

Framework for Polyclonal Antibody Drug Development: Integrating Trial Data and Literature Models

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Background

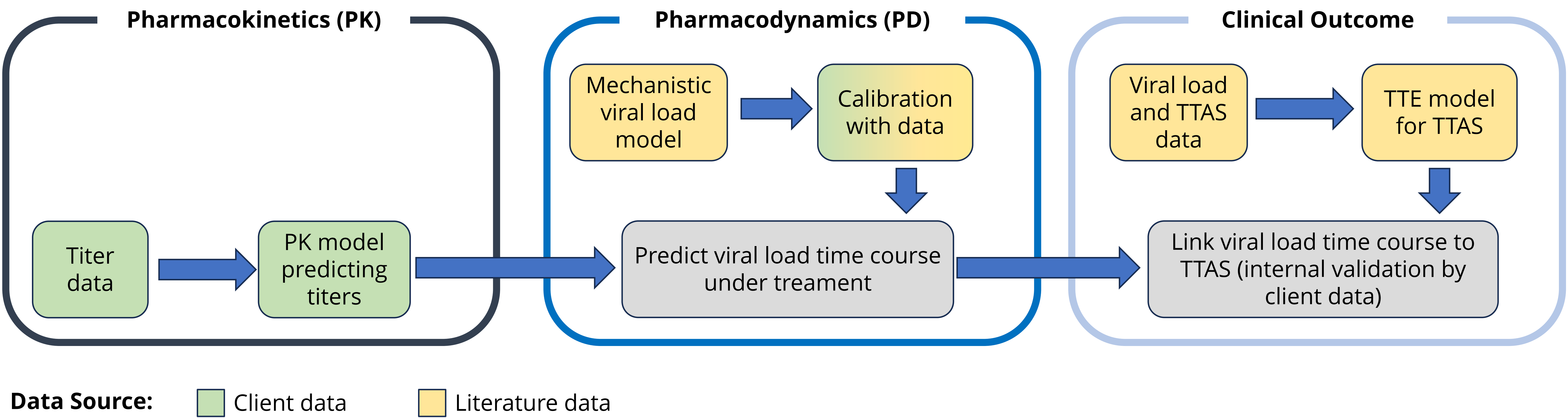
- For non-standard modalities, such as polyclonal antibodies or mRNA therapeutics, applying classical dose-exposure-response modeling can be challenging
- The challenges can arise from a variety of reasons, including gaps in the available data, multiple or the lack of suitable surrogates for classical data, for example, exposure
- SAb has developed fully human, multi-targeted immuno-globulins (IgGs) produced in transchromosomic bovines (TcB). For polyclonal, IgG-based, fully human antibodies, measuring concentration is experimentally difficult
- In this poster we present a general approach geared towards bridging some of these gaps in order to enable modelling and simulation support.

Conclusion

- Drug development of polyclonal antibodies and other, non-standard modalities is often restricted by available study data and would greatly benefit from support by modeling of PK and PD
- The integrated approach presented in this poster serves a viable tool to facilitate the bridging of data gaps and, ultimately, contributing to a more informed dose selection and justification
- The modelling process does not only help to better understand and interpret the available data but also sheds light on the limitations of the current data landscape and, consequently, uncertainty in the model predictions
- The insights gleaned from such models support a strategic Model-informed Drug Development (MIDD) approach focusing on risk management, the generation of critical information, and the reduction of uncertainty in key parameters

Methods

- Our approach combines and integrates clinical trial data with information from multiple sources. These sources can be pre-existing data, e.g., in-vitro or in-vivo pre-clinical data, or parametrized mechanistic models from literature.
- Key is the integration of such data in a meaningful way to obtain a robust model; ideally with a validation by data already generated.
- We applied this approach to SAb's SAB-176, a polyclonal fully human antibody targeting different strains of the influenza virus, in order to support the selection of doses for a Phase 2 dose finding study as describe in brief:
 - Pharmacokinetics (PK) was described by available microneutralization (MN) or hemagglutination (HAI) titers data against a range of influenza viruses
 - A PD model was developed based on published mechanistic models of influence viral load from the scientific literature [1, 2, 3]. This model was calibrated using both literature [1, 4, 5, 6] and healthy volunteer data from SAb's Phase 2a influenza challenge study.
 - Viral load was linked to time-to-alleviation of symptoms (TTAS) for otherwise healthy subjects using a time-to-event (TTE) model based on published data.
 - The TTE model was extrapolated to other patient populations (patients with a high risk of complications, clinical trial population) based on the viral load profiles. Internal validation against the observed TTAS from the clinical trial showed good agreement between data and prediction.



Results

- Complex models predicting PK to clinical outcome with reasonable robustness can be developed through integration of literature information and data as well as pre-clinical and clinical data generated in-house.
- Such models can successfully bridge data gaps and deliver insights informing the future development strategy including dose selection and justification.
- In addition, they can help to understand the drug's PK and PD effects for a range of scenarios not reflected in the data (yet), e.g., different doses, patient populations etc. – with the caveats attached to extrapolation.

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