Harmonization on PBPK platform and model qualification for regulatory assessment

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Agenda

- PBPK platform validation/qualification vs model validation/qualification
- Role of PBPK platform developers and sponsors in the validation/qualification process
- PBPK model validation/qualification within a risk assessment framework for specific applications
- Harmonization of PBPK model use in regulatory decision-making
- Reporting standards for PBPK analyses

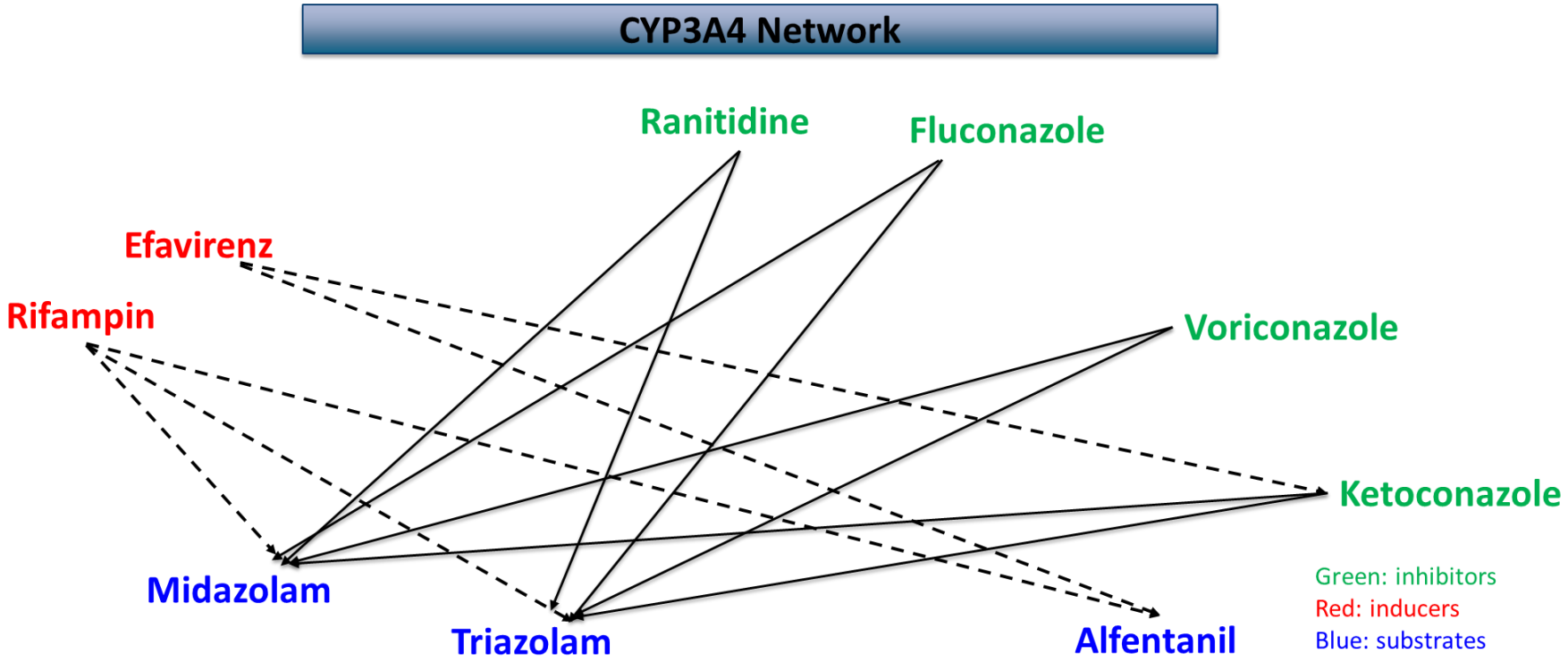
Platform Qualification

- **System parameters**:
  - System/physiological parameters critical for the context of use (CoU)
  - Reasonable assumptions for unknown parameters
  - Case studies and publications outside of CoU can be used to support the system parameters
- **Equations**:
  - Correct equations are implemented – platform documentation
  - Equations are implemented correctly
    - Rewriting the equations in a different format (e.g., Matlab) does not answer this question
    - Could sensitivity analysis with artificial data (known outcomes) be a more relevant test/confirmation?

