Conducting Clinical Trials in the Parallel Virtual Universe

Quantitative systems pharmacology (QSP) and physiologically based pharmacokinetic (PBPK) modelling can be employed to create a parallel virtual workflow throughout drug development, beginning with preclinical research and continuing through phase IV clinical studies. Many clinical trials are conducted with virtual patients prior to selecting some trials to be carried out with real patients in real life. This is done in a reiterative fashion such that insights gleaned from the virtual studies are used to inform the actual clinical trial and vice versa. Thus, the results from the real clinical trial inform the next set of virtual trials and the iterations continue throughout the drug development process until the drug enters the market. At each stage, the workflows in virtual and real space have similar study objectives and endpoints. However, the virtual trials provide an economical alternative to conducting a wide range of studies with the aim of informing fewer optimal real trials. By taking advantage of events that have already happened in the virtual world, the clinical research can progress faster, and more predictably and reliably, which has huge economic implications.

When model-informed drug development (MIDD) was first introduced, some pharmaceutical executives thought that modelling clinical trials using virtual, computer-generated patients was higher risk than conducting real-life clinical trials because the results might not be accepted by the regulatory agencies. But now that the approach has been used for 15-20 years and shown to work well, precedent has been set, and that risk is greatly diminished.

MIDD is employed throughout the drug discovery and development process. It is used to help choose the best candidate molecules, select optimal drug doses, design clinical trials, inform go/no-go decisions, and support regulatory approvals. In fact, global regulatory agencies now expect to see modelling and simulation included with new drug applications.

Drug development typically starts in the virtual world a few months or one year ahead of the real world. The arrows in Figure 1 show how information gleaned from the virtual clinical trials is used to design the next real trial. Then, when the real trial produces clinical results, they are used to optimise the next virtual trials. This feedback loop facilitates fine-tuning the clinical trial design, improving accuracy and reliability, and increasing confidence in the results throughout the drug development process.

Virtual clinical trials are based on mechanistic, physiologically based pharmacokinetic (PBPK) models, which focus on how the human body handles drugs, and quantitative systems pharmacology (QSP) models, which define the way drugs affect the body.[1] A typical QSP model consists of a pharmacokinetic module, describing absorption, distribution, and elimination of the drug, connected to a systems biology model quantitatively describing the biology of the disease and mechanisms of drug action.[2] All the available pre-clinical and clinical data are incorporated into these models in a very methodical way.

Each virtual clinical trial is also populated with a diverse participant cohort which closely resembles a real trial. Virtual participants of all ages, weights, genders, and ethnicities are included with different genetics, liver variations, and transporter and enzyme levels.

In Figure 1, the capsule in the virtual world is larger because there are many more studies being conducted there than in the real world. Virtual studies are run with many different doses and dosing schedules to determine the optimal approach to use in the real trial.

