Model-Informed Reverse and Forward Translation of Safety Risks in Drug Development

Jerome T. Mettetal

Despite major scientific investments, safety accounts for significant pipeline attrition, especially in late preclinical and early clinical development. Many failures are due to difficulty interpreting safety signals or difficulty optimizing schedules of compounds with narrow therapeutic margins. Model-informed translation can address these challenges, both through “forward” translation of early signals to future scenarios, as well as through “reverse” translation of safety data into mechanistic insight.

THE CASE FOR MODEL-INFORMED TRANSLATION IN DRUG SAFETY

Historically, safety assessment has relied on toxicology testing in multiple preclinical models coupled with generous safety margins to both identify key risks and account for uncertainty in translation of these risks across species. Unfortunately, application of this approach alone has several limitations that contribute significantly to the safety attrition rate. First, in preclinical studies many toxicological findings are often observed, and identifying which of these is a true signal and will translate to the patient setting is not always obvious. Further, in non-life-threatening or chronic diseases, these margins must often be large to account for uncertainty or increase of severity over time, which can limit doses. Finally, in severe indications where narrow therapeutic margins are common, toxicology studies alone typically provide little information on dose and schedule, eventually leading to time-consuming work in the clinic to optimize the therapeutic index empirically.

Better tools are therefore needed to translate between in vitro, preclinical and clinical results. Quantitative modeling and simulation approaches have promised to solve many of these challenges in the efficacy space by providing a quantitative framework for decision making which can aid translation by allowing one to:

1. increase statistical power by combining data across individuals, timepoints, doses, or studies;
2. interpolate between and extrapolate beyond observed data;
3. account for known differences between observed data and prediction scenarios;
4. generate and test hypotheses about exposure–response relationships.

While significant effort for translational modeling has gone to analyzing efficacy biomarkers and endpoints, a similar level of investment in translating safety signals would provide strong return on investment by strengthening the confidence in safety assessment and enhancing the interpretation of therapeutic index.

FORWARD TRANSLATION

A key question is which safety signals represents significant risk based on accurate interpretation of the therapeutic margins. On one hand, erroneously discounting an early positive signal could lead to later safety liabilities and increased attrition, while on the other hand a “no-go” decision based on falsely giving credibility to a nontranslatable finding can lead to costly stops. Taking the pharmacokinetic (PK), potency, and species differences into account simultaneously can increase confidence in this assessment. In the simplest cases, this can be accomplished through phenomenological relationships such as pharmacokinetic/pharmacodynamic (PK/PD) models to quantify the exposure–response relationship and translate from the preclinical to the clinical contexts, accounting for differences in species when known (Figure 1a). For example, in cardiovascular safety, translational assessment of safety pharmacology data is often applied to electrocardiogram (e.g., QT prolongation) or hemodynamic measurements (e.g., blood pressure) to predict the effect expected at clinical doses based on preclinical studies, including sensitivity differences between species (Figure 1a).

The increase in use of mechanistic and systems pharmacology approaches has further enhanced the translational power of safety models. These approaches allow known physiological differences between species to be accounted for mechanistically via system parameters (Figure 1b). Further, by directly representing the detailed biology of adverse pathways, in vitro data representing initiating events can be translated directly into predicted clinical
outcomes. Again, cardiovascular safety represents a well-explored example, whereby many investigators have demonstrated that in vitro ion channel and ADME parameters can be combined to predict clinical QT effects for single agents as well as for combinations of compounds. Another area where significant mechanistic work has been performed is in the hepatic safety area, where in vitro measurement of metabolic function, reactive metabolites, and bile acid transporters are combined with PK profiles to predict the dynamics of liver injury biomarkers across species.

Finally, in many cases inhibition of the target itself carries undesired effects, and can lead to a narrow therapeutic margin. For example, this is common in oncology, where targets are often essential to cellular processes in normal tissues and adverse events (AEs) are acceptable given the often life-threatening nature of the disease. The sensitivity and timing of tissue damage and recovery often differ across species for common anticancer therapy-induced toxicities, such as neutropenia. By modeling these safety endpoints alongside efficacy, the dose and schedule can be simulated to optimize the therapeutic index of the drug and prioritize dosing in the clinic. Additionally, early work with other common on target effects such as gastrointestinal toxicity has shown that rodent pathology data can be used to successfully predict differences in clinical dosing schedules for oncology compounds that damage gut tissue.

**REVERSE TRANSLATION**

Safety modeling presents a unique set of challenges and opportunities compared with modeling efficacy endpoints. First, many safety findings are “unknown-unknowns,” whereby previously unexpected AEs arise in preclinical or clinical studies with unknown mechanism. In addition, many toxicities are driven not by a single off-target pharmacology, but rather by multiple effects. For example, in the case of drug-induced liver injury, effects on metabolism and bile transporters simultaneously may drive toxicity beyond the combined effects induced individually. In these cases, not only is the translational relevance of a finding unknown, but the exact mechanism for the safety finding is not clear. On the other hand, safety modeling has a clear opportunity to increase translational understanding by investigating “exemplar” compounds with a known mechanism of action and adverse outcomes to better understand how translatable a safety signal will be in practice.

