Model Qualification Approaches for Quantitative Systems Pharmacology (QSP) and Mechanistic Physiological Models

Christina Friedrich
Rosa & Co LLC, San Carlos, CA 94070

Drug Development Advisors
Driving Scientific Innovation Since 2002

Objective: **Compare and contrast recent publications discussing QSP model qualification with Rosa's Model Qualification Method (MQM)[1,2]**

Introduction and Methods

QSP modeling is a powerful approach in model-informed drug development. QSP is an umbrella term for mathematical modeling that considers drug MOA in the context of biological disease mechanisms to improve understanding of human biology and pharmacology. Specific QSP modeling methods vary, and there is currently no one universally accepted qualification method[3]. Several recent publications discuss QSP model qualification[4,5,6], and the emerging consensus in conference publications focuses on qualification vs. traditional validation.

Mechanistic models such as the PhysioPD™ Research Platforms developed by Rosa are one established QSP approach in which biological mechanisms and drug MOA are represented mathematically. The Platforms enable simulation of protocols to gain insights into the connections between mechanisms and outcomes.

Here, we compare and contrast recently proposed QSP qualification approaches with the MQM developed for Rosa's PhysioPD Research Platforms and first presented at ACoP 2011[2].

Results: QSP Models are Qualitatively Different from PK/PD Models

There was agreement that QSP models are qualitatively different from PK/PD models, and that the differences require a shift away from a validation mindset toward a qualification or "fit-for-purpose" mindset. Cited differences include:

- Purpose: QSP models are intended to illuminate mechanisms and facilitate learning and hypothesis testing. PK/PD models are built to describe a specific data set and support narrow extrapolation, e.g., for dose selection[3,5].
- Data: QSP models make use of disparate data sources – clinical, preclinical, *in vitro* – and expert knowledge to construct a biologically meaningful mathematical representation of disease and drug mechanism[1,4,5,6]. PK/PD models use data from one or a small set of clinical or preclinical trials to infer a parsimonious model descriptive of the data, but not necessarily biologically informative[3,5]. Mechanistic PK/PD models fall somewhere in between[5].

The differences in purpose and data (see Figure 1 for examples) lead to the clear conclusion that the validation approach used for PK/PD models is neither appropriate nor sufficient for QSP models[1,5,6]. Perhaps the most compelling argument is that lack of clinical or preclinical data would make PK/PD modeling impossible, but does not prevent qualification of a QSP model[1,5]. Indeed, the need to anticipate clinical results for a novel target, given, for example, mechanistic information about that target's role in disease pathophysiology is a key motivator for QSP modeling. A second line of reasoning points out that more mechanistic models have parameters that are biologically meaningful and locally constrained based on sub-system behavior, so a global fitting approach is not appropriate[1,3].

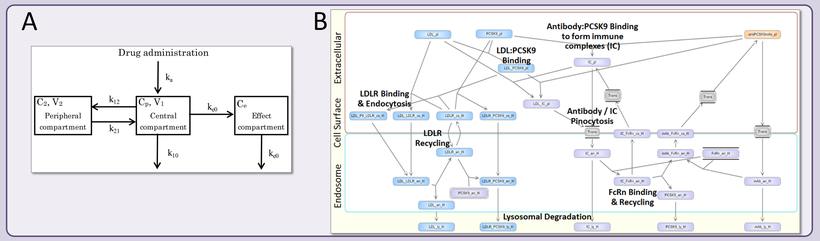

Figure 1. Illustrative examples of (A) a PK/PD model schematic used to confirm utility of a biomarker given a preclinical data set with biomarker and endpoint data[7], and (B) a QSP model, Rosa's PCSK9 PhysioPD Platform[8] used to clarify the impact of antibody properties on likely efficacy to support *in vitro* to *in vivo* translation and optimization of antibody properties.

Results: Customizable Framework, Not Prescriptive Method

QSP models vary in depth and breadth, purpose, and available data and knowledge to constrain the model behavior. Prescriptive methods that assume the existence of a particular type of data, or the application of the model to a particular type of question, are not appropriate[1,5]. Rather, a general and customizable framework is needed that can be tailored to the research context and goes beyond goodness-of-fit to a given data set. To ensure that a QSP model is fit-for-purpose, model qualification must address the questions and concerns in Table 1[1].

