulation results - Discussion/conclusion <p>2. How should model fidelity be assessed? For example, given the significant inter-study variability of PK across various studies of a given drug, should model verification focus on the ability of the model to reasonably describe the PK data from all available clinical studies in the target populations?</p> <p>2a. What other approaches should be used?</p> <p>2b. When data from multiple studies are available what external verification approaches should be utilized?</p> <p>3. What would represent sufficient information that a PBPK model is fit for its intended purpose of driving a regulatory decision, and how should this information/justification be presented in a regulatory report? For example, how should variability/uncertainty in model parameters and predictions be reported?</p>
2:55-3:25 pm	Audience questions and comments to Panel Session 2
3:25-3:45 pm	Closing remarks

Issam Zineh, PharmD, MPH, Director, OCP/OTS/CDER

Please be advised that as soon as a transcript is available, it will be accessible at <http://www.regulations.gov>. Written and electronic comments will be accepted after the hearing until April 10, 2014, Docket Number FDA-2014-N-0129. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630

Fishers lane, Ro. 1051, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>.

References

Table 1. FDA public links to clinical pharmacology review, correspondence, or label

Drug name	Links
Revatio® injection Sildenafil	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022473s000_ClinPharmR.pdf http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022473s003lbl.pdf
Cardizem LA® Diltiazem (cross labeling simvastatin)	http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021392s014lbl.pdf http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019766s087s088lbl.pdf
<i>Bosulif®</i> <i>Bosutinib</i>	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203341Orig1s000ClinPharmR.pdf
Iclusig® Ponatinib	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203469Orig1s000ClinPharmR.pdf http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203469lbl.pdf
Edurant® Rilpivirine	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202022Orig1s000ClinPharmR.pdf
Viiibryd® Vilazodone	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022567Orig1s000ClinPharmR.pdf
Xalkori® Crizotinib	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202570Orig1s000Admincorres_R.pdf
Xeralto® Rivaroxaban	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022406Orig1s000ClinPharmR.pdf
Jevtana® Cabazitaxel	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201023s000ClinPharmR.pdf

Drug name	Links
Skyla® Levonorgestrol IUD	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203159Orig1s000ClinPharmR.pdf
OPSUMIT® Macitentan	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204410Orig1s000ClinPharmR.pdf http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204410s000lbl.pdf
Imbruvica® Ibrutinib	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205552s000lbl.pdf
Simeprevir ®	http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205123Orig1s000ClinPharmR.pdf http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205123s001lbl.pdf

Table 2 – PBPK publications by the Office of Clinical Pharmacology, OTS/FDA

Area	Publications
Perspectives, Best practice	<ul style="list-style-type: none"> • Sinha, V, Zhao P, Huang SM, Zineh I, (2014) Physiologically based pharmacokinetic (PBPK) modeling: From regulatory science to regulatory policy. Clin Pharmacol Ther, accepted • Huang SM, Abernethy DR, Wang Y, Zhao P, Zineh I (2013). The utility of modeling and simulation in drug development and regulatory review. J Pharm Sci. 2013 • Zhao P, Rowland M, Huang SM (2012) Best practice in the use of physiologically based pharmacokinetic modeling and simulation to address clinical pharmacology regulatory questions. Clin Pharmacol Ther. 92:17-20. • Huang S-M, Rowland M (2012) The role of physiologically-based pharmacokinetic modeling in regulatory review. Clin Pharmacol Ther 91: 542-9. • Huang S-M (2012) PBPK as a tool in regulatory review. Biopharm Drug Dispos 33(2): 51-2 • Zhao P, Zhang L, Grillo JA, Liu Q, Bullock J, Moon YJ, Song P, Brar S, Madabushi R, Wu T-C, Booth BP, Rahman NA, Reynolds KS, Gil Berglund E, Lesko LJ, Huang S-M (2011) Applications of Physiologically-based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review. Clin Pharmacol Ther. 89:259-67
Study design	<ul style="list-style-type: none"> • Duan JZ, Jackson AJ, Zhao P (2011) Bioavailability Considerations in Evaluating Drug-Drug Interactions Using the Population Pharmacokinetic Approach. J Clin Pharmacol. 51: 1087-1100 • Zhao P, Ragueneau-Majlessi I, Zhang L, Strong JM, Reynolds KS, Levy RH, Thummel KE, Huang SM (2009). Quantitative evaluation of pharmacokinetic inhibition of CYP3A substrates by ketoconazole: a simulation study. J Clin Pharmacol. 49:351-9.
Pediatrics	<ul style="list-style-type: none"> • Leong R, Vieira ML, Zhao P, Mulugeta Y, Lee CS, Huang SM, Burckart GJ (2012) Regulatory experience with physiologically based pharmacokinetic modeling for pediatric drug trials. Clin Pharmacol Ther. 91:926-31. • Jiang XL, Zhao P, Barrett J, Lesko L, Schmidt S (2013) Application of physiologically-based pharmacokinetic modeling to predict acetaminophen metabolism & pharmacokinetics in children. CPT: Pharmacometrics & Systems Pharmacology, In Press