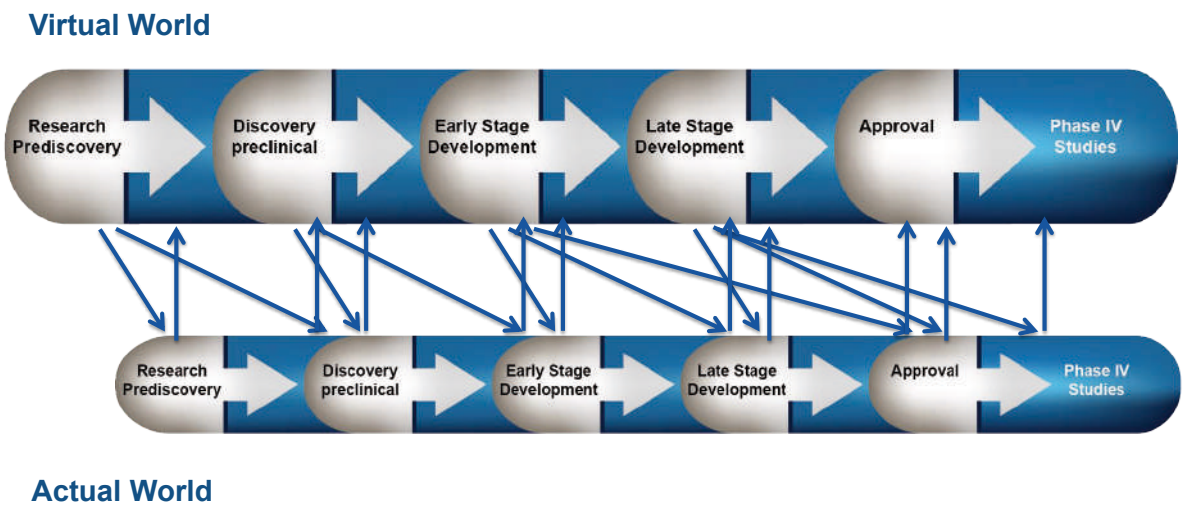

Figure 1: Exploring the Connections Between the Virtual and Real World

Investigating Drug Combinations

For example, if a patient has cancer and needs to receive a combination of drugs: What dose should they be given of each drug, in what order, and with what timing? Those decisions are complicated enough to make with two drugs but what if they need three? It is impossible to run all those clinical trials in real life, but all 20 or 30 permutations can be tested virtually. If researchers know the mechanism by which drug A works, and how drug B works, and the body clock regarding the circulation of the targets, how they come and go and resynthesize, they can determine by conducting virtual trials which drug to use first and second. Then, based on those results, the best options can be selected for investigation in clinical trials.

That was the approach we took with AstraZeneca's COVID-19 vaccine to determine the right timing for their second booster shot. Scenarios were run using a four-, six- and eight-week delay in a large, virtual study. The optimal results of seven to eight weeks were confirmed six or seven months later in a two-arm clinical study. But if AstraZeneca had waited to receive the clinical trial results before deciding on the right timing, many more people would have died, or received unnecessary extra boosts when the cycle of production for the vaccine was not high enough to supply all patients even with their first injection.

Building a Virtual Clinical Trial

To be able to build a realistic virtual clinical trial, researchers need to have a model of the disease – an animal model or a microphysiological system (commonly known as an Organ-on-a-Chip) – to use as a foundation on which to build. There also needs to be data available about the relevant enzymes, receptors, and targets in humans.

This is also an important approach to consider for orphan diseases where it may not be viable to conduct a clinical trial because there is little information available about the condition and few patients to enroll. While modelling without detailed disease knowledge is not an ideal scenario, it is often the best option to progress drug development for patients with rare diseases.

Making Virtual Trials Realistic

Consider a virtual clinical trial investigating the concentration time profile or blood pressure time profile of a drug. In a virtual trial, it is possible to obtain a sample every minute at a nominal cost. But in the real world, sampling might be scheduled to occur every hour for the first three hours, and then every four hours to provide 10 samples. But in the hospital, the nurse might be a few minutes late returning from getting a sandwich or coffee, resulting in the sample being taken at one hour and 10 minutes, rather than at one hour. Activities may not be as precise in the real world and those factors need to be incorporated as design elements into virtual clinical trials to make them more realistic. The simulation needs to incorporate some variability because the sample may be taken five minutes earlier or later than prescribed. The virtual clinical trials also need to include a small margin of error to account for an occasional mistake being made when recording a measurement or analysing an assay.

When MIDD first began, these adjustments were not made, but now a reality variation and a margin of error are incorporated into models to ensure that the virtual clinical trial results more closely resemble those gotten from a real clinical study.

Determining Statistical Power

As the cohorts included in virtual clinical trials are diverse, the study will not always produce a clear yes or no answer. Just like a real clinical study, it will depend on how many participants are recruited.

But the advantage with a virtual trial is that the study can be run initially with 2,000 people to see what the result is. Then, that cohort can split into smaller groups – perhaps 10 trials of 100 people. If at the end of that study, eight of the trials show statistical advancement of the effect, but two of them are failing, the 100-person cohort gave 80% power. But if the response from five of those 100-person cohorts is yes, and five of them it is no, the chance is now 50%. Therefore, this approach can also predict the likelihood of success based on the size of the study. It can deliver insights such as, "Don't run the study with 50 people, because the likelihood of success will only be 10%, and then you are just wasting everybody's time."

