

A technical concept for automatic PBPK platform (re-)qualification in the Open Systems Pharmacology Suite (PK-Sim® and MoBi®)

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Objectives

The recently issued draft guideline on physiologically-based pharmacokinetic modeling (PBPK) by the European Medicines Agency (EMA) [1] demands the qualification of the intended use related to the PBPK platform for any type of simulation scenario (e.g. drug-drug interactions (DDI, e.g. CYP3A4 inhibition), pediatric scaling in primarily renally cleared drugs, etc.) in regulatory submissions.

Once such a type of scenario is qualified for its use, changes in the software platform (e.g. adjusted or extended model structure, changed parameterization of a model, etc.) require requalification. The objective was to develop a technical concept of automatic requalification of the type of scenario.

Methods

PK-Sim® as part of the Open Systems Pharmacology (OSP) Suite [2] (Figure 1) is a well-established PBPK tool widely used for more than a decade.

It offers different structural models together with relevant physiological and molecular database information for PBPK modeling of small and large molecules in different animal species and human populations.

MoBi® can directly use PBPK models created in PK-Sim® but is especially designed for the de novo construction, import, or extension of systems biology and pharmacology models in an (extensible) ordinary differential equation framework.

Generally, a certain type of scenario consists of multiple simulations involving a variety of PBPK drug models (see Figure 2 for an example). A technical concept of its requalification with every new software release was developed.

