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PERSPECTIVE

A Perspective on Quantitative Systems Pharmacology Applications to Clinical Drug Development

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Over the past decade, regulatory submissions of quantitative systems pharmacology (QSP) modeling have steadily increased.[1] Although good modeling practices for early stage drug development have been published,[2] discussion on evaluating predictive performance of QSP models to inform late stage drug development is lacking. We offer three recommendations for QSP modeling and simulation for late-stage drug development: (1) maximal inclusion of clinical pharmacodynamic (PD) biomarkers; (2) a minimum model; and (3) prespecified quantitative/statistical criteria.

RECOMMENDATIONS FOR QSP MODELS TO IMPACT LATE-STAGE CLINICAL DEVELOPMENT AND BEYOND

Once a drug candidate enters its late stage development (phase II and phase III), it is critical to precisely plan its clinical trials for the goal of minimizing the risk and uncertainty associated with its toxicity and effectiveness, respectively, for the proposed indication. At this juncture, the stakes are high and QSP scientists have an opportunity to make an impact.

QSP mechanistically and quantitatively links a drug target via the key biological pathway (preferably via the shortest path in a parsimonious model) to PD biomarkers, it can simultaneously model quantitative changes of multiple PD biomarkers. Furthermore, QSP models have the unique capacity of extrapolative prediction as compared to traditional indirect response modeling or pharmacometric pharmacokinetic (PK)/PD modeling; and can prospectively select the right dosing regimen to be studied in the right patients for designing clinical trials. However, model credibility is a critical issue that needs to be addressed. QSP scientists can impact late-stage drug development by addressing the issue of how to increase model credibility to inform late-stage drug development.

Maximal rational inclusion of a drug candidate's pharmacodynamic biomarkers and clinical end points

A preclinically oriented QSP model is usually constructed to cover a biological network as granular and wide as possible for fear of missing any important biology, it is calibrated and validated to preclinical data gathered during early drug development. However, the higher the molecular granularity in a preclinically oriented QSP model where molecular data are derived from *in vitro* studies, the greater the amount of uncertainty regarding model structure and parameter values from the perspective of human biology.[3] To guide late-stage clinical development of a drug candidate, a clinically oriented model is needed. If a preclinically oriented model already exists, the modelers should avoid any identifiability and uncertainty issues due to granularity by modifying an existing model or constructing a new model. Once a medical entity enters the phase I stage development, PD biomarker and objective clinical end point data start to accumulate. The profiles of PD biomarkers following dosing of a medical entity, meaning their quantitative relations to its pharmacological and PD effects observed in early clinical studies, could be fully utilized to calibrate and validate a clinically oriented QSP model to increase its credibility.

During the clinical developments of alirocumab and evolocumab, two anti-proprotein convertase subtilisin/kexin type 9 monoclonal antibodies,[4] several plasma lipids were measured, even though reduction of low-density lipoprotein cholesterol was primarily used for their approval for marketing. In a recent QSP model by Sokolov *et al*.,[5] they utilized the data of low-density lipoprotein cholesterol, apolipoprotein B, total cholesterol, high-density lipoprotein cholesterol, triglyceride, and liproprotein (a) to simulate the therapeutic effects of alirocumab and evolocumab. This model and a rheumatoid arthritis model by Schmidt *et al*.[6] where multiple biomarkers were utilized support our viewpoint of modeling and simulating all clinically relevant PD biomarkers to increase model credibility and support applicability of its prediction to guide clinical development. A model that predicts well for multiple clinically related and pharmacologically linked PD biomarkers is more credible than a model that predicts well only for one PD biomarker. A clinically oriented QSP model with a high level of credibility could conceivably facilitate postmarketing research and development for approval of new indication(s) or new dosing regimen(s) as well.

Simple but pharmacologically and clinically meaningful

Whether a clinically oriented QSP model can be adequately qualified and validated is contingent on the balance between the quantity of patient response data and the number of model variables and parameters. Therefore, ideally, a clinically oriented model is parsimonious, with a model structure as simple as possible in the context of balancing the amount of clinical data for model qualification/validation while maintaining the connectivity between the

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pharmacological target and pathways of a medical entity and its PD responses.

PD biomarkers are often derived from disease biomarkers; biomarkers for a specific disease are related among one another in the context of human biology. The relationships between PD biomarkers and a medical candidate's pharmacological actions can be viewed as a graph comprising nodes and edges with built-in feedback loops or regulatory mechanisms. Based on the theory of graph geodesic, a shortest path of the pharmacological pathway can be determined from a molecular target to a PD biomarker. The caveat, though, is that a key feedback loop or master regulator that can impactfully upregulate or downregulate a target should not be ignored. In brief, the network of PD biomarkers and clinical end points connecting to the medial entity's pharmacological effects can be utilized and captured with the simplest model in mind.[7,8] For example, the model by Gadkar *et al*.[7] illustrates a simple but sufficient pharmacological network of an anti-anti-proprotein convertase subtilisin/kexin type 9 monoclonal antibody, cholesterol intake and elimination, as well as PK components. With an adequate amount of PD biomarker data in healthy subjects and patients for model calibration and validation, the predictive performance of a model can achieve the desired credibility and predictive power.