Qualifying PBPK Platform for DDI

Accurate prediction of DDI for a series of selected substrates and perpetrators of different strengths (one enzyme or different enzymes) qualifies Platform - confirms that equations are correct and able to capture/predict the DDI

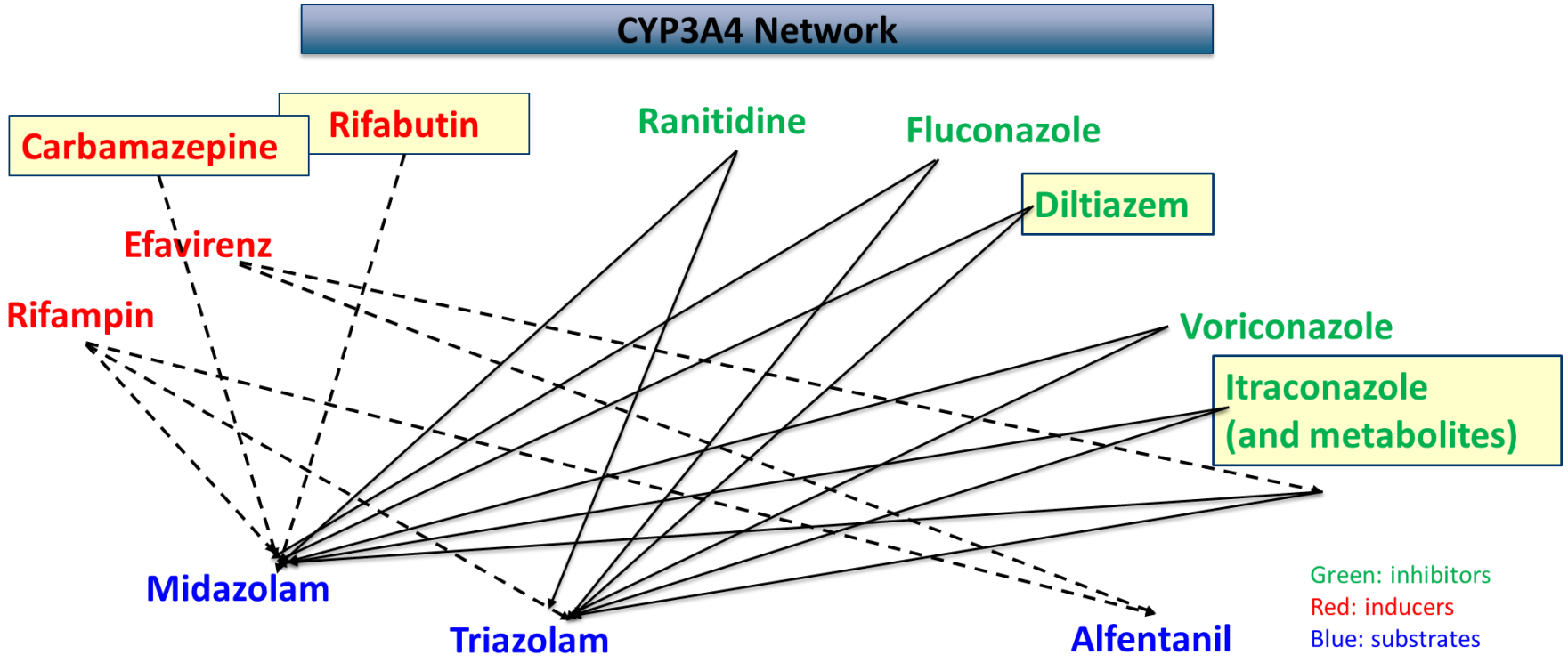
Emphasis should be placed on **diverse** (where applicable) rather than large validation dataset



Qualifying Additional PBPK Models for DDI

Additional models are simply expanding the library of qualified models for DDI Prediction

