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Modeling and Simulation in Clinical Trials: Real Potential or Hype?

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Improving experimental drug success rate[1] and accelerating clinical development[2] are top priorities for pharmaceutical companies. Careful decision making during drug development is essential to minimize development time, manage costs and improve the probability of commercial success. Recently, many of the major pharmaceutical companies have begun to explore computer-based bio-simulation strategies to help generate the information necessary to make better decisions.[3,4] These strategies go by many different names – clinical trial simulation (CTS), modeling and simulation (M&S), computer-assisted trial design (CATD), model-based drug development (MBDD), and model-informed drug discovery and development (MID3). The FDA and EMA regulatory agencies have also taken notice of M&S strategies in an effort to support improved drug development efficiencies.

Computer-based modeling and simulation has already had a beneficial impact on many different fields and industries – physics, chemistry, aeronautics, meteorology, material science, finance, and musical composition. In finance, for example, professional investors traditionally work to find a handful of undervalued companies in which to invest, a process which typically involves interviewing management teams, researching corporate strategies, and analyzing demand for products and services. Artificial intelligence is changing all of that. Quantitative-investment, or "quant," funds rely on high-speed computers and trading models that evaluate publicly available data to make investment decisions – without ever talking to management teams. Today, one quant fund named Two Sigma is the fastest growing hedge fund on Wall Street, which manages over $35 billion in assets.

Despite its promise, adoption of M&S in the pharmaceutical industry has lagged due to the complexity of modeling biological systems, insufficient scientific understanding of disease conditions, and lack of large amounts of real-world health outcome population data. Significant progress in these areas has occurred over the last decade, and M&S is now being promoted as having the potential to transform the drug development process from R&D all the way to commercialization and life-cycle management. Is this potential real or just hype?

What is Modeling and Simulation in Clinical Trials?

With regards to the drug development process, M&S involves modeling compounds, mechanisms and disease level data based on historical observations. Computer simulations are run on these models to generate information that can be used to predict outcomes, thereby improving the quality, efficiency and cost-effectiveness of decision-making.

For clinical trials specifically, a clinical trial simulation (CTS) would attempt to study the effects of a drug in a virtual patient population using mathematical models that incorporate information on physiological systems. Simulations can be used to test assumptions, improve predictability, better characterize risk and identify opportunities to optimize outcomes by observing the effects of different model inputs – an understanding of the full range of potential outcomes can be cultivated by observing the effects of more extreme model inputs than have been observed in real-world patients, for example. In this way, M&S can help investigators better plan and design clinical trials by exploring and quantifying risks prior to their start.

Examples of Modeling and Simulation in Clinical Trials

Efficacy and safety issues are of the upmost importance in clinical trials – either the substance in question does not have sufficient biological activity, or it does not have manageable toxicity. But the level of efficacy or toxicity in a drug is very much related to the dose level and schedule used. Poor dose and scheduling choices can have serious consequences for drug safety and efficacy in a clinical trial, resulting late stage failures, or registration delays as problems must be investigated and corrected. As a result, determining the proper dose and scheduling of a drug prior to the start of a clinical trial is extremely important in order to avoid a preventable failure.

The most mature application of M&S in clinical trials is pharmacokinetic modeling for dose and scheduling determination. This M&S application has been successful in predicting optimal dosing regimens from preclinical to Phase III studies.[5] By understanding patterns in the exposure-response relationship, population PK/PD analysis can also help to identify dose adjustments needed for special populations - children, the elderly, ethnic groups, patients with impaired renal/hepatic function, and patients likely to experience drug-drug interactions.[6,7]

Other uses for CTS may include answering those questions that can be difficult or impractical to answer using clinical trial methods. When the American Diabetes Association wanted to compare the effectiveness of current diabetes management approaches, for example, Archimedes Inc. simulated a 30-year clinical trial using a physiology-based model to predict outcomes in a patient population.[8] Physiology-based models strive to model disease processes at a biological level using equations that are calibrated with data from empirical sources. When properly constructed, these models can be used to identify priorities in clinical trials, facilitate design of new trials, or conduct virtual comparative effectiveness trials.

M&S also appears to have value in optimizing study design.[9] The idea is to increase the efficiency of trials by establishing appropriate trial size and collecting relevant data at optimal times to generate knowledge. Simulations are used to explore different trial designs to select the best option.

Use of M&S in clinical trials seems to have a dramatic impact on FDA approval and labeling decisions. A 2011 review conducted by the FDA found a dramatic increase in both the number of reviews with pharmacometric analysis and the impact of those analyses on drug approval and labeling decisions. Pharmacometric analysis was found to have made an important contribution to 126 drug approval decisions (64%) between the years 2000 and 2008. Additionally, pharmacometric analysis was found to impact labeling decisions in 133 applications (67%) during this time period.[10] Finally, in the midst of an influenza epidemic in 2009, the FDA used M&S to identify and approve a safe pediatric dose of an experimental drug that had never been studied in children – peramivir.