Table 1: Questions and Concerns that Model Qualification Must Address

RELEVANCE	• Is the research context clear, and has biological and functional scope been set accordingly? • Does the representation of the biology and pharmacology reflect the current state of knowledge?
UNCERTAINTY	• Given biological uncertainty, how robust are model results and conclusions? • Would recommendations change under different assumptions? • What uncertainty poses a risk to the program, and what experiments could resolve it?
VARIABILITY	• How do known differences between patients affect model results? • What biological mechanisms can explain the range of observed clinical or preclinical outcomes?
DATA	• Does the model match relevant data, at the clinical/preclinical and mechanistic level? • Are model responses to a variety of tests consistent with current knowledge and expectations?

Results: Cross-Functional Communication is Key

A point of emphatic agreement across the publications reviewed is the need for effective communication between modelers and other functional experts, e.g., from pharmacology, biology, clinical research[1,4], as well as with regulatory agencies[6]. A well-qualified QSP model can be a repository for biologic, pharmacologic, and clinical knowledge[1,3,4] and a reusable and extensible asset for a development program[1,6].

The MQM framework laid out here evolved out of Rosa's modeling practice both to facilitate effective communication and to support model qualification, i.e., addressing the questions and concerns in Table 1. Areas of specific agreement or contrasting views with other authors are highlighted in each section below. More details on the MQM can be found in[1] and[2].

QSP models can be complex and scientifically sophisticated. Frequent communication is needed to ensure that cross-functional expertise is utilized and reflected in the model, and to secure buy-in from stakeholders. Because there is no prescriptive validation approach, the team must jointly agree on the specific qualification approach to be taken to satisfy each of the eight qualification criteria (Figure 2), and progress must be documented. In Rosa's practice, a MQM document for planning and tracking is started on Day 1 and evolves along with the model.

Conclusions: Emerging Consensus

- Recent publications and conference presentations suggest that the modeling community is reaching a consensus on:
  - The utility of mechanistic and QSP models
  - The ways in which they differ from PK/PD approaches
  - The need for customizable qualification vs. a rigid validation approach
  - The need for cross-functional communication
- Careful scoping (MQM criterion 1), use of biological constraints (MQM criterion 2), and quantitative and qualitative comparisons to data (MQM criteria 7, and 8) are included in other QSP qualification criteria publications.
- The MQM's systematic consideration of uncertainty and variability and associated use of sensitivity analysis and Virtual Patients are generalizable concepts that are applicable to QSP models and enhance the qualification concepts presented elsewhere.

Results: Rosa's Model Qualification Method Compared with Other Publications

8. Model matches relevant pre-specified *quantitative* test data

MQM: QSP models should be tested against relevant quantitative data. The appropriate testing approach depends on the research context, including the intended use of the model and relevant available data. Lack of appropriate clinical data for statistical testing does not mean that the model cannot be qualified. In the absence of clinical data, particular care should be taken to investigate the possible impact of uncertainty and known variability using VPs.

Other publications: Comparison to data is universally acknowledged to be a key component of QSP model qualification. Agoram gives a nice example of a semi-quantitative assessment of maximum bronchodilation that was deemed good enough for the research purpose[5]. Peterson and Riggs comment on the qualification value of *simultaneously* matching disparate data sets[6].

7. Model results are *qualitatively* consistent with relevant data and knowledge

MQM: Every variable in a mechanistic model can be observed under actual or what-if scenarios. Model behavior can be evaluated qualitatively by visual inspection of model results under many conditions, presenting opportunities for cross-functional teams to interact with the model and gain confidence that it is fit-for-purpose. Qualitative testing is also appropriate when the data available are related, but not identical to the scenario of interest, e.g., data for different phenotypes or for related drugs. Figure 3 shows an example of qualitative testing in a Diabetes PhysioPD Research Platform.

Other publications: The necessity for qualitative testing is acknowledged, mostly by contrast to the quantitative statistical testing that is imperative for PK/PD model validation but often not possible or necessary for QSP models. In this author's opinion, the power of qualitative testing is underappreciated in current published work.

