Validation of Physiologic Models and Analysis of Uncertainty

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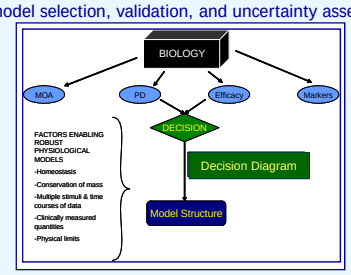
Objectives

Mathematical modeling of human physiology is becoming a standard in drug development and is a critical source of insights for medical research. Physiologic models focused on specific R&D decisions provide value and offer significant predictive power. When these models are utilized as part of a decision-making process, a limited number of scientific uncertainties are addressed by the model. However, in building physiologic models, many more scientific uncertainties – parametric and structural – are addressed, thus enabling decision makers to better understand and manage the decision's scientific uncertainties. Model validation reassures the decision maker that the model functions appropriately either when used as an exploratory tool or when used for trial design. However, medium-to-large physiologic models can be difficult to validate. Many model characteristics, such as synergies, dissynergies, and dynamics, which make physiologic models useful for complex disease and drug analysis problems, also make model validation difficult. Rosa routinely uses decision-focused physiologic modeling – PhysioPD™ modeling – to support decision-making in pharmaceutical R&D.

If physiologic models are to be used for robust decision making, then a process for model selection, validation, and uncertainty assessment is required.



Decision: Selection of lead compound

Questions:
Disease?
- Relevant biologic pathways.
- Relevant tests

MOA?
- Known/unknown mechanisms?
- Relevant biologic pathways.
- Outcome of interest

Biomarkers of efficacy?
- Known biomarkers
- Potential biomarkers

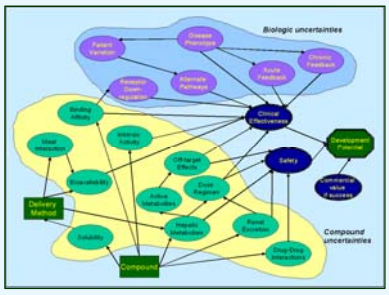
Biologic interactions?
- Known biologic pathways

Ideal biologic attributes?
- Disease outcomes
- Marketing outcomes

Uncertainties

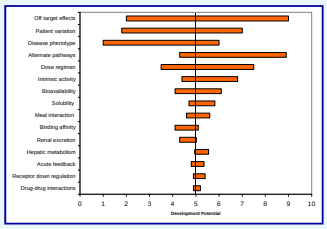
Biologic
- Alternate pathways
- Receptor down-regulation
- Acute feedback
- Chronic feedback
- Disease phenotype
- Patient variation

Compound
- Binding affinity
- Intrinsic activity
- Solubility
- Bioavailability
- Hepatic metabolism
- Renal excretion
- Meal interaction
- Dose regimen
- Off-target effects
- Drug-drug interactions



Decision Diagram showing decisions, uncertainties, and objective function for lead compound decision. Sensitivity analysis of the decision to its uncertainties can be used to prioritize uncertainties.

The final iteration of the Decision Diagram defines the minimal model structure required to evaluate the Objective Function.



Sensitivity analysis of the decision to its uncertainties can be used to prioritize uncertainties.

Methods

To evaluate model uncertainties and validate a model we use a multistep approach that has a standard set of testing criteria largely defined before the model is built, with additional criteria added as needed. The testing process is iterative throughout the model-building process.

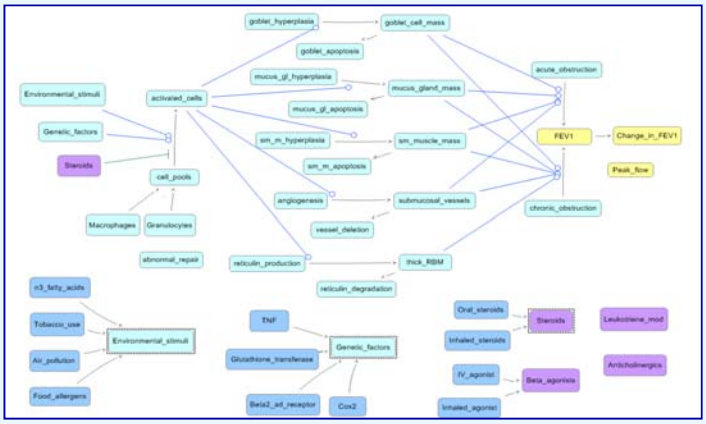
Firstly, we review the mathematical equations (differential and algebraic), pathway structure, scientific basis, and data used to build the model. Hypotheses and assumptions are rigorously documented within the model.

Secondly, we evaluate each pathway and/or module separately. Specifically, we compare its predictions to external data, which were deliberately not used to build the model. For instance, we build the model using literature data and test using client data.

Thirdly, the entire model is evaluated by comparing predicted output to data from a broad range of distinct experiments that challenge the model from different directions.

