Tutorial on IQM Tools Pro

General Dataset Specification and PMX Workflows

Integrated Solutions for Quantitative Drug Development
From Mechanistic Models to Complex Trial Simulation

Henning Schmidt, IntiQuan GmbH

Tutorial Outline

- General introduction to the IQM Tools Suite
- General introduction PMX Workflow Approaches
- General Dataset Specification
- Hands on PopPK Workflow Example (classroom possible)
- Hands on PopPK+PD Workflow Example (self study only)

henning.schmidt@intiquan.com

Tutorial Info

In large parts you will have the opportunity to get hands-on-experience

```
>> installIQMtoolsInitial
```

Commands shown in these boxes should be entered on the MATLAB command line, during the tutorial

```
********** MODEL NAME
Simple model
********** MODEL STATES
d/dt(Ad)= -ka*Ad + INPUT1
d/dt(Ac)=  ka*Ad – CL/Vc*Ac
********** MODEL PARAMETERS
ka = 0.2
CL = 0.3
Vc = 6
********** MODEL VARIABLES
Cc = Ac/Vc
```

Text shown in these boxes should be entered where appropriate (will become clear later)

henning.schmidt@intiquan.com

Tutorial Goal: „You should be able to“

- Understand the idea and power of PMX Workflow approaches
- Specify a general dataset format for your own projects
- Perform a PopPK using the IQM Tool PopPK Workflow
- Perform a PopPKPD using IQM Tools

Tutorial Outline

- **General introduction to the IQM Tools Suite**
- General introduction PMX Workflow Approaches
- General Dataset Specification
- Hands on PopPK Workflow Example (classroom possible)
- Hands on PopPK+PD Workflow Example (self study only)

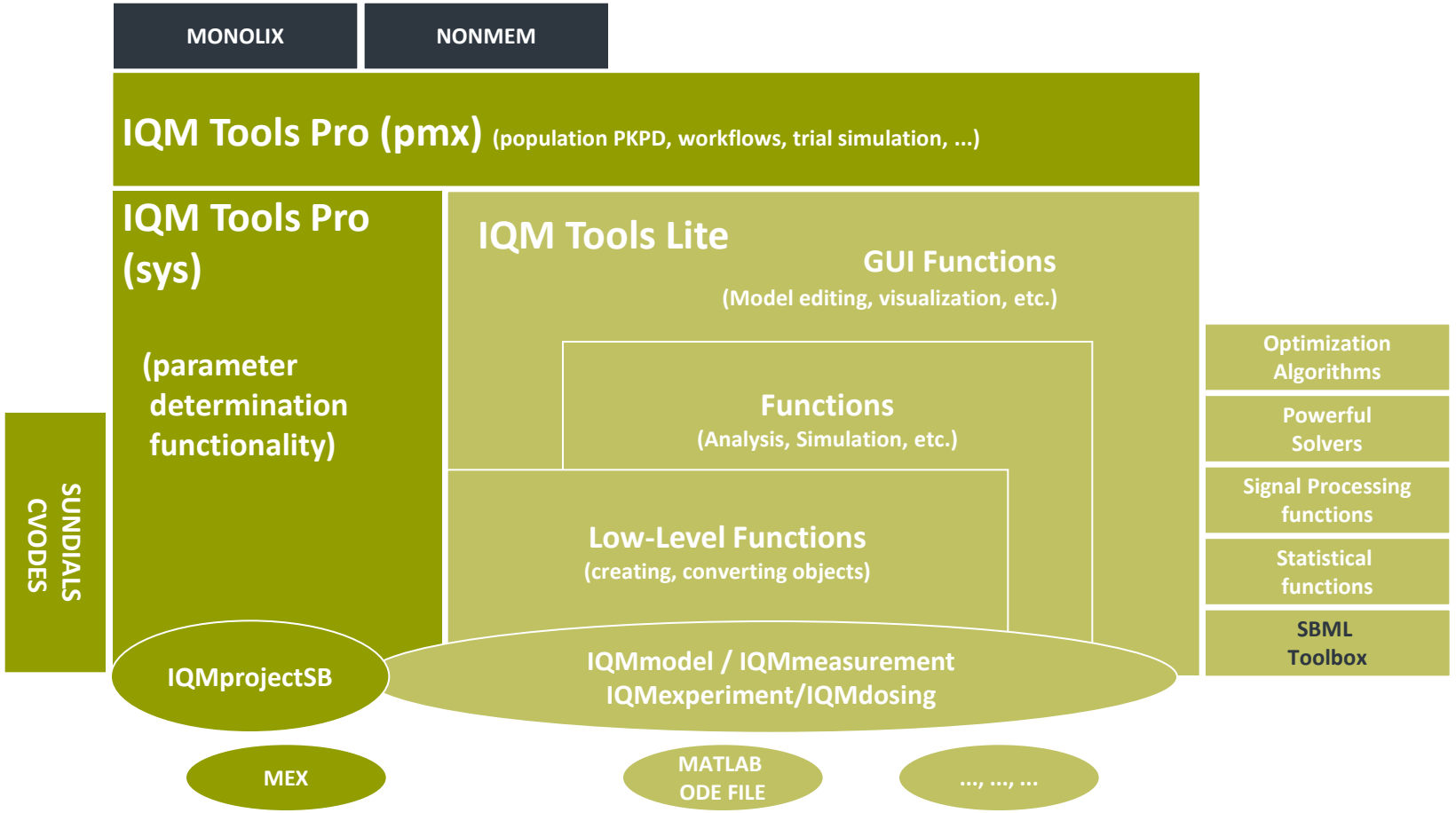
Introduction to the "IQM Tools Suite"