One potential solution is to apply “Reverse Translation,” whereby one can start with the set of known pharmacological and toxicological effects for an investigational agent or set of exemplar compounds, and use this to inform the action and potency of the compound. For empirical models, reverse translation can be performed by analyzing many exemplar compounds across preclinical and clinical systems. By modeling the exposure–response relationship across these compounds, trends between species such as sensitivity or time of onset or recovery can be quantified. Importantly, species dependencies from reverse translation of panels of exemplar compounds can be utilized to refine forward predictions (Figure 1a) and this type of approach has been frequently applied to cardiovascular QT & QRS intervals and hematological endpoints such as neutropenia (Table 1).
The unique capabilities of mechanistic models are obvious in the context of reverse translation, with AEs and toxicology data being used to extract mechanistic insight into the activity of the molecules (Figure 1b–c). Whether this is performed inductively through model estimation to inform parameters, or deductively through sensitivity analysis, the outcome is insight into which model inputs, and therefore mechanisms, are driving the observed phenomenology. This type of approach has been applied to extract information about the compound mechanism of action for heart rate and blood pressure changes, for events initiating observed hepatotoxicity, and from in vitro data for hematopoietic toxicity (Table 1). It is important to note that the data requirements for this approach are high; not only must the model’s system parameters be well informed, but there must be enough pharmacodynamic information and structural identifiability in the model to uniquely inform the drug-specific parameters.

### APPLICATION, LIMITATION, AND FUTURE DIRECTIONS

During development, decisions about investigational compounds often need to be made quickly. To rapidly respond to emergent safety findings, it is ideal that translational models are available before they are needed, since constructing them can take significant time. Prioritization of endpoints should therefore be focused on areas where AEs are common causes of attrition. Similarly, it is not necessary to apply modeling approaches to every potential safety risk, and application of translational approaches can be prioritized based on decision-making potential. In practice, several key questions can be used to triage safety modeling questions:

1. Are safety margins large enough that they do not need refinement with a model?
2. Would a translational model help predict reduction of margin with prolonged exposure?
3. Will particular patient populations likely to be more sensitive to the drug?
4. For narrow margins, will modeling provide insight into optimal dose schedules?

Finally, it is worth noting that these translational approaches are not without limitations. For example, as we get better at weeding out compounds against known safety liabilities during discovery, the adverse safety signals that are observed during development will be more likely to have come from unknown mechanisms. This can complicate our ability to confidently translate with existing models which are based on known mechanisms, necessitating even further model development. For example, as compounds with obvious ion channel activity are eliminated in discovery, traditional in silico action potential models may not be appropriate for describing ECG changes observed in development. Further, the upfront workload to develop a model for even a single mechanism can be large; phenomenological models may require the analysis of many compounds, and mechanistic models often have significant requirements in terms of key parameters and training data in the literature. As translational safety models do not require confidential data and are often noncompetitive in nature, these activities are therefore often well pursued as part of collaborations and consortia where workload, expertise, and data can be shared in order to deliver better models and more widely disseminate their benefits.

Additional Supporting Information may be found in the online version of this article.

### CONFLICT OF INTEREST

The author is an employee of AstraZeneca. No conflicts of interest are directly relevant to the contents of this article.

© 2017 American Society for Clinical Pharmacology and Therapeutics

1. Waring, M.J. et al. An analysis of the attribution of drug candidates from four major pharmaceutical companies. Nat. Rev. Drug Discov. 14, 475–486 (2015).
2. Collins, T.A. et al. Modeling and simulation approaches for cardiovascular function and their role in safety assessment. CPT Pharmacometrics Syst. Pharmacol. 4 (2015).
3. Yang, K. et al. Systems pharmacology modeling of drug-induced hyperbilirubinemia: differentiating hepatotoxicity and inhibition of enzymes/transporters. Clin. Pharmacol. Ther. 101, 501–509 (2017).
4. Venkatakrishnan, K. et al. Optimizing oncology therapeutics through quantitative translational and clinical pharmacology: challenges and opportunities. Clin. Pharmacol. Ther. 97, 37–54 (2015).
5. Shankaran, H. et al. Systems pharmacology model of gastrointestinal damage predicts species differences and optimizes clinical dosing schedules. CPT Pharmacometrics Syst. Pharmacol. (2017) [Epub ahead of print].
6. Cook, D. et al. Lessons learned from the fate of AstraZeneca’s drug pipeline: a five-dimensional framework. Nat. Rev. Drug Discov. 13, 419–431 (2014).