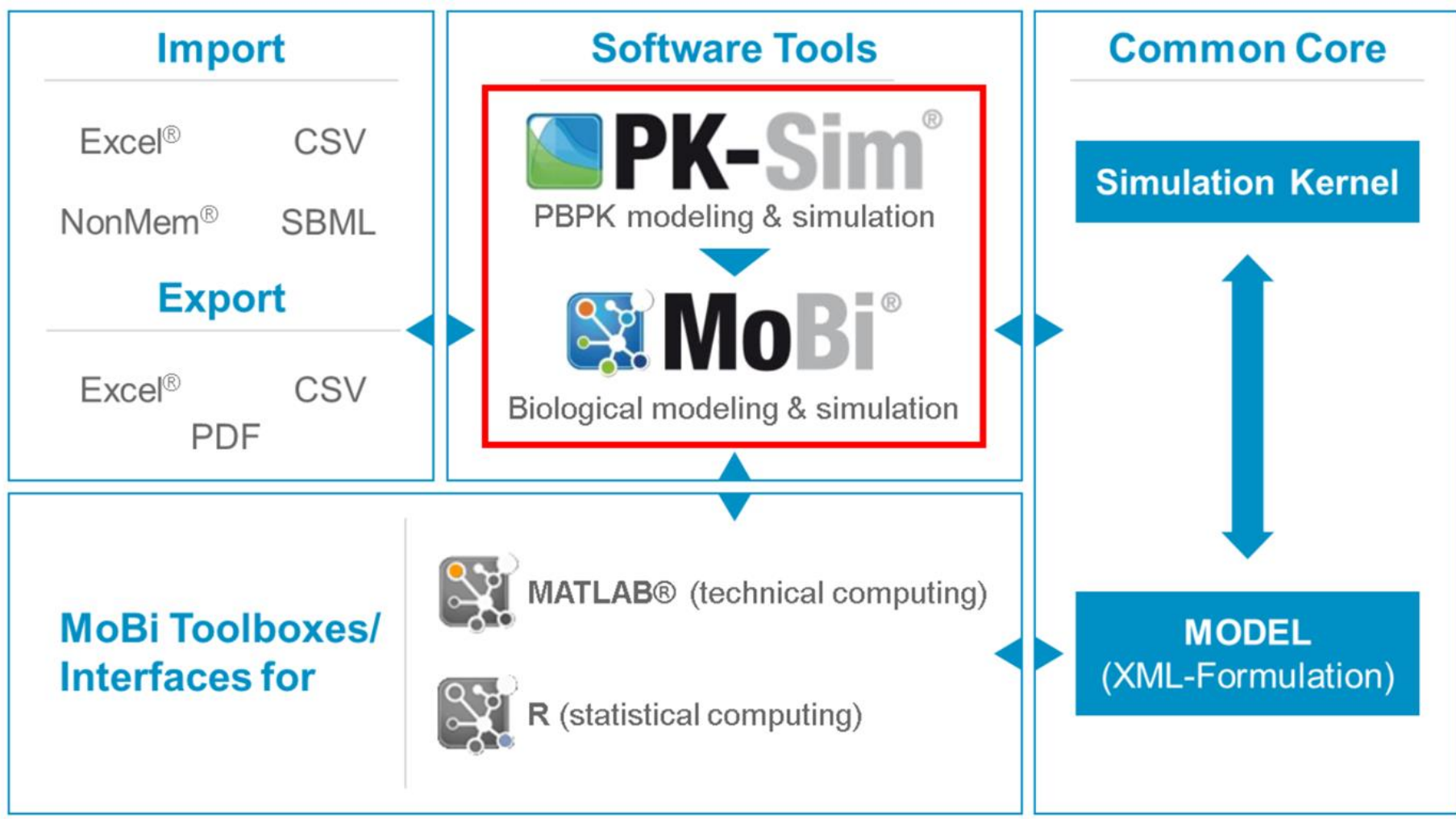
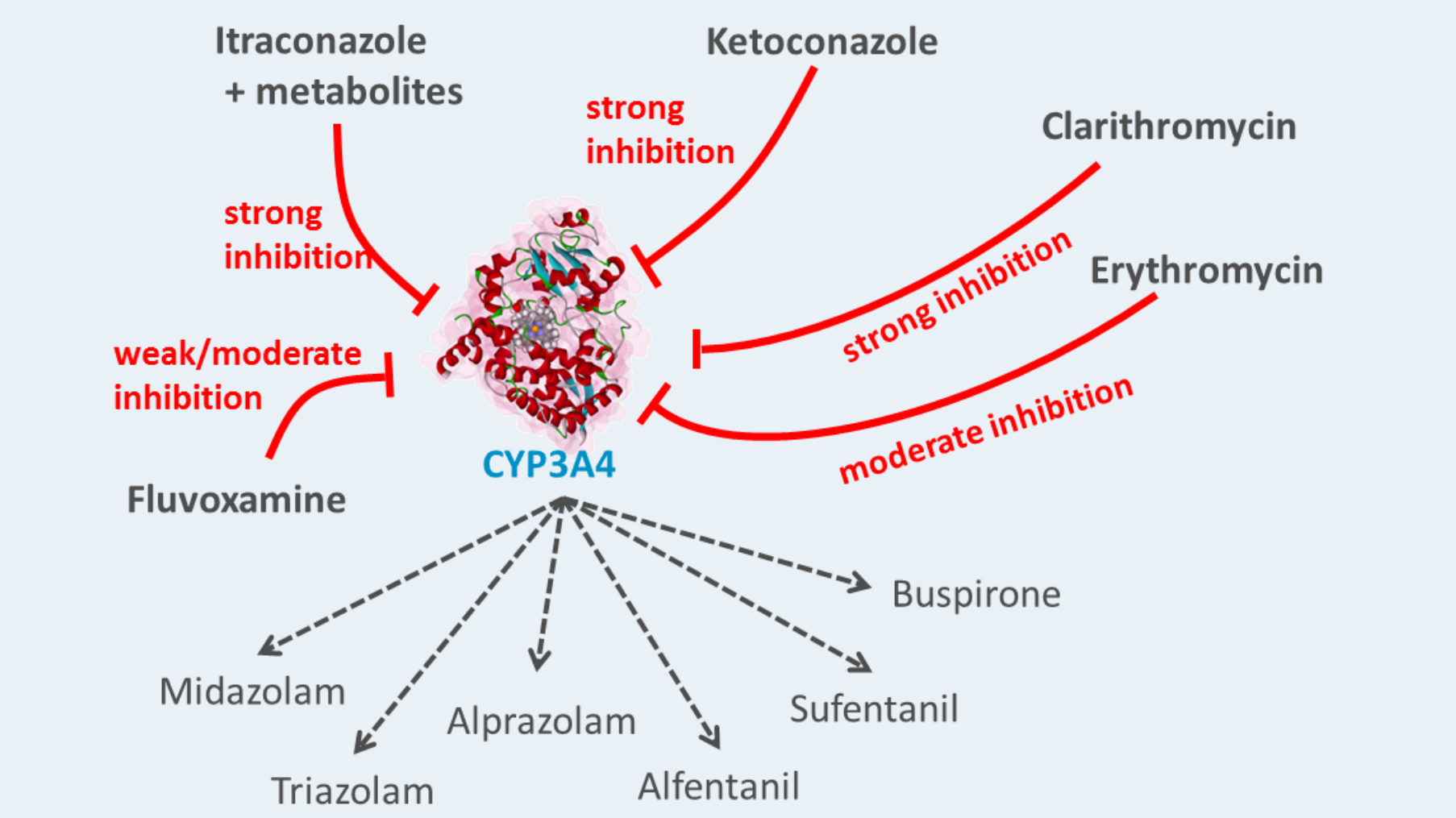


