Toward personalized medicine with physiologically based pharmacokinetic modeling

“While the prospect of truly personalized medicine that is tailored to the individual patient seems to be coming closer in reach, making this dream a reality will require answering several key questions.”

First draft submitted: 30 June 2016; Accepted for publication: 29 November 2016; Published online: 19 December 2016

Keywords: healthcare • modeling and simulation • personalized medicine • pharmacokinetic/pharmacodynamic (PK/PD) • physiologically based pharmacokinetics (PBPK) • precision medicine

The trend of personalized medicine in modeling & simulation

An existential crisis of pharma is the rapid increase of the development cost per successful new drug. The growth of the cost and time lines of developing new medications have no end in sight. Modeling and simulation (M&S) approaches have been widely used in other industries such as aircraft design, however, M&S is relatively new in drug development and healthcare. Could M&S be the Next Great Hope for ending this exponential cost growth and restoring sustainability to drug development? At the same time, can M&S make the dream of personalized medicine a reality?

The traditional approach to treating patients was the concept that ‘one dose fits all.’ However, in many cases – pediatrics, organ impairment, obesity and genetic variation – the use of doses for the ‘average patient’ can cause significant safety and efficacy issues [1]. How can we reduce the cost of healthcare while developing innovative treatments that help patients improve their quality of life?

The rise of personalized medicine is one of the biggest changes in our approach to healthcare in the last several decades. This paradigm uses genomic and proteomic information to predict patients’ medical risks, detect the presence of disease earlier and

manage their healthcare better. It is also turning out to be an economic force to be reckoned with. Indeed, a report issued by Grand View Research [2] valued this global market at \$1.01 trillion in 2014, with expected growth to reach \$2.45 trillion in 2022.

In an attempt to rein in the spiraling cost of clinical trials, many pharmaceutical companies have set up M&S departments to help optimize the design of clinical trials. As a result, the use of M&S, also known as bio-simulation, in drug development has been steadily increasing over the past 20 years. The emerging discipline of M&S draws together diverse scientific domains including biomathematics, computer science, pharmacometrics, biostatistics, pharmacology, system theories, systems engineering, software engineering, artificial intelligence and more. The diversity of this new discipline sometimes results in the challenge that people of different backgrounds do not share a common vocabulary in which to share ideas. To truly realize the potential of M&S will require building bridges between these different disciplines so that they can work together efficiently.

The emphasis on personalized medicine is a significant trend in pharmacokinetic M&S in drug development. I recently searched PubMed for the number of publications that used the keywords ‘Personalized Medicine’

Kairui Feng

*Author for correspondence:
Certara LP, Princeton, NJ, 08540, USA
Kevin.feng@certara.com

Robert H Leary

Certara LP, Princeton, NJ, 08540, USA

**FUTURE
SCIENCE** part of

fsg

and/or 'Pharmacokinetic'. The number of publications has exponentially increased since year 2005 at an average compound rate of approximately 10% per year.

Physiologically based pharmacokinetic modeling

Physiologically based pharmacokinetics (PBPK) is a relatively new M&S technique in drug development. However it can be viewed as a natural extension of traditional empirical compartmental and noncompartmental pharmacokinetic/pharmacodynamic (PK/PD) modeling techniques with increased model complexity and greater fidelity to underlying physiological mechanisms and phenomena. A review from US FDA showed that PBPK models are increasingly used by drug developers to evaluate the effect of individual patient factors on drug exposure [3]. PBPK results are also increasingly influencing FDA drug labels [4–6]. Hence, population-based PBPK models have become a powerful M&S technique for drug development from the industrial and regulatory perspectives.

PBPK models have a unique advantage by considering not only the drug and the formulation characteristics but also the underlying physiology of the individual subject and its variability within a population in prediction of drug absorption, distribution and elimination [7]. PBPK models along with appropriate human physiology data have already been shown to reduce and refine clinical trials in other areas such as drug-drug interactions and oral drug absorption [8–10]. The other advantage of PBPK approach is the possibility of extrapolations. Once the model performance is verified for a particular drug/formulation in one population, it can be assessed with increased confidence for another population with PBPK, as the formulation is the same and only the physiology is different. This makes it possible to transfer the physiological information from healthy volunteers to, for example, elderly patients, provided the physiological differences between healthy and elderly populations are well characterized. This requires incorporating inter-individual variability in PBPK models so that individuals at extreme tails of population distribution and their covariates are identified [8,11,12]. The same concept is potentially applicable to personalized medicine in that a validated population PBPK model can be used to individualize dosing by combining individual physiological information with mathematical optimization techniques.