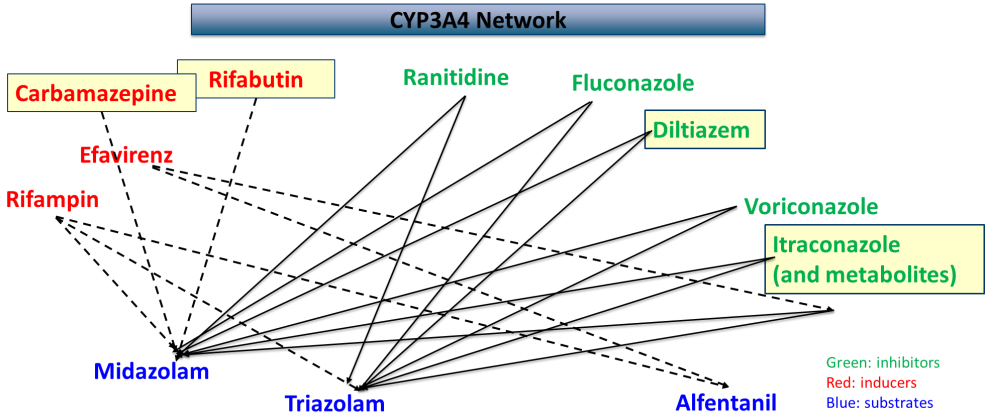
for the same protein

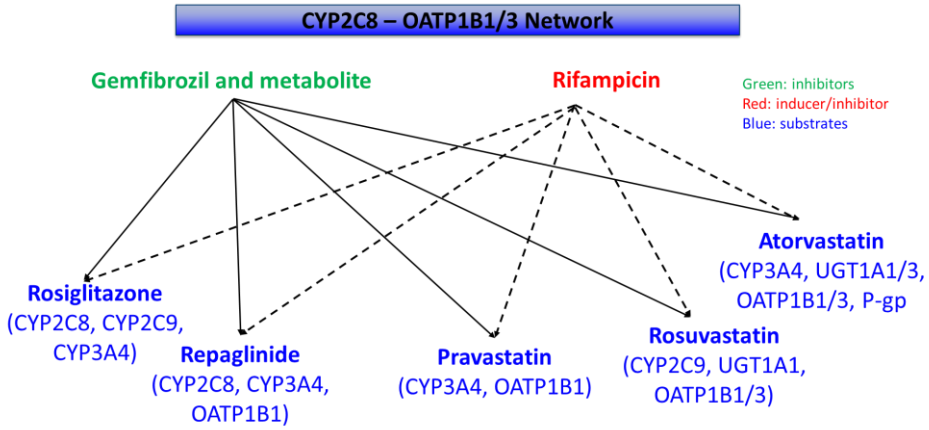


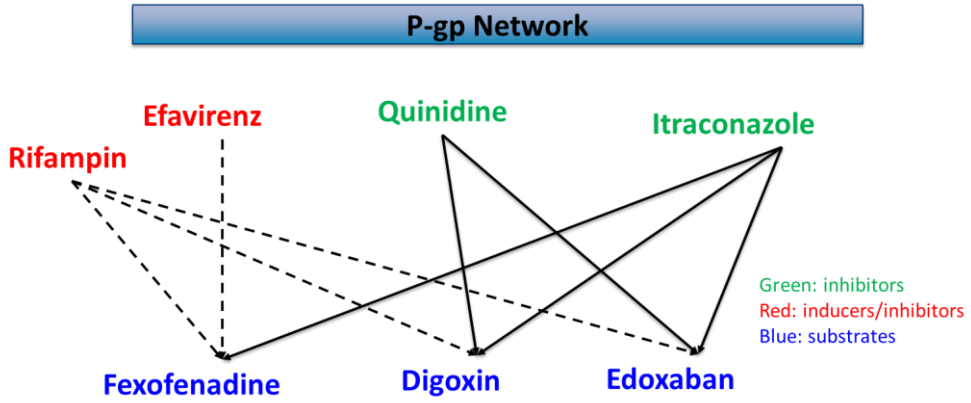
Qualifying Additional PBPK Models for DDI

Additional models are simply expanding the library of qualified models for DDI Prediction