Figure 2: Example of a qualification scenario for CYP3A4 inhibition. This simulation scenario consists of multiple inhibitor and substrate models that need to be mutually evaluated to test the predictive performance with regard to quantitative DDI predictions.



Results

For a specific type of scenario, a software processable “Qualification Plan” is constructed semi-automatically. It consists of (see Figure 3, left):

1. a minimal amount of information required to setup all simulations for the intended type of scenario in the OSP Suite.
This includes the information on primary substance specific input parameters (e.g. molecular properties like molecular weight, lipophilicity, etc.) and required input for system parameters (e.g. demographic characteristics). Additionally, a list of differences between used model values and default values stored in the physiological and molecular OSP databases for the combination of inputs above is provided.
2. additional model building steps (e.g. instructions for incorporating a-posteriori knowledge via estimation of unknown parameters from clinical data) of the respective PBPK drug models involved in the particular scenario.
3. report settings (e.g. types of plots)

The execution of the “Qualification Plan” produces:

- I. A report on the evaluation of the individual PBPK drug models with experimental data sets (i.e. standard goodness-of-fit plots, visual predictive checks).
- II. A comprehensive qualification report for the type of scenario including a predefined set of qualification measures assessing predictive performance (e.g. root-mean-square deviation (RMSD), geometric mean fold error (GMFE), etc.) and charts (e.g. observed vs. predicted data for selected pharmacokinetic parameters - e.g. AUC ratio, Cmax ratio, etc.).

Figure 4 shows exemplary output of such a qualification report for a hypothetical scenario. Multiple qualification plans can be processed simultaneously via the **PK-Sim Command Line Interface (CLI)** (see Figure 3, right).



