MODEL BASED DRUG DEVELOPMENT – WHAT IS IT GOOD FOR?

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The FDA “critical path” document characterizes model-based drug development (MBDD) as the development and application of pharmaco-statistical models of drug efficacy and safety from preclinical and clinical data to improve both drug development knowledge management and decision-making (1), (2). A less formal description of MBDD would be the development and use of mathematical models to aid answer existing and future project team questions that arise during drug development. As an analogy, many of us probably played with Lego bricks during our childhood. We could make many different models out of those bricks, but we made what we wanted to make at that point in time. In MBDD, the Lego bricks represent pieces of information and the models they are used to create (castle, house, farm, etc.), depends on what is needed (a place to defend yourself from an attack, somewhere warm to sleep, somewhere to raise cows and chickens, respectively).

More seriously, MBDD brings data from many sources together and describes it (the biomedical situation) as a whole, thus maximizing the information and understanding that can be gained from the data. All of this is done to provide answers to questions. Some examples of the different types of models that may be built are listed below.

POPULATION PK MODELING

Population pharmacokinetic (PK) models are frequently built during the development of new medicines. The population PK model can bring together information from the single ascending dose (SAD) and multiple ascending dose (MAD) studies to provide an integrated description of the new medicines’ pharmacokinetics. For example, such an approach has greater power to characterize any non-linear PK situations due to saturable absorption or elimination (3).

Population PK models built using later stage data often provide information about the influence of demographic or pathophysiological factors on the pharmacokinetics of the compound, in the target population. These models can also be used to predict unstudied situations. An example of this is a frequently performed clinical pharmacology study done to assess the influence of renal impairment on the PK of a compound. When appropriate, a further study may look at the influence of metabolic status (such as poor and extensive metabolizers of CYP2D6). While no pharmaceutical company would attempt to study the combination of poor renal function in poor metabolizers of CYP2D6, these patients do infrequently exist and their prescriber needs to decide what dose they should start treatment with. In this situation, the population PK model could be used to propose a reasonable starting dose and this model predicted information could well be included in the drug label.

DOSE RESPONSE CHARACTERISATION

Building models that describe dose-response or dose-concentration-response relationships is one of the more important MBDD activities. Traditional statistical analysis of dose response usually involves an analysis of covariance (ANCOVA), followed by multiple pair-wise comparisons. These analyses are often unable to reconcile the not infrequent occurrence in a parallel group study when a lower dose of a new compound gives rise to a better response than a higher dose. By analyzing the data using a single model, the observed response disharmony between the different dose groups can be resolved. A simulated example is presented in the figure below (Figure 1). The black line depicts the true dose response curve; the red points and vertical lines are a set of simulated possible point estimates with their associated 95% confidence intervals under the variability described by the underlying model. If this was a real life example, it would not be surprising if the project team decided that the 8 mg
Managing Director Eric Snoeck, together with other Exprimo colleagues and one of our clients (Roche), developed a comprehensive hepatitis C viral kinetic model that explained cure (4). A representation of the disease part of the model is shown in Figure 2; the assorted different viral response profiles that the model can explain are shown in Figure 3.

**MBDD IN VIRA L INFECTION**

The models that can be built vary from reasonably straightforward (population PK) to very complex. An example of a complex model is one that describes the underlying disease process and then integrates it with a PK-biomarker-clinical endpoint model. Such a model has enormous potential to support drug development decisions. SGS Exprimo’s MBDD model building thus helps to facilitate evaluation of alternative chronic hepatitis C treatment options; the ultimate aim was to develop and test hypotheses for personalizing treatments in the disease. The disease part of the model is drug independent (Figure 2) and can be applied to different or new compounds being developed to treat HCV.

If the (virtual in this case) project team did take the 8 mg dose forward to Phase III, they could face a nasty disappointment later on. The MBDD approach of building models to describe dose response, performed alongside traditional statistical multiple testing procedures where each dose level is compared to placebo, helps the project team make an informed choice about which dose(s) to study in Phase III. MBDD model building thus helps to maximize the probability of trial success.

