0.097% in the SEARCH study. The predicted incidence rate for pravastatin is zero and no events were monitored in SEARCH.

The case study demonstrates how PBPK modeling and prior physiological and pharmacological knowledge may be used to predict clinically relevant events. Clinical incidence rates in dominant patient populations can be used to extrapolate to rare-frequency events in high-risk patients and how safety risks characterized for one drug and dose can be extrapolated to other doses and drugs from the same pharmacological class by use of prior information even in the absence a full-blown mechanistic understanding at all biological levels.

5 Conclusions

A good understanding of the causal chain from drug administration via systemic and tissue exposure to intended drug effects and adverse events is the determinant of success in clinical drug development. M&S helps to bridge gaps in our understanding and thereby reduces uncertainty and enables new quantitative insights. Today's modeling technologies allow very detailed integrated representations of biological, physiological, and pharmacological process at all levels from molecular interactions to organism-level physiology. Within the framework of detailed mechanistic modeling, knowledge gaps can be bridged using explicit assumptions or empirical relationships. State-of-the-art pharmacology uses M&S techniques to rigorously test hypotheses and plan new experiments.

References

Cartwright ME et al (2010) Proof of concept: a PhRMA position paper with recommendations for best practice. Clin Pharmacol Ther 87:278–285

Cohen A (2008) Pharmacokinetic and pharmacodynamic data to be derived from early-phase drug development-designing informative human pharmacological studies. Clin Pharmacokinet 47:373–381

US Food and Drug Administration (1999) Guidance for industry: population pharmacokinetics, 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), February 1999

Edginton AN, Schmitt W, Willmann S (2006) Development and evaluation of a generic physiologically based pharmacokinetic model for children. Clin Pharmacokinet 45(10):1013–1034

Eissing T, Kuepfer L, Becker C, Block M, Coboeken K, Gaub T, Goerlitz L, Jaeger J, Loosen R, Ludewig B, Meyer M, Niederalt C, Sevestre M, Siegmund HU, Solodenko J, Thelen K, Telle U, Weiss W, Wendl T, Willmann S, Lippert J (2011) A computational systems biology software platform for multiscale modeling and simulation: integrating whole-body physiology, disease biology, and molecular reaction networks. Front Physiol 2:4

El-Khatib FH, Russell SJ, Nathan DM, Sutherlin RG, Damiano ER (2010) A bihormonal closed-loop artificial pancreas for type 1 diabetes. Sci Transl Med 2:27ra27

Empfield JR, Leeson PD (2010) Lessons learned from candidate drug attrition. IDrugs 13:869–887

Ette EI, Williams PJ (2004) Population pharmacokinetics I: background, concepts, and models. Ann Pharmacother 38(10):1702–1706