VALUE-FOCUSED DRUG DEVELOPMENT STRATEGIES OF THE FUTURE

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Mounting healthcare and research and development (R&D) costs, high drug attrition rates leading to decreased numbers of new molecular entity approvals, and growing demands from regulators and payers indicate that a paradigm shift is needed to improve efficiency and productivity across the drug development continuum.

By thinking differently – Thinking Without Borders® – to tackle the impossible, we create new methods and approaches that can infuse the R&D ecosystem and add value. Unless an approach meaningfully impacts certainty, efficiency or cost, it does not add value.

Model-informed drug development (MIDD) is a quantitative and mechanistic 'in silico' modelling and simulation approach that is central to informing and creating value in drug-development programs (Figure 1). Rather than thinking of MIDD methods as being peripheral to drug development, when applied in a fit-for-purpose manner, MIDD improves certainty in decision-making, adds efficiency, may reduce cost to the drug-development process, and improves the ethical aspect of development by minimising unnecessary human or animal trials. Regulatory agencies, such as the US Food and Drug Administration (FDA), employ and encourage the use of in-silico tools in clinical trials to improve drug development and make approvals more efficient.[1] The FDA's Center for Drug Evaluation and Research (CDER) uses modelling and simulation to 'predict clinical outcomes, inform clinical trial designs, optimise dosing, predict product safety and evaluate potential adverse event mechanisms'.

MIDD tools focus on the drug (pharmacokinetics and pharmacodynamics, PKPD, population PK), the disease (quantitative systems pharmacology, QSP) and/or mechanistic details (physiologically based pharmacokinetics, PBPK), which, together with other complementary techniques, can be deployed across the development cycle. Another approach, Pharmacology to Payer (P2P), creates a framework that links relevant end points across adjacent disciplines to health economic value. With the increasing need to justify the pricing of medicines to society and payers, P2P aligns developers, regulators and payers earlier in the drug development program to enable accelerated access to affordable medicines.

Difficulty in accessing patient populations, scientific issues with bridging from healthy adult populations, and the operational and ethical issues in executing clinical trials are challenges encountered in development programs. The following are several examples of how MIDD has created value in accelerating the development of safe and effective therapeutics for pediatric populations and orphan diseases.

In the first example, a quantitative clinical pharmacology strategy was used to establish safe and effective dosing for the treatment of influenza in infants[2]. Existing data on children older than one year suggested a similar response to the anti-viral therapy oseltamivir; however, earlier toxicology findings heightened diligence impacting the move to infants. To overcome this challenge, a quantitative clinical-pharmacology adaptive trial design was developed where PK modelling from the first study informed the second study. Modelling and simulation was used to analyse the pooled PKPD data and account for design differences, including different formulations. Within six months of submission, oseltamivir was the first therapy approved by the FDA, and then later by the EMA, for the treatment of influenza in infants as young as two weeks old.

A novel MIDD approach was used to inform the design of a Human Challenge Model clinical trial resulting in accelerated development of a respiratory syncytial virus (RSV) therapeutic to pediatrics[3]. The translational medicine MIDD bridging program resulted in numerous benefits, including: predicting dose to yield therapeutic exposures in infants under two years old; shorter trial lengths; reduction in the number of patients needed; significant cost and time savings; high-quality science published in the *New England Journal of Medicine*; and data that enabled robust decision-making, including a US$1.75-billion transaction. Furthermore, the MIDD clinical strategy created a regulatory precedent for entry into RSV-infected infants early in a development program, and provided insights that will help guide future clinical trials.

Mechanistic approaches, such as PBPK, have been used to understand the mechanisms of how a drug is metabolised, so that the potential drug–drug interactions (DDI) across different patient populations could be understood and used to inform dose and regiment. PBPK models were used to gain a better understanding of Imbruvica®, an anti-therapeutic used for the treatment of rare diseases including mantle cell lymphoma and chronic lymphocytic leukemia[4]. PBPK was able to inform the Imbruvica label, provide guidance to clinicians, including 24 individual DDI scenarios removing the requirement to evaluate such DDIs in clinical trials, and provided a dose-optimisation strategy for individuals.

The final example of MIDD as it relates to health economic value is the development of a P2P influenza model to determine the cost utility of oseltamivir as the antiviral therapy used under various pandemic

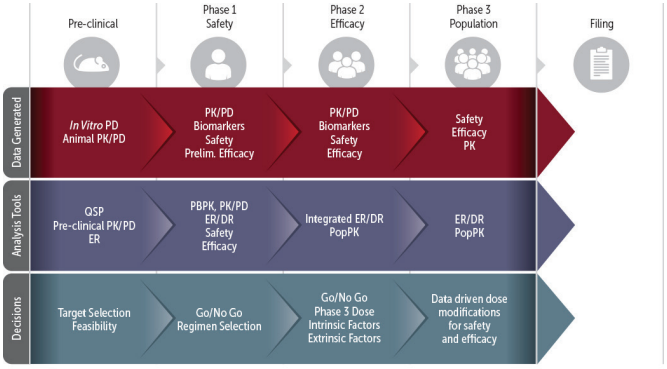

Fig 1. Model-informed Drug Development Methods

scenarios.[5] The proof of concept spanned and linked drug PKPD, epidemiological and health economic end points. The framework enabled all key stakeholders to use a common platform to simulate novel interventions that might impact society, and informed decision-making by all parties in 'what if' scenarios. Most importantly, the model facilitated transparent discussions on cost to society and cost to payers early in the development process, and on how a drug may be placed in the healthcare system.

When deployed in a fit-for-purpose manner, model-informed drug development methods play a key role in driving value in the drug-development process. MIDD approaches improve drug success rates by more accurately predicting efficacy and safety, and better characterising sources of drug response variability at early, less costly stages of development. Further, an MIDD framework can be valuable to create patient-centric alignment of key stakeholders throughout the drug-development process to ensure future development of safe, targeted, efficacious and affordable drugs that address unmet medical needs.

References

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Craig Rayner will be speaking at AusBiotech 2017.

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