Pharmaceutical Research, Vol. 17, No. 3, 2000

Commentary

Clinical Trial Simulation in Drug Development

Peter L. Bonate[1,2]

Received July 6, 1999; accepted December 11, 1999

Clinical trial simulation is the application of old technologies, e.g., Monte Carlo simulation, to a new problem, that problem being how to maximize the information content obtained during the drug development process with an intent to have the greatest chance of "success" in a clinical trial. When the information content of the drug is high, then simulation provides a method to synthesize that information into a coherent package that indicates the sponsor has good control over the pharmacology of the drug. From a purely financial point of view, what simulation offers pharmaceutical companies is the possibility of reducing the number of required studies, maximizing the chances for success in a clinical trial, and possibly shortening development time; all outcomes which will reduce drug development costs. The purpose of this paper is to introduce clinical trial simulation to the reader by discussing its potential in drug development, to briefly review the literature, and to make recommendations and caveats regarding its use.

KEY WORDS: Monte Carlo; computer assisted trial design; modeling.

INTRODUCTION

Although we are not even aware of it, everyday we reap the benefits of simulation. In doing a very brief search on the Internet for uses of simulation in everyday life, one can find many interesting uses that they might not have been cognizant of. Chances are, the car you are driving was at least partly developed based on computer simulation; everything from the engine, to how the car hood closes, to the assembly line used to build it. In 1998, the Dodge Intrepid and Chrysler Concorde were the first cars built entirely using computer simulation. As you drive to work, the timing of traffic lights may have been optimized using traffic simulation (although some may debate this point). The tires used on the car, e.g., the particular rubber composition, the arrangement of the threads and etching, etc., have probably been designed using simulation. The composition of the plastic coffee cup you drink from while driving was probably developed using simulation. As you get to work, the arrangement of the office space may have been optimized for ergonomics.

The government, particularly the military, has long been a proponent of simulation having a number of centers that utilize simulation technology, some dedicated to that very purpose, including Los Alamos National Laboratories, the National Simulation Center, and the Battle Simulation Center. In 1996, the United States government signed the Nuclear Ban Test Treaty which bans all test explosions. In an effort to counter any opposition to the treaty, the government agreed to spend 45 billion dollars over the next ten years to develop simulation technology to validate the reliability of nuclear bombs without actually detonating them. Recently, it has been alleged that China has stolen state secrets from the United States. Part of those secrets included the simulation technology to build a virtual nuclear bomb.

Simulation is routinely used to improve the safety of air travelers. The National Air and Transportation Safety Board (NATSB) has recently called on Boeing to change the design of the rudders on their planes because of a failure in their control mechanism. The NATSB issued this recommendation based on computer simulations of the crash of flight USAir 427 over Pittsburgh in 1994. The Federal Bureau of Investigation recently used similar methods to show that the crash of flight TWA800 over New York Harbor in 1997 was not caused by sabotage.

Simulation is also widely used for entertainment. Microsoft Flight Simulator® is one of the most widely known video games on the market. Other types of video software that use simulation technology included military games and pinball programs. Many business managers routinely use gaming simulation to optimize schedules and reduce costs.

SIMULATION IN THE BIOMEDICAL SCIENCES

Modeling and simulation are sometimes used synonymously because they both use an abstraction of some real system for prediction and control. But, for our purposes we will distinguish between the two in that a model is any mathematical construct built from basic processes or data relating inputs to outputs and simulation[3] as building upon these models by

[1] Quintiles, Clinical Pharmacokinetics, PO Box 9708 (L4-M2828), Kansas City, Missouri 64134.

[2] To whom correspondence should be addressed. (e-mail: pbonate@qkan.quintiles.com)

[3] Simulation is often referred to as the Monte Carlo method, a term introduced by von Neumann and Ulam during their top-secret work on the atomic bomb at Los Alamos during World War II as a tongue-in-cheek reference to the gambling casinos in Monte Carlo (15).