The new era of personalized medicine

PBPK models have already helped in individualized treatment such as paracetamol overdose [13], individualization of medications in children [14], and application to temozolomide in brain tumors [15].

Leveraging biosimulation technology will help lower costs for pharmaceutical sponsors, clinicians, payers and patients. Whether the objective is to determine first-in-human dosing or individualized dosing regimens, all M&S tools can share the same core computational engines. These engines can then be linked to end users through desktop, web and smart phone applications. Likewise, the cost of drug development can be optimized using the same core engines with pharmacoeconomic techniques. Finally, the drug label description of clinical usage can be optimized using the same core engines with the addition of Bayesian optimization techniques. Leveraging this integrated technology from the beginning of drug development all the way through patient care will reduce costs by streamlining the transitions between different phases of drug development and the transition from drug development to patient care.

Nonadherence to prescribed medications is a common and significant barrier to effective treatment. It is also very difficult for clinicians to detect using only traditional methods such as subjective questionnaires. Critical decision making is hindered by having to rely on such subjective interpretations. Thus, quantitative, objective measures of systemic exposure from PK/PD models can help shed light on medication adherence. This novel use of population PK/PD analysis demonstrates one of the many ways that biosimulation technology is transforming the pharmaceutical industry. Optimal control theory combined with mathematical modeling to provide a systematic way to determine an optimal intervention schedule was proposed by Banks *et al.* [16] to help to address nonadherence in the context of personalized dosing.

Due to the large number of mathematical parameters in PBPK models, Bayesian types of algorithms can be used for the optimization of individual treatment. One such notable current dosage optimization approach in the Pmetrics and Bestdose software from the USC Laboratory for Applied Pharmacokinetics [17] evolved from a sequence of increasingly efficient nonparametric methods introduced in the context of traditional PK/PD nonlinear mixed effects (NLME) modeling [18–20]. The nonparametric population estimation methods were combined with formal control theory to optimize doses to achieve a best overall fit (according to some optimization criterion). Nonparametric approaches are particularly natural and easily applied in this context since they give rise to Bayesian posteriors for each subject that have finite numbers of discrete support points. Thus, the control theory problem reduces to optimizing a functional of a finite number of trajectories, each of which has a different Bayesian posterior probability. We believe this approach is readily extensible to PBPK models.

Optimization technique and control theory are important to resolve the personalized treatment problems. However, more physiological data from individual characteristic information are required to build the individual level of PBPK models. Within the roadmap of physiome interoperability for personalized drug development [21], 'omics' data in pharmacogenomic biomarkers will help overcome the bottleneck in model development and make it possible for PBPK models to be used for personalized treatment.

Future perspective

Personalized medicine with physiologically based pharmacokinetic modeling still has a long way to go. While the prospect of truly personalized medicine that is tailored to the individual patient seems to be coming closer in reach, making this dream a reality will require answering several key questions. How will regulatory agencies approve drug labels that are tailored to individuals based on a patient's individual genetic, physiological and environmental characteristics? In theory, individualized drug labels could lead to a practically infinite number of drug labels. How would the FDA even review and approve these labels? In the future, we envision that personalized drug labels are in an electronic format that clinicians can transmit via smart phone. In the era of personalized medicine, how would clinicians match individual treatment plans to patients? And how would patients manage these new customized treatment plans? What would a patient do if he misses a dose or takes the dose at the wrong time? Would he take an extra dose to compensate for missing the dose? Building a technological infrastructure that supports personalized medicine will be a critical step in delivering precision medicine to patients. Once new technology becomes available allowing individual physiological data to be matched with PBPK model parameters, clinicians could do a treatment plan by

directly linking to individual healthcare database and healthcare plan policies provided by payers.

In addition to our scientific interest in precision medicine, one of the authors also has a personal tie to this issue. One of his family members has had hypertension for many years. In the future, perhaps she will be able to use a smart phone app that tells her when to take her medication and what dose she should take. In August 2015, the FDA approved the first 3D-printed drug for epilepsy. Indeed, the smart phone app could potentially be coupled to 3D printing technology to enable real-time printing of pills with the optimal dose.

This smart phone app would also be able to advise her on what to do when she has missed a dose or taken a short drug holiday. The relative was very interested in this application because she said that when she forgets to take her medication, she gets confused as what to do. Or, she would measure her blood pressure and get a high reading and would again be confused on what to do. New technologies such as smart phone apps and 3D printing may be important tools in improving the safety and efficacy of treatments for patients and their quality of life.

Acknowledgements

Helpful discussions were held with various Certara staff members, and special thanks is due to Suzanne Minton for help in reviewing the manuscript.