Example for the qualification scenario and execution of multiple qualification scenarios via PK-Sim Command Line Interface (CLI)

```
Version: 7.3.0
Individuals: [-]
Population: [-]
Name: "Healthy adult",
Seed: 2091875,
Settings: {
  NumberOfIndividuals: 100,
  ProportionOfMales: 50,
  Age: {
    Min: 20.0,
    Max: 60.0,
    Units: "years"
  },
  Individual: [-]
},
Compounds: {
  Name: "SuperDrug",
  PlasmaProteinBindingPartner: "Albumin",
  Lipophilicity: [-],
  FractionUnbound: [-],
  Solubility: [-],
  CalculationMethods: {
    "Cellular partition coefficient method - PK-Sim Standard",
    "Cellular permeability - PK-Sim Standard"
  },
  Parameters: [-]
},
Protocols: {
  Name: "Study",
  ApplicationType: "IntavenousBolus",
  DosingInterval: "Single",
  Parameters: [-]
},
Simulations: {
  Name: "S1",
  Model: "Comp",
  Solver: {
    Name: "LSODES",
    OutputInterval: [-],
    Population: "Healthy adult",
    Compounds: {
      Name: "SuperDrug",
      CalculationMethods: {
        "Cellular partition coefficient method - PK-Sim Standard",
        "Cellular permeability - PK-Sim Standard"
      },
      Parameters: {
        Name: "Study"
      }
    },
    HashResults: false
  },
  ParameterIdentification: {
    Name: "P1",
    Simulations: [-],
    Configuration: [-]
  },
  QualificationPlans: {
    name: "Q1",
    steps: {
      type: "ParameterIdentification",
      parameterIdentification: "P1",
      identifierParameterSimulation: "S1"
    },
    reports: {
      "VPC plot 1": [-]
    }
  }
}
```

```
C:\Temp\PK-Sim 7.3>PKSim.CLI.exe --help
PKSim 7.3.0.0 Beta
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run      Start batch run by loading a set of batch json files, running all simulations and exporting results
snap     Start snapshot workflows by loading a set of project (or snapshot) files and creating project files
export   Start project export by loading the given project file and export all or selected simulations
help     Display more information on a specific command.
version  Display version information.

C:\Temp\PK-Sim 7.3>PKSim.CLI.exe snap --help
PKSim 7.3.0.0 Beta
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USAGE:
Create snapshot file from project files:
PKSim.CLI snap --input <SnapshotFolder> --logLevel Information --output <ProjectFolder> --snapshot
Create project files from snapshot files using short notation:
PKSim.CLI snap -p --input <ProjectFolder> --logLevel Information --output <SnapshotFolder>
Create project files from snapshot files and only log errors:
PKSim.CLI snap --input <ProjectFolder> --logLevel Error --output <SnapshotFolder> --project

-i, --input      Required. Input folder containing all project or snapshot files to load.
-o, --output     Required. Output folder where project or snapshot files will be exported.
-p, --project    Create project files from snapshot files.
-s, --snapshot   Create snapshot files from project files.
-l, --log        Optional. Full path of log file where log output will be written. A log file will be created.
-a, --append     Optional. true to append data to the file; false to overwrite the file (default).
--logLevel      Optional. Log verbosity (Debug, Information, Warning, Error). Default is Information.
--help          Display this help screen.
--version       Display version information.

C:\Temp\PK-Sim 7.3>PKSim.CLI.exe snap -i C:\Temp\QualificationProjects\Input -o C:\Temp\QualificationProjects\Output
INFO: PK-Sim[0]
Starting snapshot run with arguments:
Input Folder: C:\Temp\QualificationProjects\Input
Output Folder: C:\Temp\QualificationProjects\Output
Log File:
Log Level: Information
```

Figure 3: Left: Qualification plan example
Right: Automated (batch) execution of different qualification scenarios