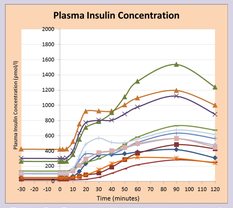

Figure 3. Example of a qualitative check. A selection of Virtual Patients are visually checked for two-phase insulin secretion as appropriate for disease severity.

6. Relevant clinical variability is reproduced

MQM: Analysis of clinical variability in the mechanistic modeling context often focuses on illuminating the mechanistic sources of variability to support research objectives such as identifying responder patient types or designing a next-generation compound to have broader efficacy. Clinical variability can be reproduced by creating and simulating a range of VPs with diverse parameter values reflecting PK variability, known pathway variability, and uncertainty. The qualification criteria should be decided based on the research context. Spanning the range of responses or reproducing the distribution of responses may both be appropriate qualification criteria.

Other publications: Clinical variability is generally considered as part of a PopPK – type approach. The notion of using mechanistically diverse VPs to span the range of clinical responses without necessarily matching the distribution is not in wide use, though the use of mechanistically diverse virtual populations that reproduce distributions has been previously reported[9].

5. Model captures relevant known pathway variabilities

MQM: Pathway variability exists if there are data from patients showing that different pathways play a role in pathophysiology for different patients. For example, the relative degree of insulin secretion vs. insulin resistance in diabetes pathophysiology is an area with known pathway variability. Mechanistic models can be used to investigate, using different VPs, the degree to which known pathway variability may impact outcomes.

Other publications: The publications currently reviewed did not focus on known pathway variabilities. An interesting published example is the use of eosinophilic vs. neutrophilic asthma VPs in the assessment of anti-IL-5 therapy[10].

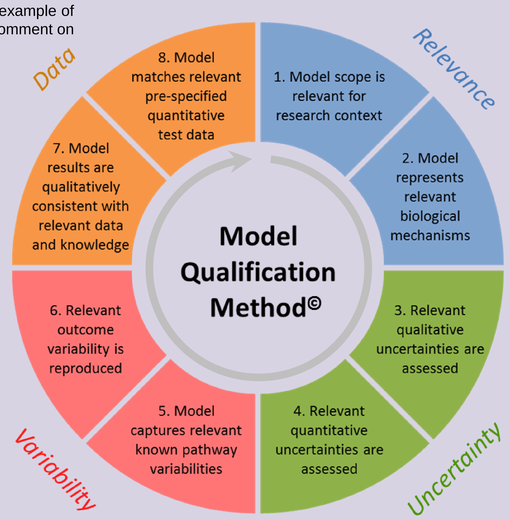

Figure 2. Rosa's Model Qualification Method

1. Model scope is relevant for research context

MQM: Research context includes the key research question and intended application of model results, the biological system of interest, the current state of data and knowledge, and time and resource constraints. All of these factors should be considered in determining model scope. Research context and scope decisions are documented throughout the project.

Other publications: There is agreement on the need to be explicit about the purpose of the model[4,5]. For example, Agoram recommends beginning the qualification process with a clear statement of the objective and additionally draws an explicit connection between the purpose of the model and the model evaluation criteria[5].

2. Model represents relevant biological mechanisms

MQM: The model should represent biology with a graphical model representation to facilitate communication and assessment by cross-functional teams. Parameters have intrinsic meaning and should be based on data where possible, and appropriate sub-system behaviors reflecting mechanistic understanding.

Other publications: The utility of a graphical representation of biology for communication is explicitly discussed or strongly implied in the other publications that were examined. The evaluation of component sub-models emphasized in[5] is consistent with this MQM criterion.

3. Relevant *qualitative* uncertainties are assessed

MQM: *Qualitative* uncertainty refers to knowledge gaps about how biological components interact, while *quantitative* uncertainty refers to the degree or rate of the interaction. Mechanistic models are ideally suited to evaluate the implications of alternative qualitative hypotheses. Qualitative uncertainties must be documented and assessed to the extent appropriate to the research context (Table 2).

Other publications: Qualitative uncertainty is not generally distinguished from quantitative uncertainty. Peterson and Riggs emphasize the value of the model in uncovering scientific knowledge gaps[6].