Area	Publications
Drug interactions and pharmacogenetics	<ul style="list-style-type: none"> • Vieira MdLT, Kim M-J, Apparaju S, Sinha, V, Zineh I, Huang SM, Zhao P (2014) PBPK model describes the effects of co-medication and genetic polymorphism on systemic exposure of drugs that undergo multiple clearance pathways. Clin Pharmacol Ther, In Press • Wu F, Lu G, Zhao P, Jamei M, Huang SM, Bashaw ED, Lee SH (2014). Predicting Nonlinear Pharmacokinetics of Omeprazole Enantiomers and Racemic Drug Using Physiologically Based Pharmacokinetic Modeling and Simulation: Application to Predict Drug/Genetic Interactions. Pharm Res, accepted • Einolf HJ, Chen L, Fahmi OA, Gibson CR, Obach RS, Shebley M, Silva J, Sinz MW, Unadkat, JD, Zhang L, Zhao P, (2013) Evaluation of various static and dynamic modeling methods to predict clinical CYP3A induction using in vitro CYP3A4 mRNA induction data. Clin Pharmacol Ther. Online • Vieira ML, Zhao P, Berglund EG, Reynolds KS, Zhang L, Lesko LJ, Huang SM (2012) Predicting drug interaction potential with a physiologically based pharmacokinetic model: a case study of telithromycin, a time-dependent CYP3A inhibitor. Clin Pharmacol Ther. 91:700-8 • Zhao P, Zhang L, Huang SM (2009) Complex Drug Interactions: Significance and Evaluation. Enzyme- and Transporter-based Drug-Drug Interactions, by Pang, Rodrigues, and Raimund, Springer-Verlag New York.
Organ impairment	<ul style="list-style-type: none"> • Grillo JA, Zhao P, Bullock J, Booth BP, Lu M, Robie-Suh K, Berglund EG, Pang KS, Rahman A, Zhang L, Lesko LJ, Huang SM (2012) Utility of a physiologically-based pharmacokinetic (PBPK) modeling approach to quantitatively predict a complex drug-drug-disease interaction scenario for rivaroxaban during the drug review process: implications for clinical practice. Biopharm Drug Dispos. 33:99-110 • Zhao P, Vieira Mde L, Grillo JA, Song P, Wu TC, Zheng JH, Arya V, Berglund EG, Atkinson AJ Jr, Sugiyama Y, Pang KS, Reynolds KS, Abernethy DR, Zhang L, Lesko LJ, Huang SM (2012). Evaluation of exposure change of nonrenally eliminated drugs in patients with chronic kidney disease using physiologically based pharmacokinetic modeling and simulation. J Clin Pharmacol. 52:91S-108S. • Hsu V, Vieira ML, Zhao P, Zhang L, Zheng JHM, Anna Nordmark A, Gil Berglund E, Giacomini KM, Huang SM (2013) Towards Quantitative Modeling of the Effect of Renal Impairment and Probenecid Inhibition on Kidney Uptake and Efflux Transporters using PBPK, Clin Pharmacokinet, Online

Area	Publications
Pregnancy	<ul style="list-style-type: none"> • Ke AB, Nallani SC, Zhao P, Rostami-Hodjegan A, Unadkat JD (2013). Expansion of a PBPK Model to Predict Disposition in Pregnant Women of Drugs Cleared via Multiple CYP Enzymes, Including CYP2B6, CYP2C9 and CYP2C19. Br J Clin Pharmacol. In Press • Ke AB, Nallani SC, Zhao P, Rostami-Hodjegan A, Isoherranen N, Unadkat JD. (2013) A Physiologically Based Pharmacokinetic Model to Predict Disposition of CYP2D6 and CYP1A2 Metabolized Drugs in Pregnant Women. Drug Metab Dispos. 41:801-13 • Ke AB*, Nallani SC, Zhao P, Rostami-Hodjegan A, Isoherranen N, Unadkat JD. (2012) A PBPK Model to Predict Disposition of CYP3A-Metabolized Drugs in Pregnant Women: Verification and Discerning the Site of CYP3A Induction. CPT: Pharmacometrics & Systems Pharmacology 1, Published online 26 September 2012 • Ke AB, Rostami-Hodjegan A, Zhao P, Unadkat JD (2014). Pharmacometrics in pregnancy: an unmet need. Annu Rev Pharmacol Toxicol 54:53-69.