Conversely, the results may demonstrate that it is not necessary to run a study with 1,000 people at 97% confidence if it is possible to achieve the same result with 95% confidence using just 300 people.

Investigating Potential DDIs

Virtual trials can also help to determine the likelihood of drug-drug interactions (DDIs) occurring when patients are taking co-medications. This is very important because it would not be practical or ethical to test all the potential drug combinations in real clinical trials.

To underscore the challenge involved: for a real clinical trial with 500 participants, at least 5% of them would need to be taking the specific co-medications to be able to detect a signal, even for the strongest DDI.[7] Furthermore, there have been cases where a pharmaceutical company has decided not to take a drug forward because the risk of DDIs was considered too high to manage.

Reverse Translation

Virtual PBPK modelling also allows researchers to investigate scenarios that would be impossible to test in clinical studies, such as measuring toxicological or pharmacological responses to a drug in a human brain, kidney or fetus.

In the past, researchers used to "humanize" pre-clinical data by extrapolating directly from animals to humans, just using allometry to account for their difference in weight. But mice are not the same as humans! We now use an approach called reverse translation where we start with the animal data, then go back to determine which mechanisms created those responses, and forward to reproduce those effects in human form in a model by adding the relevant blood flows, receptors, and enzyme turnover.

For example, a PBPK model can be developed which can predict a drug's nephrotoxicity risk in humans using *in vivo* study results from pre-clinical species and adding species-specific differences in renal physiology such as glomerular filtrate rate, blood flow and renal drug transporter expression/substrate affinity.[4] Reverse translation is used to determine what drug doses and concentrations may cause some nephron-toxicity and must never be used in humans.

A similar approach can be taken to investigate fetal exposure to drugs travelling across the placenta. In this case, a feto-maternal PBPK model is developed using toxicity data from pre-clinical species combined with knowledge of the rapid changes in anatomy, biochemistry and physiology that occur as a fetus grows during pregnancy.[5]

