Considerations for Adapting Previously Built Models for New Quantitative Systems Pharmacology Research

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Objectives: To provide guidance and suggest methodologies for adapting existing quantitative systems pharmacology (QSP) models for new research.

Methods: Rosa has adapted existing proprietary and published models or model components across many therapeutic areas for new research in its PhysioPD™ Platforms. Adaptation required assessing the existing models for their original research context and their potential fit-for-purpose for the new research application. Components of the research context for a model include: (1) key research question(s) or decision(s) to be made, (2) available data and knowledge, (3) time and resource constraints, and (4) input from and acceptance by key team stakeholders. The research context then informs evaluation of the model scope, relevance of biological uncertainty and variability, and model testing.

Results: Some existing models have been effectively adapted for new research programs. This required significant technical and scientific attention. In other cases, the existing model was found to be a poor match for the new research context, and development of a new, focused model was judged to be more efficient. Considerations for evaluating model scope, uncertainty, variability, and testing have been identified and documented to guide future efforts and are summarized in Table 1.

Conclusions: Adapting existing models for new research is feasible, but drug development teams should do so with appropriate expectations and a high level of care. Considerations of the original and new research contexts can guide the evaluation of a model’s suitability, as well as ensure stakeholder acceptance, which is a critical (yet often underappreciated) component of project success. Use of the guidelines helps with the decision making process and to ensure the finished model is fit-for-purpose.
Table 1: Suggested considerations for evaluating previously built models for new research applications.

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<th>Criteria</th>
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| **Scope**      | Does the model represent appropriate biology?  
|                | Include necessary biological components and processes?  
|                | Appropriate level of biological detail (especially for your target areas)?  
|                | Does it represent the appropriate timeframe (e.g., minutes vs. years)?  
|                | Does it represent the phenotype (e.g., therapeutic area, severity) of interest?  
|                | Is the size and complexity appropriate to the time and resources you can apply?  
|                | Is the biology represented appropriately?  
|                | Is the embedded biological knowledge current?  
|                | Is the original research context clear?  
|                | Are assumptions clearly stated?  
|                | Are assumptions appropriate for the new research context?  
|                | Are data and parameter sources appropriate for the new research context?  |
| **Uncertainty**| Does the publication identify key knowledge gaps and associated assumptions?  
|                | Does the publication evaluate the impact of key uncertainties via sensitivity analysis or “what if” scenario testing?  
|                | Does the publication include multiple virtual patients to explore biological uncertainty that is relevant to the new research context?  |
| **Variability**| Does the publication identify known pathway variability?  
|                | Does the publication evaluate the impact of pathway variability via sensitivity analysis or “what if” scenario testing?  
|                | Does the publication comment on clinical variability?  
|                | Are multiple relevant virtual patients included?  
|                | If virtual patients are included, how do they differ from each other mechanistically?  
|                | If virtual patients are included, what clinical phenotype and response to therapy do they represent?  |
| **Qualitative Testing** | Were relevant experts consulted to assess if model results looked reasonable?  
|                | Were relevant sources of information for qualitative testing identified and used, e.g., clinical data from related therapeutic areas, or relevant non-clinical data?  
|                | Were what-if experiments performed to assess model behavior?  
|                | Are subsystem behavior tests described, with appropriate data references?  |
| **Quantitative Testing** | Were relevant clinical data for the drug of interest used for testing?  
|                | Were relevant clinical data for drugs in the same therapeutic area used for testing?  
|                | Were multiple disparate types of model perturbations tested and compared to relevant data?  
|                | Did the model perform adequately, given the new research context?  
|                | Does the model include relevant clinical outcome measures and/or biomarkers?  
|                | Is it clear how the outcome measures were derived from the represented biology?  
|                | Were population-level outcomes reproduced with appropriate range and distribution of outcomes?  |