HTPK Simulations Using the New REST API

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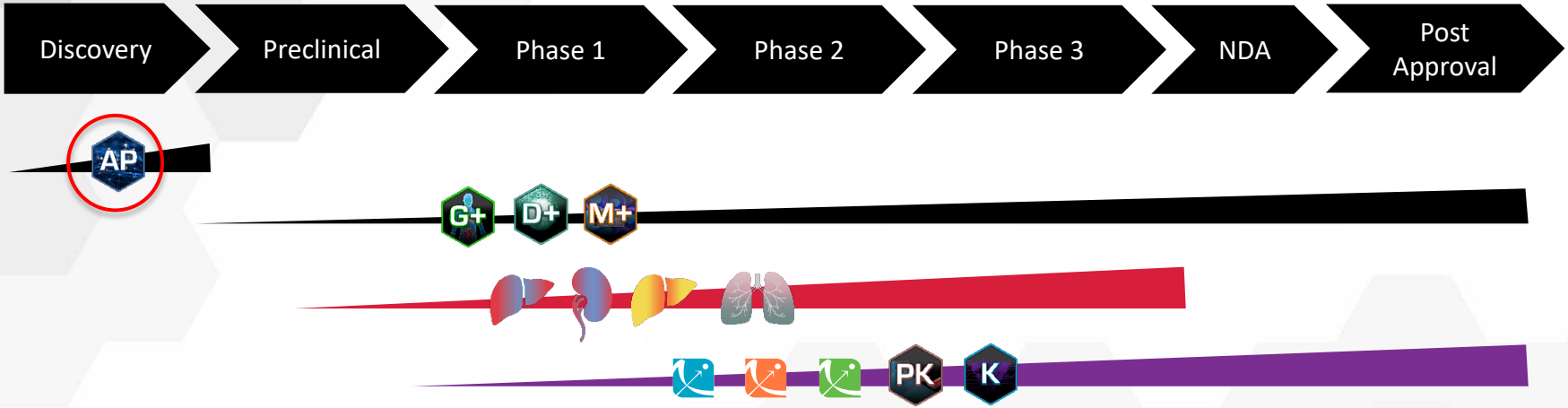
Please note: this presentation, including questions from the audience, is being recorded and may be made available.

ADMET Predictor



Property Prediction
Physicochemical
Metabolism
Transporters
Toxicity
ADMET Risk

Model Building
Molecular+atomic descriptors
Regression, classification
Uncertainty, confidence

Cheminformatics
Scaffold clustering
R group analysis
Matched pairs

Design
Discover virtual compounds with optimal property profiles

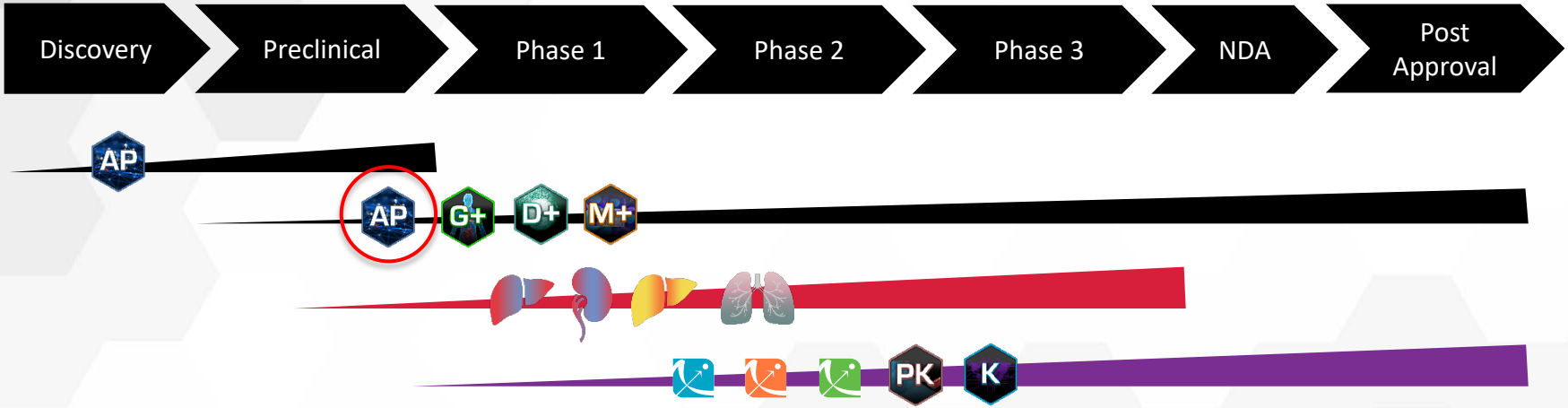
MIDD+22
Model Informed Drug Development +