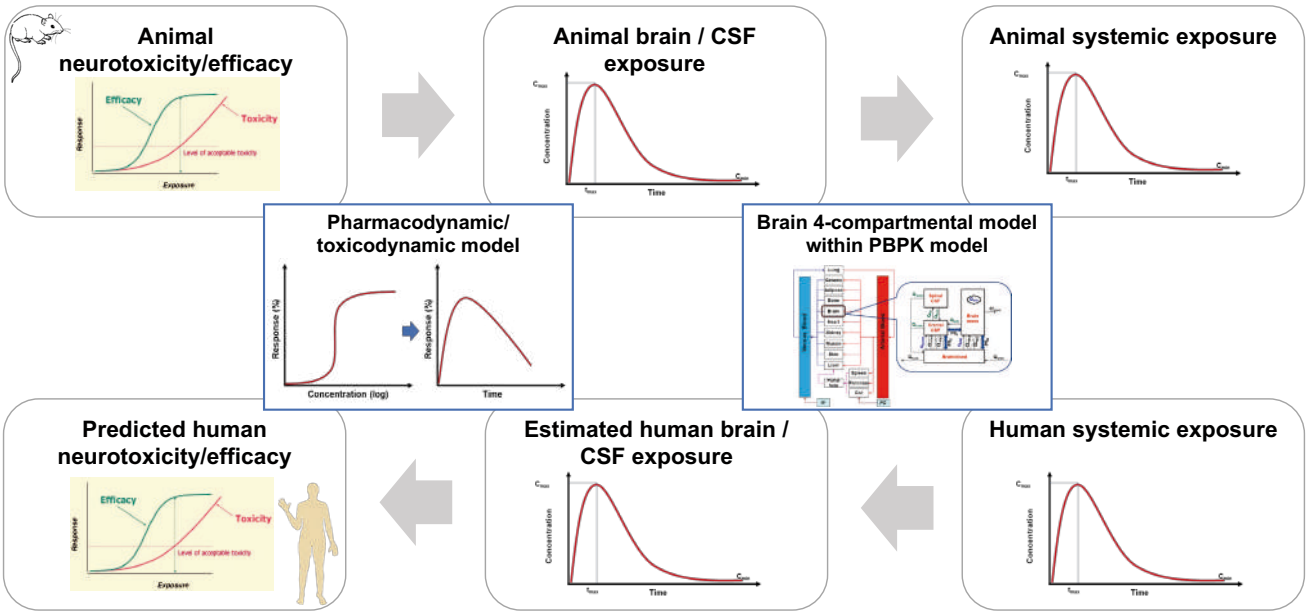

Figure 2: Prediction of Pharmacological Efficacy and Neurotoxicity Using Brain PBPK Modeling. Reprinted from the Journal of Neurochemistry.[6]

In Figure 2, PBPK modelling is employed to estimate human brain tissue/cerebrospinal fluid (CSF) exposure to a drug and predict its pharmacological efficacy and neurotoxicity.[6] Initially, the effectiveness of different drug doses is assessed in pre-clinical species and a pharmacodynamic/toxicodynamic model is used to determine the response-exposure relationship. Then a PBPK model of the human brain is used to factor in species differences such as CSF volume and flow rate and brain transporters.

The top right-side graph shows concentration versus time, and the top middle graph indicates temporal changes of effect. One reflects the physiological elements, which are determined by the enzymes, etc., and the other shows the pathways for the effect and the number of targets that are engaged. The effect of the drug dose over time can be seen, but instead of just looking at the end result, the focus is on linking it to the concentration at the site effect, resulting from engagement with the targets.

In the bottom row, the arrows are reversed because the model is being rebuilt based on knowledge of what happens in humans. In many cases, the mechanism is shared between humans and animals, hence it is assumed that they have the same engagement to targets. However, QSP models can incorporate the knowledge of variations in pathway to effects and the differences in the level of targets between animals and humans, which are obtained by analysis of relevant tissues and organs. Hence, the picture is just adjusted when humans have different numbers of those receptors.

Schizophrenia Case Study

But the conduct of successful virtual clinical trials, just like real clinical trials, requires medical researchers and modelers with extensive expertise. For example, when creating a virtual clinical trial to investigate smoking, the modelers needed to know not only how many cigarettes the participants were smoking, but also what type, and how deeply they were inhaling. That latter detail helped to determine whether the participants were keeping smoke in their lungs, which could cause enzyme induction.

While the association is unclear, people with schizophrenia tend to smoke a lot. A sponsor had a drug X to treat schizophrenia, which was metabolized by the hepatic enzyme cytochrome P450 1A2 (CYP1A2), which is induced by smoking.[9] But when those patients were hospitalised, they were not allowed to smoke, so the enzyme was de-induced and became less active. Therefore, if the patients were given their normal drug dose, it would intoxicate them, because the enzyme was not present to turn it over.

The researchers applied their knowledge of the pertinent metabolic pathway, and how much of it was going to be affected, to the model to determine the effect of smoking reduction on the drug. Then they determined how much each patient's drug dose should be reduced, and on what day of their hospitalization that new dose should be applied. While a confirmatory clinical study was still required, their modelling identified the best clinical path, and removed the need for an exploratory clinical study. Their research also illustrated how, going forward, many smoking studies can be conducted as virtual studies.[12]

Valuable Resource

Underscoring the value of MIDD, Allerheiligen reported in a 2014 paper in Clinical Pharmacology and Therapeutics that during the previous three years the Modeling and Simulation group at Merck had "delivered more than half a billion dollars in cost avoidance [for studies not conducted], and it continues to enable approximately 10 critical decisions per year."[3]

Conclusion

Virtual clinical trials save time because they reduce the number of drug combinations and various conditions in which the drugs must be studied in actual clinical trials. They obviate the need for conducting many large studies (which take longer to recruit participants) by making the likelihood of success clear with smaller studies. They also help to ensure that a study is not initiated which is too small to answer the question posed and will need to be redone. While it is still necessary to conduct clinical studies, there are many instances in which a virtual clinical trial will produce the same answer, faster, and at a much lower cost.

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