Information Sharing and Automation of PK Calculations for Efficient Project Support
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Data storage alone is not sufficient
Access makes the difference

Efficiency – Relevance – Real-time – Integrity
Workflow in Drug Discovery

High quality data
Consistency & accessibility

Knowledge generation
Find patterns & relationships

Informed decisions
Right compound & target

For value generation efficient access to data is crucial

Efficient access
- Structured data storage
- Combination of different data sources
- Automation of workflows

Visual exploration
- Panel of exploratory tools
- Catalogue of pre-defined analysis
- Flexibility by interactive visualizations
- PKPD and statistical analysis

• Interpretation of results
• Clear documentation and communication

Talk

Replacements for manual workflows to enable exploratory analysis using Spotfire and Pipeline Pilot (Discengine)

Former Workflow for pharmacokinetic calculations
Compilation of in vivo and in vitro data

Manual collection from different sources:
- Internal databases with different user interfaces
- Excel sheets from assay owners
- Data management software
Filtering, Pivoting, and Calculations

- Manual input and updates in Excel files
  → Decrease in efficiency

- Different methods for calculations
  → Dependent on user different results might be reported

- Potential to do mistakes or do not use different methods

New PKPD Module in SpotAPP
Prototype enabling project-specific analyses and views

Visualizations with interactivity
Custom parameters
Concepts for the PKPD Module Design

Goal:
- Provide facilitated processing of PKPD data for DMPK experts and provide key visualizations for project teams

Key principles:
- Automation using a central R script
- Implementation of different calculation methods
  - Comparison and selection of most appropriate workflow
- Simple customization of script behavior per project

Intrinsic Liver Clearance from in vitro Hepatocytes

Results using different calculation methods

- **Intrinsic clearance [mL/min/kg]**: Measure for liver capacity to metabolize compound
- **In vitro/in vivo extrapolation IVIVE**: Confidence in clearance translation and dose estimate for human?
- **For calculation**: Parameter needed that corrects for binding effects in **in vitro incubation medium**

- **Houston method** Estimate unspecific binding
- **Assume no binding**

**SpotAPP**

**SpotAPP**
Interactive Database Information Link for SDPK Data on Animal Level

Storage and access of in vivo PK and PKPD data

For PKPD analysis pharmacokinetic (PK) and pharmacological data (PD) have to be combined and have to be easily accessible.
Concentration Time Profiles (PK) in Spotfire
Overview on available data

Result tables are loaded into predefined Spotfire templates.

Discngine/Pipeline Pilot

Concentration Time Profiles (PK) in Spotfire
Linear/nonlinear concentration-dose dependency
PKPD Data in Spotfire
Overview on available data

Enzyme inhibition by tested compound

Cross table for selections

Compound might have been tested in different experiments

PKPD Data in Spotfire
Pharmacological response per experiment
PKPD Data in Spotfire
Pharmacological response over plasma concentration

Easy switch to semi-log plots
Impact

**Tools for efficient data access using flexible and customizable solutions**

- Pipeline Pilot protocols can be implemented in Spotfire/Discngine and in other applications like SpotAPP

- Quick and informative overview on generated data with quality assessment (controls over time, extreme values)
- Easy evaluation of different calculation methods
- Consistent results due to same methods used for calculations and processing
- Time savings
  - Calculations and updates without manual input
  - Processed and formatted data for detailed data analysis
- Control of which data is exposed to project teams to avoid overloading

**Direct interaction with customers needed to ensure engagement !!**

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Graphical data exploration is the first step in data analysis

It enables to

- Comprehend information quickly
- Display information in a way that is meaningful
- Find relationships, patterns, and understand data
- Identify areas that need attention or improvement
- Clarify which factors influence experimental results

… without using more elaborate PKPD methods
We need …

- The combination of multiple data sources
- An automatic and up-to-date project data delivery
- The possibility for customized data processing (filtering, pivoting, calculations)
- Efficiency (spending less time preparing data)
- Evaluation of different calculation methods to identify most suitable for specific project

… to enable pharmacokinetic (PK) calculations
e.g. in vitro-in vivo extrapolation (IVIVE), early dose estimates

PK Calculations with Direct Access to PK Profiles in SpotAPP

- Implementation of PK calculations ready for all projects
- Scaling of in vitro hepatocyte/microsome clearance with IVIVE (different methods for estimation of fraction unbound in experiments)
- Estimation of human dose for best case scenario (100% absorption, hepatic clearance as main pathway, IVIVE established)
- Efficacy index Ei

- Interactive visualization of concentration-time profiles from database (database information link)
Example 1: In vivo Concentration-Time Profiles (PK)

Goals

- **Overview** on generated data (compounds, conditions)
- Download and processing for interactive, exploratory analysis (dose normalizations, harmonization of units)
  - Quality of measured data
  - Identification of compounds with linear/nonlinear PK properties
  - Inter-individual variability for concentrations measured in different animals
- Formatting for further PK analysis in additional software packages
  - Time saving and reduction of copy/paste errors

**Customers:** DMPK experts, project teams

Example 2: In vivo PKPD project data

Goals

- **Overview** on generated data (compounds, conditions, dose, time points)
- Download and processing for interactive, exploratory analysis (normalizations, mean and variability within dose groups)
  - PD effect over time, plasma and brain concentrations
  - Brain/plasma distribution
  - Identification of animals with extreme values
  - Quality control for reproducibility of negative and positive controls
- Formatting for further PKPD analysis in additional software packages
  - Time saving and reduction of copy/paste errors

**Customers:** Project teams, M&S scientists
Doing now what patients need next