0724-8741/00/0300-0252$18.00/0

Table 1. Similarities and Differences Between Modeling and Simulation

Modeling	Simulation
Sensitive to assumptions	Sensitive to assumptions
Sensitive to black-box criticisms	Sensitive to black-box criticisms
Uses data	Builds upon models based on data
Useful method for data summarization	Useful method to summarize complex inter-relationships between variables
Relates inputs to outputs	Incorporates random variability into model and assesses its effect long-term
Random variability is a nuisance variable	Random variability can be incorporated in the simulation
Looks back in time	Looks forward in time
Can identify which variables are more important than others	Can identify which variables are more important than others
Cannot be replicated	Can be replicated

incorporating random variability into the model in attempt to understand its long-term impact. Given these definitions, a number of similarities and differences arise between the two terms (Table 1). The bottom line is that modeling looks back in time, whereas simulation looks forward in time allowing us to make better predictions of future outcomes.

The medical field has been surprisingly slow in accepting simulation technology, perhaps because of the reticence to accept that humans can be "modeled." This same reticence was seen in the aerospace and defense industries, but particularly with the aerospace industry. Johnson (1) presents a very interesting article comparing the aerospace industry to the pharmaceutical industry. When simulation began to be introduced in the 1960's, most scientists were experimentalists in the sense that they were all trained to go build a rocket, if it flies, okay. If not, go build another rocket. A similar attitude is seen in the pharmaceutical industry: do a study, if it works, great. If not, go do another study. In fact, Johnson (1) reports that many such parallels exist between the pharmaceutical and aerospace industry, a conclusion also reached by Urquhart (2). Johnson (1) also suggests that the aerospace industry, which has embraced simulation technology and is beginning to reap its rewards, is possibly more complicated because as many as 500 variables need to be modeled and accounted for, whereas clinical pharmacologists tend to work with far fewer.

The one group within the biomedical community that has embraced simulation has been the statisticians. Unfortunately, this group has been quite myopic focusing on theoretical distributions of test statistics or the power of new statistical tests compared to gold standards. Surprisingly, few have taken the initiative to incorporate all sources of variability into a simulation and to take a step back from the forest to see the trees. However, statisticians can be credited with the concept of clinical trial simulation (CTS) so it is not really fair to be too harsh on them.

Simulation of clinical trials is not really a new phenomenon. Indeed, it is simply the application of old technologies to a new problem, that problem being how to maximize the information content obtained during the drug development process with an intent to have the greatest chance of "success" in a clinical trial. A reporter once said that technology is tricky business. Take one step forward into the void and you will be seen as a visionary with everyone clamoring to follow. But take two steps into the void and you could end up like Apple Computer's LISA—a door stop in an elementary school classroom. Many view CTS as three steps forward, all smoke and mirrors. But, simulation is like anything else: garbage in = garbage out. When the information content on a drug is high, then simulation provides a method to synthesize that information into a coherent package that indicates the sponsor has good control over the pharmacology of the drug.

WHY IS CLINICAL TRIAL SIMULATION NECESSARY?

Despite needing only two pivotal efficacy studies in support of a New Drug Application (NDA), the average number of studies in support of an NDA in the 1990s was 60 (3). Almost half of the studies used to support efficacy claims did not reach statistical significance with a myriad of reasons for their failure (Table 2), most relating to the design of the phase III studies (4). Concurrent with these problems is the near exponential increase in expenses related to drug development since 1980. Granted, many of these studies were probably not efficacy studies, but studies used to characterize pharmacokinetics in special populations, drug interaction studies, etc. Nonetheless, common sense would indicate that not all these studies may have been necessary.

It is imperative that drug manufacturers learn how to do things faster and cheaper to remain competitive. Clinical trials need to be optimized given the information at hand. Simulation may become a key player by identifying what studies need to be done and in identifying which studies may be superfluous for drug development. Because CTS is a multi-disciplinary function, it forces the key players, e.g., the clinical pharmacologist, pharmacokineticist, statistician, preclinical pharmacologist, etc., to sit down and discuss what is known and what is not known about the drug and how that information ties together.

Table 2. Why Clinical Trials Fail

- Drug is a lemon
- Inadequate clinical trial design
- Wrong study population
- Wrong dose
- Wrong statistical analysis
- Wrong effect being studied
- Low statistical power
- Loss of knowledge as the drug is "handed-off" during the development process
- Poor pharmacokinetics

Note: Compiled from Hale *et al.* (16).

WHAT CAN SIMULATION PROVIDE?