SimulationsPlus
Cognigen DILIsym Services Lixoft

High Throughput Pharmacokinetics: Vision

- Develop a simplified tool for non DMPK experts
- Provide reasonable estimates of important pharmacokinetic parameters at the discovery stage
- Avoid the need to input experimental values
- Identify potential development issues as early as possible, even before compounds are synthesized
- Allow fast processing of thousands of compounds

ADMET Predictor: HTPK Module



PBPK Simulations

%Fa, %Fb

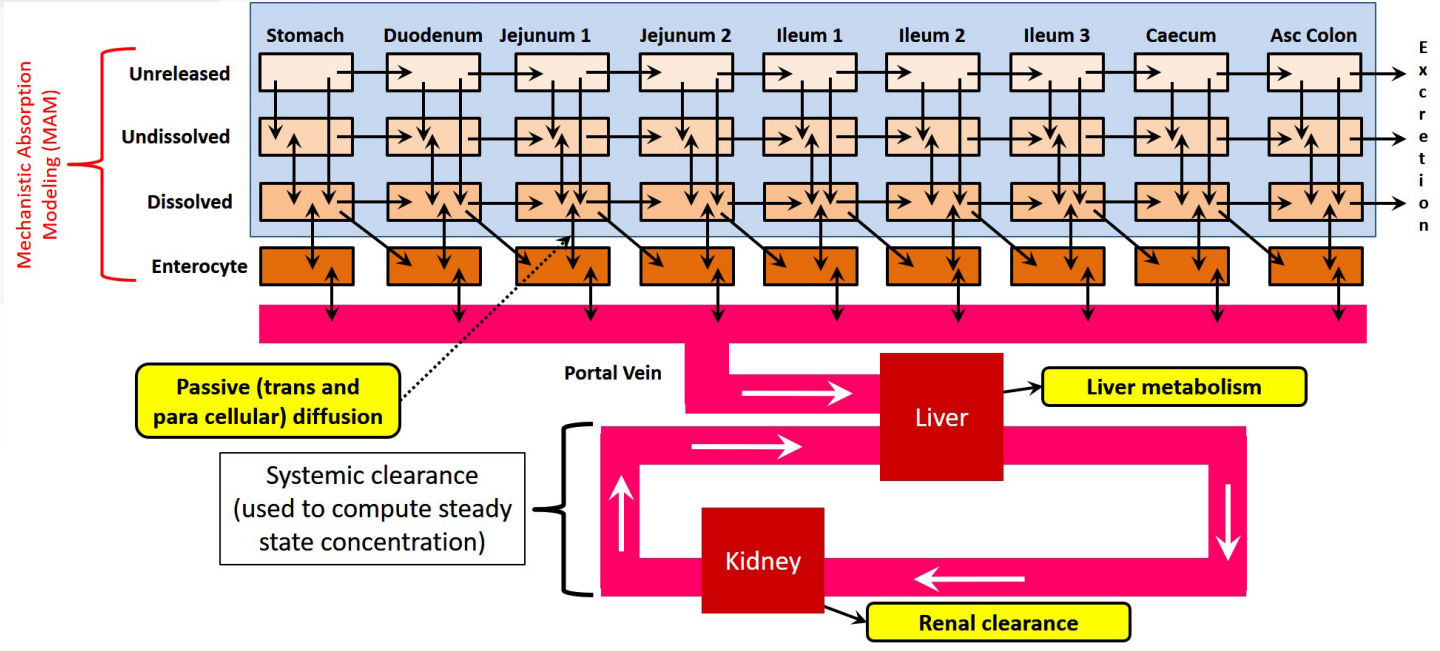
Cmax, Tmax, AUC, CL, $T_{1/2}$

Cp-time curves

Optimal dose

PBPK Simulation Methodology

ACAT™ Model* + Compartmental Model



* Advanced Compartmental Absorption and Transit Model

HTPK Input Parameters

Requires input parameters such as compound solubility and intrinsic clearance

- Default parameters are loaded from **HIA files** in ADMET Predictor installation folder

Portion of a default HIA file:

<RefSolubility>**S+Sw|S+Sw**</RefSolubility>
<RefClearance>**CYP_HLM_CLint|CYP_HLM_CLint**</RefClearance>