for other proteins



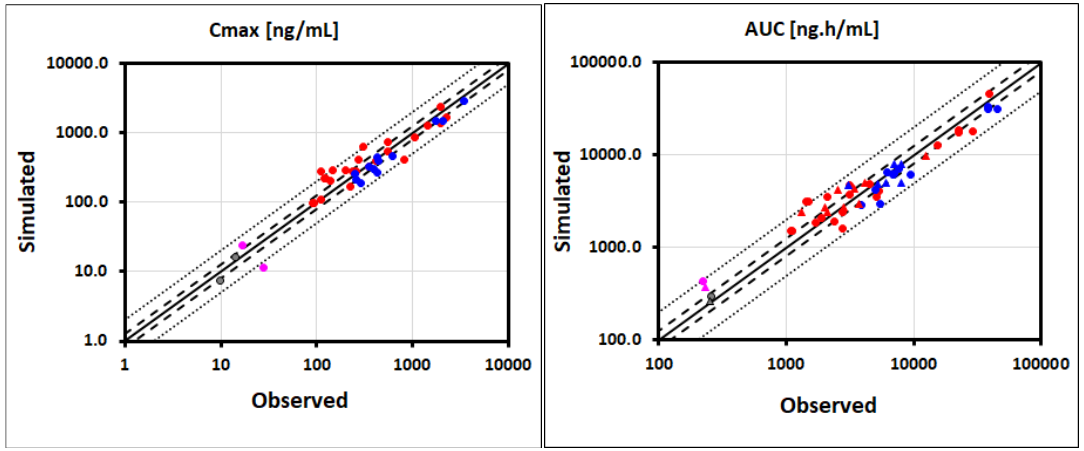




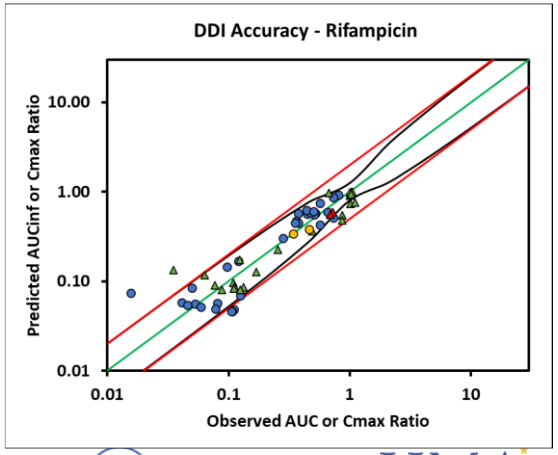
New system parameters (if relevant) will need to be documented

Model Validation

- Model includes ALL relevant mechanisms
- Model is sensitive to changes in relevant input parameters
- Model ADEQUATELY captures/predicts PK of the compound for reference scenario
  (e.g., compound alone for DDI predictions)



- Model has ability to predict effect in question, for example:
  - Captures known DDIs (to predict DDIs for new scenarios - other substrates, other dosing scenarios, administration routes, etc.)
  - Captures contributions of different elimination pathways (to predict DDIs)
  - Captures all relevant mechanisms (to predict PK in other populations – this would be linked with platform qualification for extrapolation to different populations)



Roles and Responsibilities

- **Platform developer**:
  - Sound science – equations and default system parameters
  - Documentation and information allowing regulator to verify the equations and system parameters
  - Standard models (and documentation) if relevant for a specific CoU (e.g., standard models for DDI predictions)
  - Documentation updates and model updates/revalidation (as relevant) with platform version updates
- **User of the platform**:
  - Model construction and validation for specific compound and CoU (i.e., ensure relevant mechanisms are included)
  - Justification and validation of changes to default system parameters

Qualifying Next Versions

- How to qualify the next software version:
  - Clearly describe the changes in the new version
  - Focus on requalifying only the parts of the program which have changed
    - Requalifying of the sections of the program that changed – rerun test cases to ensure that the modification resulted only in intended changes and improved predictions where applicable
    - Remaining sections of the program – rerun test cases to show that unintended changes were not introduced
- Qualifying updated compound models supplied with the software:
  - Describe the changes in the model and explain why the model was changed (i.e., more accurate values for input parameters became available, etc.)
  - Describe and demonstrate the performance of the updated compound model

Model and Platform Validation/Qualification within Risk Assessment Framework

- **Model:** Use of part of observed data to calibrate model, then prediction of remaining observations with reasonable accuracy without modifying the model
    - Reasonable means a level of accuracy sufficient to make well-informed project decisions
        - Varies by development stage
        - Varies by impact of the model
    - Consider variability in compound's PK – model cannot give more accurate prediction than clinical study
- **Platform:** The same platform will be used in different stages of drug development and for applications with varying impacts
    - The more conservative criteria for level of accuracy need to be used
    - Still need to consider variability in PK of compounds used for qualification – different prediction errors may be applicable for different compounds in the platform qualification dataset

Geography Does Not Change the Science

- Similar mechanisms were proposed by FDA and EMA
  - Platform qualification vs. fit-for-purpose model (possibly model master file)
- Harmonization of platform qualification requirements will increase use of these pathways
  - Harmonize requirements for platform qualification
  - Can the same report/documentation be accepted by multiple agencies?
  - Can we push the boundaries and accept qualification across agencies?

Conclusions

- Platform and model qualification process has the potential to streamline and accelerate the review process for specific drug product applications, but cases are rare
- Possible reasons for slow uptake of the qualification process
  - Resource demanding process (even more so if different process and requirements apply across agencies)
  - Uncertainty about conditions/process and expectations
  - Uncertainty about expectations from individual reviewers

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Thank you

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