Modeling and Simulation Throughout the Drug Development Process

The pharmaceutical industry is slowly beginning to adopt M&S across many different aspects of the drug development process. One example is the use of M&S to assess structure-affinity relationships of experimental drug compounds to predict toxicity and safety.[11] Results of these kind of simulations are increasingly being utilized by regulatory agencies. Another example is the use of M&S to predict the overall cost-effectiveness of new medicines in the health technology assessment process.[12] M&S is also being used to provide for more effectively management of a biopharma company's R&D development portfolio.[13]

The opportunities for cost and time savings in the drug development process by utilizing M&S are enormous. This economic incentive is being supported by the rapid growth of computational power and patient health data, along with advances in scientific understanding. Because of this "perfect storm" combination of factors, scientists are starting to utilize M&S to tackle some of medicine's toughest what-if questions, and new applications for M&S throughout the drug development process are being discovered rapidly.

Conclusion

While adoption of M&S by the pharmaceutical industry has been slower than in other industries, recent years have seen M&S utilized in all phases of the drug development process. M&S practices support knowledge-based approaches that can make drug development processes more efficient and informative, thereby enhancing return on investment for drug developers in today's challenging business environment. M&S offers drug developers in pharmaceutical companies the opportunity to quantify problems, test assumptions, increase predictability, improve decision-making, and ultimately lower costs.

As advances in computational power, patient health data, and scientific understanding continue to grow, M&S will likely play a larger role in the development of lifesaving medicines – in terms of supporting both pharmaceutical company internal decision-making, and applications for regulatory approval. Increased reliance on M&S will lead to new, more collaborative ways of working, as experts from diverse fields will be required to come together to frame the questions and quantify assumptions for simulations. Ultimately, these collaborative efforts will serve to improve the drug development process, leading to better medicines delivered to patients in a timelier fashion.

References

1 "Clinical development success rates for investigational drugs," Nature Biotechnology 32, 40-51 (2014). Michael Hay et al. Available at: http://www.nature.com/nbt/journal/v32/n1/full/nbt.2786.html#access

2 Drug Approvals - From Invention to Market...A 12-Year Trip. MedicineNet.com http://www.medicinenet.com/script/main/art.asp?articlekey=9877

3 "Building a Modeling Culture in Manufacturing at Pfizer," Pharmaceutical Manufacturing, 2011. Joe Cancelarich. Available at: http://www.pharmamanufacturing.com/articles/2011/023/

4 "Novartis Savors Early Modeling Success,"Bio-IT World, March 2009. John Russell. Available at: http://www.bio-itworld.com/pb/2009/03/19/novartis-modeling-stanski.html

5 "Pharmacokinetic and Pharmacodynamic Modeling of the Relationship Between TAK-442 Exposure and Clinical Outcome In Patients Undergoing Elective Knee Arthroplasty," Blood 2010 116:3326; Stringer et. al. Available at: http://www.bloodjournal.org/content/116/21/3326?sso-checked=true

6 "Use of Modeling and Simulation in the Design and Conduct of Pediatric Clinical Trials and the Optimization of Individualized Dosing Regimens," CPT Pharmacometrics Syst Pharmacol. 2015 Nov; 4(11): 630–640; Stockmann et. al. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4716585/

7 "The pharmacokinetics and pharmacodynamics of cisatracurium in critically ill patients with severe sepsis," Br J Clin Pharmacol. 2012 May; 73(5): 741–749; Liu et. al. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3403201/

8 "Life Cycle Modeling and Simulation: Current Practice and Future Impact on Health Care Innovation and Delivery," Therapeutic Innovation & Regulatory Science 47(2) 175-182; O'Kelly et. al. Available at: http://journals.sagepub.com/doi/abs/10.1177/2168479012471831

9 "Model-Based Optimal Design and Execution of the First-Inpatient Trial of the Anti-IL-6, Olokizumab," CPT Pharmacometrics Syst Pharmacol. 2014 Jun; 3(6): e119; Kretsos et. al. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4076804/

10 "Impact of Pharmacometric Analyses on New Drug Approval and Labelling Decisions A Review of 198 Submissions Between 2000 and 2008," Clinical Pharmacokinetics 50(10):627-635 · January 2011; Lee et.al. Available at: https://www.researchgate.net/publication/296935744_Impact_of_Pharmacometric_Analyses_on_New_Drug_Approval_and_Labelling_Decisions_A_Review_of_198_Submissions_Between_2000_and_2008

11 "(Q)SAR modeling and safety assessment in regulatory review," Clin Pharmacol Ther. 2012 Mar;91(3):529-34; Kruhlak NL et. al. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22258468

12 "Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment," Pharmacoeconomics. 2006;24(4):355-71; Philips et. al. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16605282

13 "Lifecycle Modeling and Simulation: Applications in Clinical Development," Applied Clinical Trials, Apr 15, 2014; Garrett et. al. Available at: http://www.appliedclinicaltrialsonline.com/lifecycle-modeling-and-simulation-applications-clinical-development?pageID=2

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