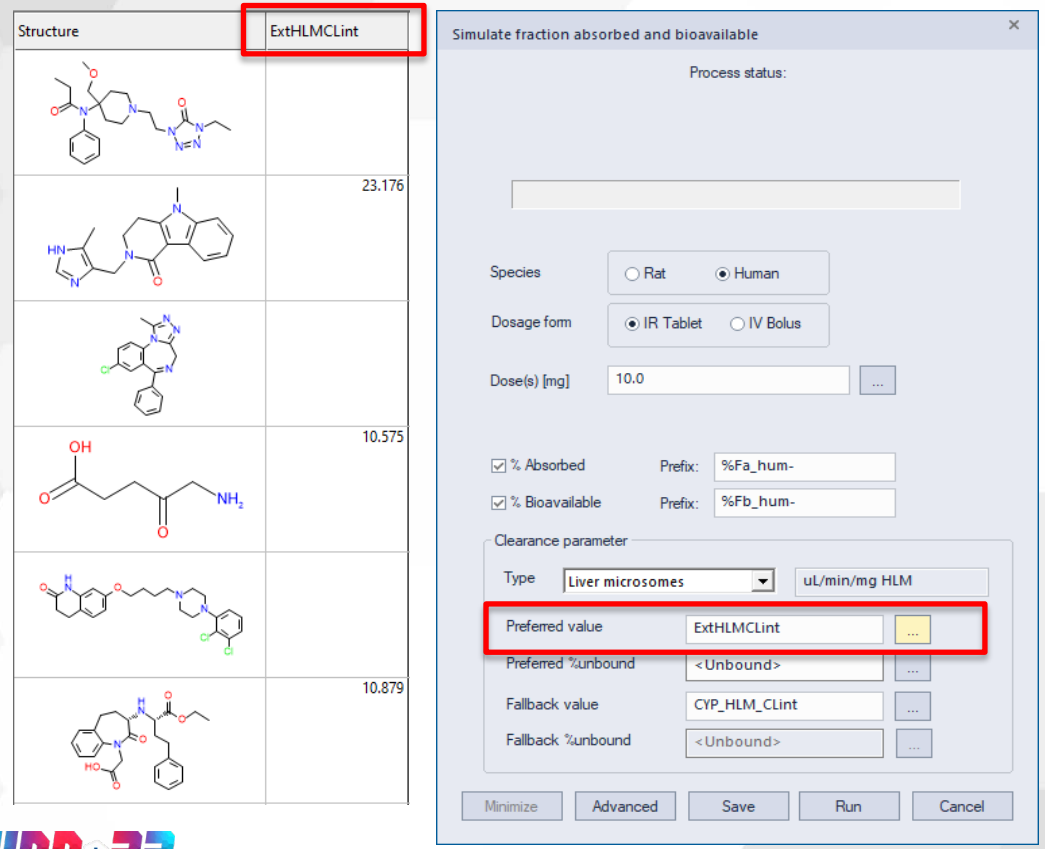
- Use ADMET Predictor's built-in models to predict solubility and clearance

Portion of a modified HIA file:

<RefSolubility>**ExtSolub|S+Sw**</RefSolubility>
<RefClearance>**ExtHLMCLint|CYP_HLM_CLint**</RefClearance>

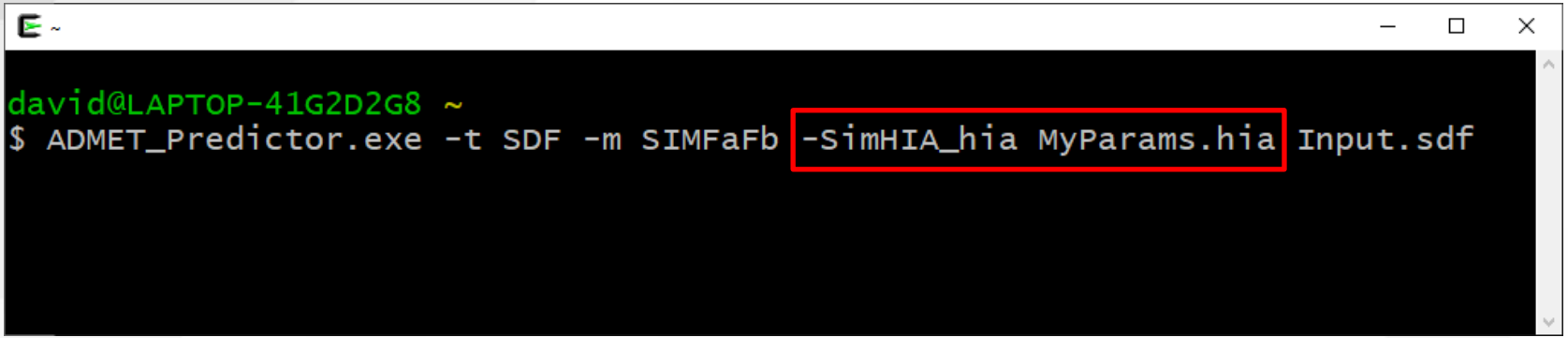
- Use values called **ExtSolub** and **ExtHLMCLint** if present for a particular compound, and otherwise use the ADMET Predictor models
- ExtSolub and ExtHLMCLint could be experimental values or model predictions