Simulation can be used to augment drug development programs by providing an integrated summary of data to regulatory authorities. With the passage of the FDA Modernization Act, sponsors may submit a NDA with a single well-controlled clinical trial and supporting data. Simulation can be quite compelling supporting data. Simulations that accurately predict observed data indicate the sponsor has a good grasp of the pharmacology of the new chemical entity (NCE) and the adequacy of the clinical trial in support of the NCE. By forcing the sponsor to define *a priori* known relationships and assumptions regarding the pharmacology of the NCE, simulation can be used to define weak links in the development process and the impact of uncertainty on the outcome of a study.

Simulation may improve the probability of "success" in an efficacy trial by allowing the user to ask "What if" questions (Table 3). For instance, given the information on-hand what is the effect of a 10% increase in the non-compliance rate? What if the maximal effect for the drug is really less than we think. How much less before the power of the study is so low that treatment effects cannot be reliably detected. How will a change in the inclusion criteria affect the outcome? Simulation can also build in financial costs associated with a trial so that the aim of the simulation is to minimize trial costs given a particular study design.

Simulation may also be used to predict starting doses in man. Currently, allometric scaling is one of the preferred methods for dose selection for a first-time-in-man study (5). Under that paradigm, some summary measure of the pharmacokinetics across animal species, such as mean clearance and volume of distribution, is used to predict what the pharmacokinetics will be in humans. From this, a single point estimate of the pharmacokinetics in humans is estimated without regard to error or variability. Simulation may be used to provide a better grasp on the variability in pharmacokinetics in humans and possibly provide a better point estimate for the pharmacokinetic in humans as well. These are just a few of the benefits that simulation may offer the pharmaceutical industry. Table 4 presents some of the questions that simulation may answer based on stage of drug development.

DOCUMENTED USES AND BENEFITS

CTS is so new that few studies have been published. Some of the following uses do not deal specifically with drug development, but are cited for their use of simulation as a problem solving tool in clinical trials. Elashof *et al.* (6) used a Markov chain model to study the incidence of ulcer recurrent and healing process. They used their model to show that current trial designs were inadequate to support ulcer recurrence prevention claims and proposed a new experimental design which would unambiguously support such claims.

Table 3. What Can Simulation Provide

- Forces the sponsor to identify what knowledge is on hand and what is missing and uncertain
- Allows the sponsor to identify the impact of uncertainty on trial outcomes
- May result in cheaper, more cost effective studies
- May result in trials with fewer adverse events
- Allows the user to "test drive" trials on a computer before implementing them
- Can answer "What if?" questions

Barlow *et al.* (7) used simulation to study the analysis plan in the Silicone study, a clinical trial comparing two surgical treatments for retinal detachment associated with proliferative vitroretinopathy in non-diabetics. Because of the possibility of the retina redetaching postoperatively, some patients may undergo repeated surgery. Due to the unethical nature of repeated treatment administration on a patient after several failures, some patients were allowed to be switched to the other treatment. Simulation was used to evaluate the effect of switching using two different analysis scenarios: ignore that treatments have been switched and analyze the data based on the initial treatment assignment for all patients or all switched patients are treated as failures regardless of outcome. Simulations showed that both analysis scenarios resulted in significant loss of power and bias in treatment effect estimation.

Gooley *et al.* (8) used simulation to find an optimal dose of T-cells to be used in bone marrow transplantation patients with HLA-mismatched unrelated donors. The goal was to find a dose such that the risk of moderate to severe graft-versus-host-disease was less than 15% with no more than a 5% rejection rate. Their simulation showed that using a standard dose-escalation scheme used for oncolytic agents, there was an unacceptably high risk of an erroneous dose conclusion.

Brooks *et al.* (9) used simulation to design the sequential monitoring plan for the AVID trial (Antiarrhythmic Versus Implantable Defibrillators Study), a National Institutes of Health sponsored study comparing two treatments, antiarrhythmic drug therapy (amiodarone and sotalol) versus implantable cardiac defibrillators for patients who have survived a major arrhythmic event. The primary endpoint was death. The authors studied three different test statistics and use functions. They showed that the ability to detect treatment effects was heavily influenced by choice of test statistic and use function. These simulations were used to convince the Data Safety Monitoring Board that a non-standard monitoring scheme was better than more typical alternatives.