Financial & competing interests disclosure

We are currently employed by Certara, which is engaged in software development and consulting in areas related to this article. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

References

- 1 Mould DR, D'Haens G, Upton RN. clinical decision support tools: the evolution of a revolution. *Clin. Pharmacol. Ther.* 99(4), 405–418 (2016).
- 2 Grand View Research. Personalized medicine (PM) market analysis by product (PM diagnostics, PM therapeutics, personalized medical care, personalized nutrition & wellness) and segment forecasts to 2022. (2015). www.grandviewresearch.com/industry-analysis/personalized-medicine-market
- 3 Zhao P, Rowland M, Huang SM. Best practice in the use of physiologically based pharmacokinetic modeling and simulation to address clinical pharmacology regulatory questions. *Clin. Pharmacol. Ther.* 92(1), 17–20 (2012).
- 4 FDA, Drug label, OLYSIO, highlights of prescribing information. (2013). www.accessdata.fda.gov/drugsatfda_docs/label/2013/205123s000lbl.pdf
- 5 FDA, Drug label, Imbruvica™ clinical pharmacology and biopharmaceutics review(s). (2013). www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf
- 6 FDA, Drug label, OPSUMIT clinical pharmacology and biopharmaceutics review(s). (2012). www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204410Orig1s000ClinPharmR.pdf
- 7 Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A. The Simcyp® population-based

- ADME simulator. *Expert Opin. Drug Metab. Toxicol.* 5(2), 211–223 (2009).
- 8 Rowland M, Peck C, Tucker G. Physiologically-based pharmacokinetics in drug development and regulatory science. *Annu. Rev. Pharmacol. Toxicol.* 51, 45–73 (2011).
- 9 Yeo KR, Jamei M, Rostami-Hodjegan A. Predicting drug-drug interactions: application of physiologically based pharmacokinetic models under a systems biology approach. *Expert Rev. Clin. Pharmacol.* 6(2), 143–157 (2013).
- 10 Kostewicz ES, Aarons L, Bergstrand M *et al.* PBPK models for the prediction of *in vivo* performance of oral dosage forms. *Eur. J. Pharm. Sci.* 57, 300–321 (2013).
- 11 Jamei M, Dickinson GL, Rostami-Hodjegan A. A framework for assessing inter-individual variability in pharmacokinetics using virtual human populations and integrating general knowledge of physical chemistry, biology, anatomy, physiology and genetics: a tale of ‘bottom-up’ vs ‘top-down’ recognition of covariates. *Drug Metab. Pharmacokinet.* 24(1), 53–75 (2009).
- 12 Zhao P, Zhang L, Grillo JA *et al.* Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review. *Clin. Pharmacol. Ther.* 89(2), 259–267 (2011).
- 13 Zurlinden TJ, Heard K, Reisfeld B. A novel approach for estimating ingested dose associated with paracetamol overdose. *Br. J. Clin. Pharmacol.* 81(4), 634–645 (2016).
- 14 Leeder JS, Brown JT, Soden SE. Individualizing the use of medications in children: making Goldilocks happy. *Clin. Pharmacol. Ther.* 96(3), 304–306 (2014).
- 15 Ballesta A, Zhou Q, Zhang X, Lv H, Gallo JM. Multiscale design of cell-type-specific pharmacokinetic/pharmacodynamic models for personalized medicine: application to temozolomide in brain tumors. *Pharmacometrics Syst. Pharmacol.* 30(3), e112 (2014).
- 16 Banks HT, Hu S, Jang T, Kwon HD. Modeling and optimal control of immune response of renal transplant recipients. *J. Biol. Dyn.* 6, 539–567 (2012).
- 17 Jelliffe R, Schumitzky A, Bayard D *et al.* Human genetic variation – dynamic models, bayesian feedback control, and maximally precise drug dosage regimens. *Curr. Pharmacogenomics Person. Med.* 7, 249–262 (2009).
- 18 Mallet A. A maximum likelihood estimation method for random coefficient regression models. *Biometrika* 73, 645–656 (1986).
- 19 Schumitzky A. Nonparametric EM algorithms for estimating prior distributions. *Appl. Math. Comput.* 45, 141–157 (1991).
- 20 Leary RH, Jelliffe R, Schumitzky A, Van Guilder M. An adaptive grid non-parametric approach to pharmacokinetic and dynamic (PD/PD) modeling. In: *Proceedings 14th IEEE Symposium on Computer-based Medical Systems*. 389–394, Bethesda, MD, USA (2001).
- 21 Thomas S, Wolstencroft K, de Bono B, Hunter PJ. A physiome interoperability roadmap for personalized drug development. *Interface Focus* 6(2), 20150094 (2016).