

An application of SAS in model based drug development

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ABSTRACT

Modeling and simulation are increasingly used to evaluate the merits of study designs in the context of a drug development program as a whole. The application described in this presentation involved 'scenario analyses'. A 'scenario' in this context is a plausible profile of the safety and efficacy of a treatment, for a clinically reasonable range of doses. The scenario analyses helped a multifunctional development team assess the design of the phase IIb part of a development program in terms of ultimate success in phase III. Several scenarios were simulated, some favourable to the study treatment, some unfavourable. Two strategies for the design of the phase IIb stage were compared, one using a conventional dose-finding approach with dose group comparisons vs. placebo; and one using dose-response curve modeling (based on recommendations from the ICH E4 guideline).

The simulations highlighted risks associated with the conventional designs, and clarified the advantages and limitations of the dose-response curve approach.

INTRODUCTION

Student (W.S. Gosset) was one of the first to use simulation. In his 1908 paper "The probable error of a mean", he described his efforts to use simulation to check results from his newly-invented t-test. Stanilaw Ulam used simulation to estimate how often a game of patience will 'work out', and later (1946) he realized that it could help in designing the atomic bomb. But only relatively recently has simulation been used to help in the design of clinical trials and development programs. Why use modeling and simulation to assess a study design when traditional estimation of power and type I and type II errors have worked so well for so long? Increased use of adaptive designs may have encouraged wider use of simulation, because adaptive designs generally require simulation in order to estimate their power and rate of false positive findings. Another motive for turning to simulation is that useful estimates of power for the dose-response curve approach can be obtained via simulation, but are not easily available from standard power-estimation software. In fact generally, statisticians and clinicians have been asking questions about study and program design that were difficult to answer with the standard techniques revolving around power and sample-size calculations. In a recent application, Quintiles' statisticians used modeling and simulation to address the following questions:

- What is the power of a complex adaptive design to detect a treatment effect?
- How likely is a study to find the "best" dose from a dose-response curve?
- How can we design a program to stop early if there is a safety issue, while maintain sufficient power if the treatment is safe?
- If we have a large Phase IIb program to find the right dose, can we reduce the size of our phase III program without compromising the chances for success of the entire program.

MODEL BASED DRUG DEVELOPMENT

Model based drug development is a fuzzy term. It can mean

- Modeling the biological mechanism of the treatment – "pharmacometrics"
- Using a regression model to explore the dose-effect profile of a treatment (as opposed to comparing results for each dose versus results from placebo)

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- Modeling a study or studies, simulating pseudo-subjects in a drug development program from early dose-finding phase IIa through dose selection phase IIb to pivotal final phase III
- A combination of any of the above

This paper describes an example of the third kind, where the workings of a chain of studies in a drug development program are simulated.

THE MERITS OF MODELING AND SIMULATION.

At a recent DIA meeting, representatives of both FDA and EMEA (Robert O'Neill and Rob Hemmings respectively) expressed support for the use of modeling and simulation of scenarios to improve drug development : Hemmings declared 'I had a dream; 10 years from now there will be no drug development programs without clinical scenario simulations.'

Modeling and simulation helps to evaluate the merits of any given study design in terms of ultimate success in phase III. Evaluating a study in terms of the success of the whole program makes sense, because the design of a study should take account of what studies came before and will come after. Thus, where safety is already well known from previous studies, a dose-ranging study can be designed to concentrate on establishing the most efficacious dose in the safe range. Where only small safety studies have been performed, the dose-ranging study that follows will need to be more complex and will need to involve more doses, so that both efficacy and safety requirements are met by the chosen dose. Similarly, if extensive phase II studies are designed so that a reliable picture of dose-effect relationships are planned to be available before phase III, it may be possible to have a smaller phase III program but still maintain an acceptable probability of success for the program as a whole.