Glaxo Wellcome, Inc. used simulation in support of drug labeling for cisatracurium, an neuromuscular blocker (10). Using population pharmacokinetic-pharmacodynamic analysis and appropriate model validation techniques, Glaxo Wellcome convinced the Food and Drug Administration of dosing recommendations on the product label. Simulations showed that faster onset of effect would occur in the presence of an inhalational anesthetic and slower in patients with renal dysfunction, observations included in the package insert.

Gieschke *et al.* (11) used simulation to select a dosing regimen for a phase III study for an oral anticancer agent being developed by Hoffman-La Roche and to examine what the impact might be on the efficacy/adverse event profile of the drug given a 50% reduction in the dose. Simulations showed that the dosing regimens being proposed were equally efficacious given the degree of knowledge on hand.

Hale *et al.* (12) used simulation to choose the sample size, study power, and experimental design for a clinical trial studying the pharmacokinetic-pharmacodynamic relationship of mycophenolate mofetil, a pro-drug, immunosuppresive agent used in combination with cyclosporin and corticosteroids for the prevention of acute organ rejection in renal transplantation.

Table 4. Bottom-Line Questions Simulation May Answer Categorized by Stage of Development

I	Starting dose for first time in man
	Prediction of multiple-dose pharmacokinetics given single-dose pharmacokinetics
	Potential impact of drug interactions on pharmacokinetics/pharmacodynamics
	Potential impact of renal and/or hepatic dysfunction on pharmacokinetics/pharmacodynamics
II, III	Selection of doses for Phase II/III
	Number of subjects to achieve a given level of power
	Dose to use to achieve a given target concentration in a certain percentage of patients in the population
	What statistical test achieves the greatest power under the conditions at hand
	Comparison of alternative experimental designs
IV	Comparison of drug to other marketed products (involves simulation of competing product)
	Effect of potential drug interactions on pharmacokinetics/pharmacodynamics

Subjects were randomized to one of three target area under the curve (AUC) levels rather than to differing doses because simulations based on phase II data indicated that AUC had much greater power than dose. Pharmacokinetic-guided dosing resulted in reduced within-group pharmacokinetic variability. There was a significant relationship between mycophenolic acid, the active component of mycophenolate mofetil, and AUC.

Lockwood *et al.* (13) used simulation to study the distribution of outcomes from two phase II studies with CI-1008, a GABA-agonist for the treatment of chronic neuropathic pain and used that data to select the appropriate dose for phase III studies. Using a combined pharmacokinetic-pharmacodynamic model (with incorporation of placebo effect) the model showed that pre-defined efficacy metrics were within 30% of the observed value 80% of the time. Simulations also showed that given the sponsors choices for doses to be used in phase III, there was a high likelihood in choosing a minimally effective dose that was either too high or too low and that the sponsor should consider changes to the current manufactured doses.

CHALLENGES AND CAVEATS

CTS will challenge pharmacokineticists in ways they may not be used to. Not many pharmacokineticists or clinical pharmacologists have the background or tools to do simulation (14). One cannot simply sit down, use a software package, and do quality simulation, no matter how easy the software is to use. Expertise in simulation requires knowledge of random number generation (Does your software package have a truly 'random' number generator?), random variate generation (What do you do if the program you are using doesn't offer the distribution you need?), verification and validation techniques (Are the right equations being chosen? Are those equations being solved correctly?), sensitivity analysis (Which variables are really important?), etc. However, the lack of educational opportunities by universities is slowly changing as a few universities, most notably Georgetown University, are offering post-doctoral research in this area.

CTS is the new application of an old technology and has an unproven track record. There is no guarantee that the time and effort devoted to modeling and simulating a system may return cost-effective, beneficial results. Sometimes outright failures may occur. It is also unclear if CTS can speed drug development. In fact, it may be just the opposite. CTS forces the sponsor to slow down a bit, catch their breath, and analyze what data they have on-hand. Despite these obstacles, simulation may play an increasing role in drug development as companies look for alternatives to traditional drug development processes. Other barriers are shown in Table 5.