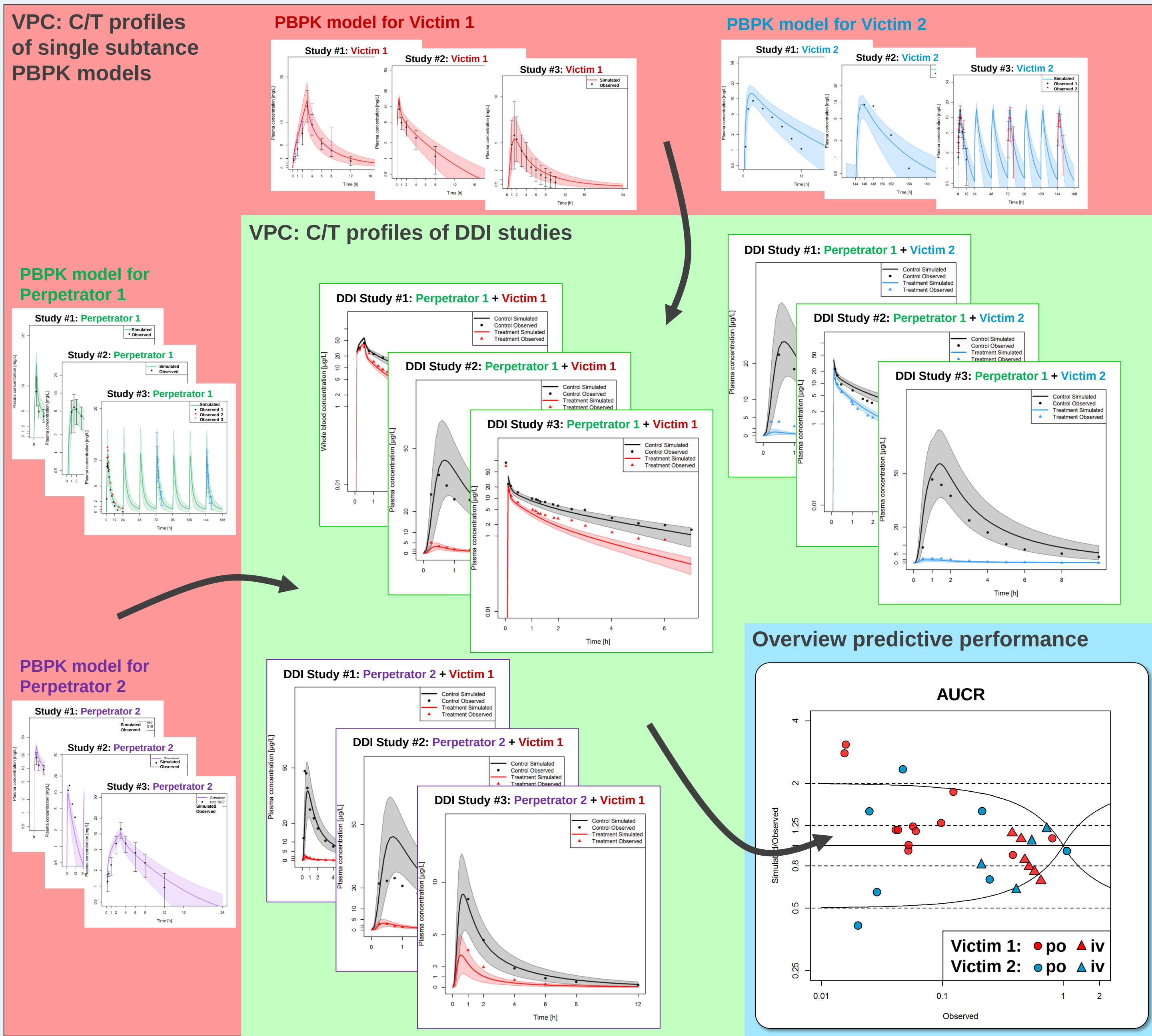


Figure 4: Exemplary potential extracts of a qualification report for a hypothetical qualification scenario with regard to induction of a metabolizing enzyme. **Red box:** visual predictive checks demonstrate the suitability of the individual substance models to describe the PK of the respective substances over different clinical studies. **Green box:** visual predictive checks demonstrate the suitability of the mutually coupled PBPK models to describe clinical DDI studies. **Blue box:** A comprehensive summary plot allows evaluation of the complete qualification scenario over all involved PBPK models.

Conclusions

A technical concept is presented to produce comprehensive (re-)qualification reports automatically. This enables an efficient assessment both for sponsors and regulatory bodies and thereby provides full traceability and transparency of all steps. (Re-)qualification reports can be generated and distributed for every new version of the Open Systems Pharmacology Suite.

References

- [1] European Medicines Agency. Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation (2016).
- [2] Open Systems Pharmacology Suite website and user manual at www.open-systems-pharmacology.org