AN APPLICATION OF MODELING AND SIMULATION

In the example of modeling and simulation that we are describing, the mechanism of action of treatment was not well understood, and data was available from animal studies and healthy subjects only. The broad options were a high risk strategy to explore few doses or a more cautious approach exploring a greater number of doses. The outline of the program was as follows:

- Small Phase IIa dose escalation study to identify the highest safe dose
- Phase IIb to identify the safe dose with highest model-predicted efficacy for further development
- Phase III to provide sufficient evidence of safety and efficacy for regulatory approval

The aim of the modeling and simulation was to help to identify a suitable phase IIb program when the options were

- a dose-response curve approach using linear regression, as described in ICH E4
- a comparison of individual doses vs. placebo

The multifunctional clinical team made use of the simulations to assess the designs both in terms of ultimate success in phase III and in terms of the ability to "fail early" if the treatment did not in fact work as expected.

Such simulations of a program or a single study are sometimes referred to as 'scenario analyses'. By a 'scenario' in this context is meant a plausible profile of the safety and efficacy of a treatment, for a clinically reasonable range of doses. For this program, a number of scenarios were simulated, some favourable, some unfavourable to the study treatment.

Using simulations helped clinicians think quantitatively and fostered dialogue between project management, clinical, regulatory and statistical functions. With regard to the design of the program, using simulations allowed both the statisticians and the non-statisticians to deepen their knowledge about what each of the designs was good at:

- the high risk strategy of comparing one or two doses with placebo in phase IIb excelled at getting the best dose approved in phase III, when the scenarios were most favourable (i.e. when all doses were safe and higher doses were more efficacious)

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- what was not clear to the statisticians, and was highlighted by the simulations, was that the “high risk” strategy of comparing just one or two doses with placebo in the phase IIb was also good at stopping early when no dose was viable (i.e. when no dose was both efficacious and safe)
- a strength of the dose-response curve approach was that it had the ability to pick the best safe dose when some doses were unsafe; seeing this demonstrated by simulations helped to reassure those on the multifunctional team who did not like the dose-response curve approach because it might not provide “solid” evidence in phase IIb via a simple comparison of active and placebo groups.

With regard to the implementation of the simulations, the exercise showed

- the importance of a clear and fairly detailed specification as an aid to rapid independent QC of simulation programming
- macros to simulate studies can and should be designed so as to be re-used easily
- post-study dose selection algorithms, which are an important part of simulating a development program, are not as easily modularised for re-use, compared with the simulations of the studies themselves
- simulations by their nature provide safety and efficacy outcomes in many different combinations: catering for all possible combinations provides a challenge to the programmer.

SAS is the standard language of the pharmaceutical industry, but the R language was used to QC the SAS implementation, and proved a compact tool in implementing a solution. However, work so far indicates that SAS tends to perform simulations more quickly than R, especially when modeling simulated data using ANCOVA or other generalised linear models.

NEXT STEPS

Clinical Pharmacology experts estimate how much of the administered dose actually works in the subject's body (Pharmacokinetics or PK), and how much is required in the body to get an effect (Pharmacodynamics or PD). As a next step, statisticians are working with Clinical Pharmacology experts to incorporate this PK/PD information into the simulations for phase II and phase III studies, allowing the simulations to reflect more accurately the likely mechanism of the treatment. Software already exists that incorporates PK/PD findings as user-input equations that generate simulated patients for a study. Pharsight's Trial Simulator is one example of such software.

Drug development programs can be assessed in terms of how they affect the expected net present value (NPV) of a treatment or a whole portfolio. Expected NPV can also be incorporated into simulations to evaluate the merits of study or program design, not just in terms of treatment success, but also in terms of “value for money”. This extra measure of success assesses the degree to which early investment in a program may “pay for itself” in terms of extra time on patient in the market, for example.

CONCLUSION

Use of modeling and simulation allowed statisticians and non-statisticians to inform themselves about the strengths and weaknesses of a selection of approaches to developing a new treatment, in terms of ultimate success in phase III, and enabled the multifunctional team tasked with the development to think quantitatively about the chain of research that leads to approval of a treatment.

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