Table 5. What is Needed for Acceptance of Simulation Technology by the Pharmaceutical Community

- Better surrogate markers for drug effect
- Better understanding of compliance patterns
- Better understanding of the link between pharmacokinetics and pharmacodynamics
- An industry leader willing to use this technology as an integral part of their drug development process
- Management buy-in
- More training for clinical pharmacologists and pharmacokineticists
- Education of the pharmaceutical community on the benefits (and limitations) of simulation
- Clear understanding of potential financial benefit
- Understanding of the concept and its uses

SUMMARY

Clinical trial simulation is a rapidly evolving area with many drug companies starting to take an increased interest in it. Clearly, companies that close the knowledge gap between empiricism and information will have a greater competitive edge than companies that do not. Simulation is one analytical tool that may help close that gap. It is unclear whether companies are actively interested in simulation as a tool in drug development, or passively interested in an attempt to remain competitive should simulation live up to its potential (14). From a purely financial point of view, what simulation offers pharmaceutical companies is the possibility of reducing the number of required studies, maximizing the chances for success in clinical trials, and possibly shortening development time; all outcomes which will reduce drug development costs.

REFERENCES

1. S. C. D. Johnson. The role of simulation in the management of research: What can the pharmaceutical industry learn from the aerospace industry? *Drug Info. J.* **32**:961–969 (1998).
2. J. Urquhart. Comparative regulation of drug and aircraft development: Lessons for regulatory reform? *Clin. Pharmacol. Ther.* **62**:583–586 (1997).
3. Boston Consulting Group. (1993). Analysis of Pharmaceutical Manufacturers Association (PMA) data.

4. C. Peck. (1999). Presented at the Best Practices Workshop in Clinical Trial Simulation, Arlington VA. Quoted in.
5. I. Mahmood and J. D. Balian. The pharmacokinetic principles behind scaling from preclinical to Phase I protocols. *Clin. Pharmacokin.* **36**:1–11 (1999).
6. J. D. Elashoff, G. G. Koch, and G. Y. Chi. Designing a clinical trial to demonstrate prevention of ulcer recurrents: modeling simulation approaches. *Stat. Med.* **7**:877–888 (1988).
7. W. Barlow and S. Azen. The Silicone Study group: The effect of therapeutic treatment crossovers on the power of clinical trials. *Contr. Clin. Trials* **11**:314–326 (1990).
8. T. A. Gooley, P. J. Martin, L. D. Fisher, and M. Pettinger. Simulation as a design tool for phase I/II clinical trials: An example from bone marrow transplantation. *Contr. Clin. Trials* **15**:450–462 (1994).
9. M. M. Brooks, A. Hallstrom, and M. Peckova. A simulation study used to design the sequential monitoring plan for a clinical trial. *Stat. Med.* **14**:2227–2237 (1995).
10. V. Schmith. (1995). Can population pharmacodynamics influence labeling? Three examples. Presented at the American Association of Pharmaceutical Scientists annual meeting.
11. R. Gieschke, B. G. Reigner, and J.-L. Steimer. Exploring clinical study design by computer simulation based on pharmacokinetic/pharmacodynamic modeling. *Int. J. Clin. Pharmacol. Ther.* **35**:469–474 (1997).
12. M. D. Hale, A. J. Nicholls, R. E. S. Bullingham, R. Hene, A. Hoitsma, J.-P. Squifflet, W. Weimer, Y. Vanrenterghem, F. J. Van de Woude, and G. E. Verpooten. The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. *Clin. Pharmacol. Ther.* **64**:672–683 (1998).
13. P. A. Lockwood, E. H. Cox, J. W. Mandema, J. R. Koup, W. Ewy, and R. J. Powell. (1999). Computer Assisted Trial Design (CATD) to support dose selection for CI-1008 in chronic neuropathic pain trials. Presented at Best Practices in Modeling and Simulation Workshop, Arlington, VA, Feb 1999.
14. M. Gauthier: Clinical trial simulation. *App. Clin. Trials* **6**:22–25 (1997).
15. R. Y. Rubinstein. *Simulation and the Monte Carlo Method*, John Wiley and Sons, Inc., New York, 1981.
16. M. Hale, W. R. Gillespie, S. Gupta, N. Tvk, N. Holford. Clinical trial simulation: Streamlining your drug development process. *App. Clin. Trials* **5**:35–40 (1996).