**MBDD IN PAEDIATRICS**

Used in pediatrics, MBDD mitigates the practical and ethical constraints present when performing studies in children. A MBDD approach allows for less data to be collected in fewer subjects which is helpful since the underlying variability across the age range of 0 to 18 years can be far more considerable than the variability observed in adults. Further, while reasonable assumptions can be made about scaling adult pharmacokinetic parameters into children using well defined size and maturation factors, scaling biomarker or clinical endpoint responses is fraught with questions. Implementing a MBDD approach allows the influence of the assumptions made to be tested by running virtual clinical trials before the first child is dosed. The model and the simulated virtual trials are part of an iterative process to design the best possible study. This aids the goal to collect sufficient data in the children to answer the study question while ensuring that no more children than necessary are included. The models can also be used to ensure that a minimal, yet sufficient, number of blood samples are taken.

**Figure 1:** The true dose response is shown in black and the observed change from placebo (with 95% CI) is shown in red.

**Figure 2:** Representation of the extended HCV viral kinetic model. Infectious HCV virions (VII) infect target cells (T), creating productively infected hepatocytes (I). Uninfected hepatocytes (T) are produced at rate s and die at rate d. Infected hepatocytes die at rate δ. A density-dependent proliferation of hepatocytes (I) is assumed. Infectious (VII) and non-infectious (VNI) virions are produced at rate p and cleared at rate c. Peginterferon-α-2a dose-dependently inhibits the production of new virions (P), and ribavirin dose-dependently renders a fraction of newly produced virions non-infectious (VII). SVR, defined as the status of having an undetectable viral load at 24 weeks after completion of treatment, is the primary clinical end point desired to be predicted in the treatment of hepatitis C. HCV, hepatitis C virus; SVR, sustained virologic response.

**Figure 3:** The viral kinetic model characterizes the complexity and diversity of clinically observed HCV viral kinetics in patients with hepatitis C virus infection treated with peginterferon -2a alone or in combination with ribavirin, and links the kinetics to clinical outcome. This is achieved by the implementation of a viral-eradication cure boundary and incorporation of left-censored data, largely excluded from analysis in earlier studies, in a simultaneous analysis of a wide spectrum of peginterferon -2a and ribavirin treatment regimens in 2,100 patients. EVR, early virologic response; HCV, hepatitis C virus; LLOQ, lower limit of quantification; RVR, rapid virologic response.

The developed viral kinetic model provided a framework for mechanistic exploration of treatment outcome and facilitated evaluation of alternative chronic hepatitis C treatment options; the ultimate aim was to develop and test hypotheses for personalizing treatments in the disease. The disease part of the model is drug independent (Figure 2) and can be applied to different or new compounds being developed to treat HCV.
CONCLUSION

The MBDD activities performed by SGS Exprimo efficiently aid in bringing the right dose of new, safe, and effective medicines to the patients who need them. We at SGS Exprimo are extremely proud of our track record—we have performed over 300 MBDD projects, all delivered on time and to the highest scientific standards. Global feedback received from regulatory assessors who read the reports of our MBDD analyses has been consistently good and always supported clients drug development decision at the right time.

In conclusion, the answer to the question ‘What is MBDD good for?’ is ‘Better drug development decisions, made at the right time’.

REFERENCES


ABOUT SGS

SGS Life Science Services is a leading contract service organization providing clinical research, analytical development, biologics characterization, biosafety, and quality control testing. Delivering solutions for bio-pharmaceutical companies, SGS provides Phase I-IV clinical trial management services encompassing clinical project management and monitoring, data management, biostatistics, and regulatory consultancy. SGS’s clinical unit located in Antwerp, Belgium has a total of 92 beds, and has successfully met the standards of the US FDA, GCP, ICH, ISO guidelines and directives and local regulatory bodies. For optimized early phase clinical trials, SGS features sample tracking for safety lab data interfaced with Oracle for PK samples, full eSource clinic automation (EDC), a GMP pharmacy for on-site formulation, and a Biosafety Level 2 quarantine facility.

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