Table 2. Possible Qualitative Uncertainty Resolutions

Document and proceed with most likely hypothesis	Appropriate if impact is localized, distal to the focus of the research, or transient.
Simplify model structure to avoid modeling uncertain area explicitly	Appropriate if possible without compromising the model's ability to address research questions.
Resolve definitively, i.e., eliminate all but one hypothesis through data and/or modeling analysis	May require significant resources, which is warranted if model predictions relevant to the research question are sensitive or likely to be sensitive to the uncertainty.
Maintain multiple hypotheses in model to explore explicitly	Appropriate if model predictions are sensitive to the uncertainty and if more than one hypothesis satisfies all constraints.

4. Relevant *quantitative* uncertainties are assessed

MQM: Many parameters needed for QSP models are bounded but not fully determined by available data. Sensitive parameters and model-based exploration of their systemic effects should be undertaken, e.g., via sensitivity analysis and simulations of "Virtual Patients (VPs)". Each VP is one complete model instance with a unique set of parameters and consistent with all data constraints. A VP is not a collection of randomly sampled parameters, but rather a biologically plausible alternative hypothesis of disease and drug mechanisms.

Other publications: Assessment of sensitivity to parameter uncertainty is mentioned in[4,5,6] and sensitivity analysis is highlighted as an important tool. The systematic creation and deployment of Virtual Patients has not been highlighted as a key mechanism for evaluating the impact of uncertainty in these recent publications, though their use has been documented in prior work, including[7,8].

References

1. Friedrich, C., A Model Qualification Method for Mechanistic Physiological QSP Models to Support Model-Informed Drug Development. CPT Pharmacometrics Syst Pharmacol, 2015.
2. Friedrich, C., et al. Qualifying Mechanistic Physiological Models for Use in Pharmaceutical Discovery and Development. in ACoP. 2011. San Diego, CA.
3. Jusko, W.J., Moving from basic toward systems pharmacodynamic models. J Pharm Sci, 2013. 102(9): p. 2930-40.
4. Visser, S.A., et al., Implementation of quantitative and systems pharmacology in large pharma. CPT Pharmacometrics Syst Pharmacol, 2014. 3: p. e142.
5. Agoram, B., Evaluating systems pharmacology models is different from evaluating standard pharmacokinetic-pharmacodynamic models. CPT Pharmacometrics Syst Pharmacol, 2014. 3: p. e101.
6. Peterson, M.C. and M.M. Riggs, FDA Advisory Meeting Clinical Pharmacology Review Utilizes a Quantitative Systems Pharmacology (QSP) Model: A Watershed Moment? CPT Pharmacometrics Syst Pharmacol, 2015. 4(3): p. e00020.
7. Nakatani, Y., et al., A small-animal pharmacokinetic/pharmacodynamic PET study of central serotonin 1A receptor occupancy by a potential therapeutic agent for overactive bladder. PLoS One, 2013. 8(9): p. e75040.
8. Friedrich, C. Quantitative Systems Pharmacology (QSP) informs *in vitro* to *in vivo* translation for PCSK9 antibody. in ACoP. 2014. Las Vegas, NV.
9. Shoda, L., et al., The Type 1 Diabetes PhysioLab Platform: a validated physiologically based mathematical model of pathogenesis in the non-obese diabetic mouse. Clin Exp Immunol, 2010. 161(2): p. 250-67.
10. Waters, S.B., et al., Treatment with sitagliptin or metformin does not increase body weight despite predicted reductions in urinary glucose excretion. J Diabetes Sci Technol, 2009. 3(1): p. 68-82.
11. Yuraszeck, T., M. Zhu, and I. Singh. A Population-Based Approach to Systems Pharmacology (SP) Modeling of the Effect of Blinatumomab in Adult B-Precursor Acute Lymphoblastic Leukemia Patients. in ACoP. 2014. Las Vegas, NV.
12. Lewis, A.K., et al., The Roles of Cells and Mediators in a Computer Model of Chronic Asthma. International Archives of Allergy and Immunology, 2001. 124(1-3): p. 282-286.

For more information about this work, please contact:
Christina Friedrich
Rosa & Co LLC
(650)784-0771
cfriedrich@rosaandco.com