Genomic mutations can cause physiological abnormality leading to development of diseases and contribute to differential patient responses to a treatment. The impact of genetic mutation on PD responses has been leveraged to calibrate QSP models; however, applications seen in literature seem to be limited to predicting phase II results.[7] Inclusion of genetic mutations in QSP modeling, which are associated with differential patient responses, can conceivably be expanded to facilitate patient stratification for phase III trials. Hopefully, successful examples of QSP modeling with inclusion of genetic mutations to facilitate phase III trials would soon be seen in literature.

Prespecified quantitative and statistical criteria in the context of application

The results of a clinical trial are usually accepted based on the objective of the trial and on whether the results meet the specific predetermined statistical criteria. It seems natural that the quantitative and statistical expectations for the outcome of a clinical trial is referenced for making the decision to accept a QSP model extrapolation. The higher the decision risk is, the more stringent the criteria need to be. This is critical if QSP predictions are to be used as the primary evidence to support a milestone in the late-stage development process. Clinical variability of a PD biomarker as well as PK variability can be referenced to define the criteria prior to conducting modeling and simulation. Importantly, the predetermined quantitative and statistical criteria need to be thoughtfully defined for each context of use and its related decision risk. This is, however, challenging. Without doubt, the QSP community's concerted efforts are needed to achieve this milestone.

The stakes at late-stage drug development include cost, patient safety, and effectiveness. To support the credibility of a QSP model and to gain stakeholders' confidence in its prediction, prespecified quantitative and statistical measures for evaluating the prediction of a QSP model are needed. The criteria used to calibrate and validate a model should not be a moving target for the convenience of claiming a model has been calibrated and validated. The following questions would need to be addressed:

- What quantitative and statistical criteria are considered adequate to provide the level of confidence needed for the credibility of a model and for a context of use?
- Is the two-fold criterion used by the physiologically-based pharmacokinetic community[9] applicable to QSP for all PD predictions? How about the confidence interval range, 95% or 90%, within which predicted values should fall? Are these criteria applicable across the

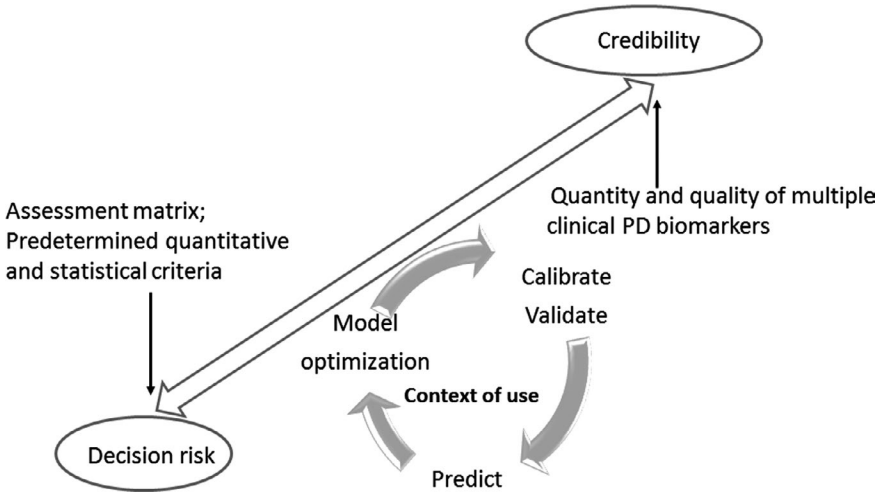

Figure 1 Quantitative systems pharmacology (QSP) models to guide late-stage drug development should be iteratively calibrated and validated to (1) maximize model credibility with adequate amounts of pharmacodynamic (PD) biomarker data of high quality and (2) minimize decision risk with context-specific predetermined quantitative/statistical criteria.

board or stringent enough to accept a prediction and apply it to guide the design of a Phase 3 trial?
- Should the decision risk be part of the equation when one contemplates what criteria to be applied?
- What would the consequences in harming patients be if a decision made to move forward with the dosing regimen selected by QSP for the phase III trial turns out to be inadequate?
- Can the criteria for designing a phase III trial be the same as those for a phase II clinical waiver?

SUMMARY

The workflow of QSP modeling to guide the development of a medical entity would consist of (1) modeling with preclinical granular data to fully explore the profile of a candidate and guide the early stage of its development program; (2) maximizing use of efficacy and safety PD biomarkers in a clinically oriented model; (3) conducting pharmacologically and clinically meaningful risk-based QSP modeling and simulation with a parsimonious model; and (4) fully utilizing the unique extrapolation capability of QSP by validating a QSP model with specific predetermined quantitative and/or statistical criteria for its context of use. QSP modeling should aim to minimize decision risk while maximizing model credibility (**Figure 1**). Along with this notion, the QSP community needs to collaborate to address (i) what constitutes the clinical credibility of QSP modeling; (ii) what the risk-based assessment matrix is; and (iii) what the risk-based quantitative and statistical criteria for individual elements in the assessment matrix are needed for model validation in the context of an intended application. Referencing the Standard by American Society of Mechanical Engineers (ASME)[9,10] for the framework of assessing model credibility regarding context of use, model validation, decision risk, and applicability of a QSP model may well be the first step.

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