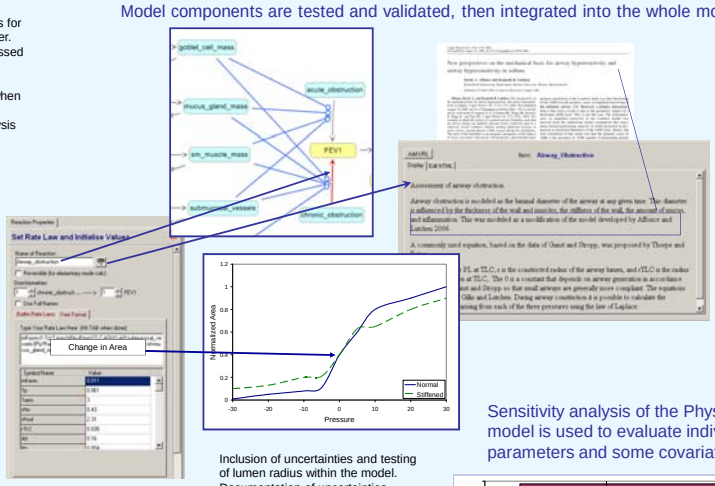
Finally, we use sensitivity analysis to establish biologically sound parameter ranges and to measure parameter accuracy to determine whether the accuracy is appropriate for how the model will be used: for exploration, trial design, or otherwise.

Large physiologic models provide significant insights, but can be difficult to assess and validate.



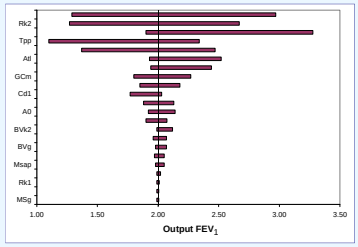
PhysioPD models range from simple to very complex.

Model components are tested and validated, then integrated into the whole model.

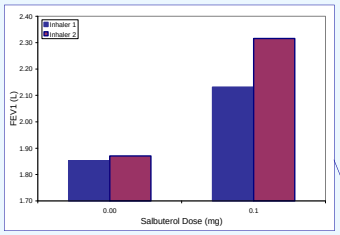


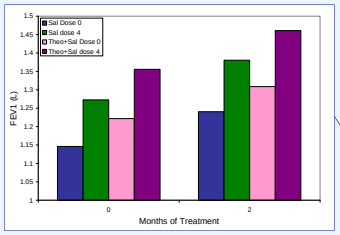
Inclusion of uncertainties and testing of lumen radius within the model. Documentation of uncertainties enables model testing.

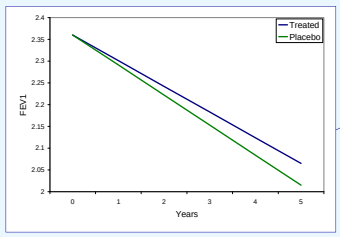
Sensitivity analysis of the PhysioPD model is used to evaluate individual parameters and some covariates.



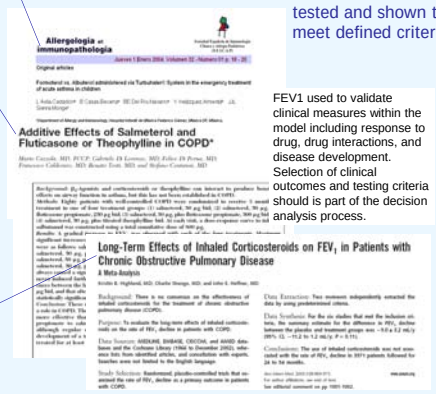
Parameters are varied over a 100-fold range. The x-axis is the model outcome of interest – forced expiratory volume in 1 sec. – and the y-axis lists the ordered parameters as they vary within the model. The analysis is done with the assumption that all parameters are set independently. This analysis is used to identify sensitive areas within the model and the underlying biology, thus guiding further experimentation, testing, and subsequent model refinement.





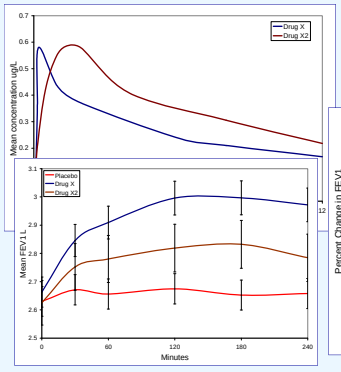


The entire model is tested and shown to meet defined criteria.

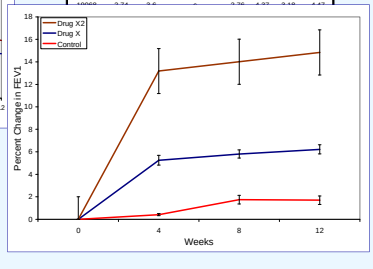


FEV1 used to validate clinical measures within the model including response to drug, drug interactions, and disease development. Selection of clinical outcomes and testing criteria should is part of the decision analysis process.

Trial simulation with the model provides additional testing and validation of the model.



	Day -7			Day 1		Day 7	
Patient	FEV1	FCV	Treatment Assignment	FEV1	FCV	FEV1	FCV
18753	2.74	4.1	c	2.86	4.17	2.91	3.47
18776	2.64	3.9	b	2.76	4.67	2.96	4.27
18902	3.14	4.1	c	2.2	3.27	2.61	3.57
18951	3.09	4.4	b	3.07	4.07	2.66	4.57
18956	2.99	4.4	a	3.58	4.97	2.46	4.97
18978	2.43	3.5	a	2	3.17	1.99	3.07
18998	3.3	4.3	b	2.51	3.37	2.69	4.87
19025	3.81	5.2	a	2.56	4.77	3.08	4.27
19043	2.23	3.4	b	3.38	4.77	2.2	3.57



A decision focus makes it possible to validate large physiologic models

The validation process is critical whether the model is used for exploration or for decision making. Such validation requires that the assumptions and hypotheses used to develop the model be explicit. The validation process produces scientific insights that can be translated to increase decision-maker understanding. Validation also results in insights that further the understanding of complex chronic diseases and novel drug targets.

Decision-focused validation and uncertainty analysis should be an integral part of how physiologic models are developed and used.

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