HTPK Using Graphical Interface



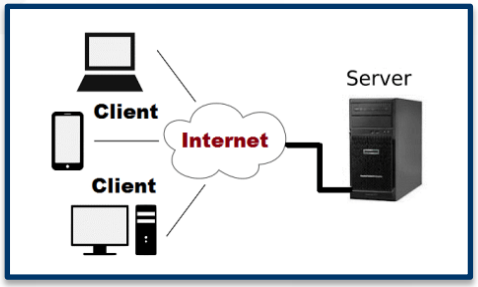
- When using the GUI, input parameters are modified using an options window
- Any numeric spreadsheet column can be selected as an input parameter
- The default HIA files do not need to be modified, although doing so prevents having to change parameters repeatedly in the GUI

HTPK Using Command Line



- When using the command line, input parameters **must** be specified in the HIA files, which are loaded when ADMET Predictor is run
- Users can either modify the default HIA files or specify custom files on the command line (above)

HTPK Using REST API



- ADMET Predictor runs as a service on a remote server
- Clients request predictions using JSON-formatted HTTP messages
- API facilitates use of ADMET Predictor by any third-party software, and prevents having to install ADMET Predictor on multiple client machines
- Model loading and other time-consuming initializations occur only once, when the service starts up, so predictions are faster than with command line
- Licenses are retained by the service and jobs run serially, so prediction requests are never blocked due to license unavailability

HTPK API Requests

```
POST /predict_fafb HTTP/1.1
Host: 192.168.1.26

{
    "compounds" : [
        {
            "id" : "ACAMPROSATE",
            "mol" : "C(=O)(NCCCS(=O)(=O)O)C",
            "ExtHLMCLint" : "4.14785661",
            "ExtSolub" : "445.72407685"
        }
    ],
    "parameters" : {
        "RefSolubility" : "ExtSolub|S+Sw",
        "RefClearance" : "ExtHLMCLint|CYP_HLM_CLint",
        "molformat" : "smiles",
        "species" : "human"
    },
    "properties" : [
        "%Fa",
        "%Fb",
        "Cmax",
        "Tmax",
        "AUC"
    ]
}
```

- Service reads default HIA files on startup, and parameters are reinitialized to defaults at the start of each new job
- Custom parameters are specified in the HTTP request body (figure at left)
- Only parameters that differ from defaults need to be specified
- Missing values are allowed, as with the GUI and command line

HTPK API Responses

```
HTTP/1.1 200 OK

{
    "status" : "complete",
    "jobid" : 1,
    "results" : {
        "ACAMPROSATE" : {
            "%Fa" : {
                "value" : "92.360000"
            },
            "%Fb" : {
                "value" : "79.750000"
            },
            "Cmax" : {
                "value" : "171.040000"
            },
            "Tmax" : {
                "value" : "1.480000"
            },
            "AUC" : {
                "value" : "525.770000"
            }
        }
    }
}
```

- The HTTP response contains predicted values and any error messages

Cp-Time Curves Using API

```
POST /predict_fafb HTTP/1.1
Host: 192.168.1.26

{
    "compounds" : [
        {
            "id" : "ACAMPROSATE",
            "mol" : "C(=O)(NCCCS(=O)(=O)O)C",
            "ExtHLMCLint" : "4.14785661",
            "ExtSolub" : "445.72407685"
        }
    ],
    "parameters" : {
        "RefSolubility" : "ExtSolub|S+Sw",
        "RefClearance" : "ExtHLMCLint|CYP_HLM_CLint",
        "molformat" : "smiles",
        "species" : "human",
        "cptime"  : "0.2"
    },
    "properties" : [
        "%Fa",
        "%Fb"
    ]
}
```

20% sampling

- In upcoming APX.4, estimated Cp-time curves can be collected during simulations
- Multiple compounds can be processed simultaneously
- Collected time points and concentrations can be sampled to reduce network bandwidth

Cp-Time Curves Using API

```
HTTP/1.1 200 OK

{
    "status" : "complete",
    "jobid" : 1,
    "results" : {
        "ACAMPROSATE" : {
            "%Fa" : {
                "value" : "92.360000"
            },
            "%Fb" : {
                "value" : "79.750000"
            }
        }
    }
    "cptime" : {
        "ACAMPROSATE" : "Time [h]\tCp [ng/mL]\n0.00000000\t0.00000000\n..."
        }
}
```

- Cp-time data are provided in the HTTP response

HTPK Using REST API

Software Demonstration

SimulationsPlus

MIDD+22

Model Informed Drug Development

Q&A

Questions & Answers