- The IQM Tools Suite is provided freely and as open source
- The IQM Tools Suite consists of two main packages
  - IQM Tools Lite
  - IQM Tools Pro
- The whole is based on MATLAB (www.mathworks.com)

IQM Tools Lite	Model, experiment, measurement & dosing representation, simulation, analysis functions, optimization, signal processing, statistical functions, etc.
IQM Tools Pro	Systems biology/pharmacology and PMX functionality, clinical data analysis, nonlinear mixed effect modeling, clinical trial simulations, high speed simulation through transparent C-code interface

henning.schmidt@intiquan.com

Modular Design of the IQM Tools Suite



henning.schmidt@intiquan.com

IntiQuan

Requirements

- **MATLAB R2013b (or later)**
  - Optional but very useful: Parallel Toolbox to allow for better runtimes of the examples

- **Required 3rd party software**
  - Monolix Version 4.2.3 (or later) (http://www.lixoft.org)
  - NONMEM Version 7.2 (or later) (http://www.iconplc.com)

  - The tutorial uses both. If only one of them is installed, then this is fine, but the tutorial scripts might need to be changed accordingly – and if MONOLIX was used on purpose due to numerical issues with NONMEM – then using NONMEM might not produce the adequate result.

Where to get IQM Tool Suite from?

- Free download of IQM Tools Suite available from the IntiQuan webpage

- The IQM Tools Suite is distributed as a ZIP file with both IQM Tools Lite and IQM Tools Pro included

- Unzip this ZIP file on your computer at a location where you want to store the IQM Tools

How to Install the IQM Tool Suite?

- Start MATLAB
- Change into the “IQM Tools Suite” folder
- Read and update custom information in setup files:
  - IQMlite/SETUP_PATHS_TOOLS_IQMLITE.m
  - IQMpro/SETUP_PATHS_TOOLS_IQMPRO.m
- Execute the “installIQMtoolsInitial” script

You need to execute the “**installIQMtoolsInitial**” script once after obtaining a copy of IQM Tools. This will compile required libraries.

After this first installation, you can use the function “**installIQMtools**” to install IQM tools. This needs to be done each time you exit and start MATLAB again. This is on purpose for compliance and reproducibility reasons.

If you do not care about compliance, you might want to consider the use of a startup.m script (see http://www.mathworks.com/help/matlab/ref/startup.html).

Installation of optional 3rd party software

- Please follow the providers instructions when installing optional 3rd party software.

- Update the **IQMpro/SETUP_PATHS_TOOLS_IQMPRO.m** file with the relevant information, as shown below for an example implementation

```
% NONMEM (currently tested version: 7.2)
PATH_SYSTEM_NONMEM_WINDOWS                  = 'nmfe73';
PATH_SYSTEM_NONMEM_UNIX                     = 'nmfe72';

% NONMEM PARALLEL
PATH_SYSTEM_NONMEM_PARALLEL_WINDOWS         = '';
PATH_SYSTEM_NONMEM_PARALLEL_UNIX            = 'nmfe72par';

% MONOLIX STANDALONE (version >= 4.3.2)
PATH_SYSTEM_MONOLIX_WINDOWS                 = 'C:\LOCAL\Monolix\Monolix432s\bin\Monolix.bat';
PATH_SYSTEM_MONOLIX_UNIX                    = '/CHBS/apps/dev_apps/Monolix/4.3.2/Standalone/Monolix432grid-Matlab2008/bin/Monolix.sh';

% MONOLIX STANDALONE PARALLEL (version >= 4.3.2)
PATH_SYSTEM_MONOLIX_PARALLEL_WINDOWS        = '';
PATH_SYSTEM_MONOLIX_PARALLEL_UNIX           = '';
```

IQM Tools' Documentation

- **MATLAB style help**

```
>> help IQMlite
>> help IQMpro

>> help IQMsimulate
>> help IQMexportCSVdataset

>> doc IQMlite
>> doc IQMsimulate
```

- IQM Tools Tutorials with examples
  - Part 1: IQM Tools Lite (General Model Specification, Simulation, etc.)
  - Part 2: IQM Tools Pro (MEX / Systems Biology/Pharmacology Projects)
  - Part 3: IQM Tools Pro (Basic Pharmacometrics)
  - **Part 4: IQM Tools Pro (General Dataset Specification and PMX Workflows)**
  - Part 5: IQM Tools Pro (Advanced Clinical Trial Simulations)
  - Part 6: IQM Tools Pro (Linking Systems Pharmacology Models to Clinical Data)

- IQM Tools – Workshops
  - Given on demand and on some conferences during a year

henning.schmidt@intiquan.com

Tutorial Outline

- General introduction to the IQM Tools Suite
- **General introduction PMX Workflow Approaches**
- General Dataset Specification
- Hands on PopPK Workflow Example (classroom possible)
- Hands on PopPK+PD Workflow Example (self study only)

Workflow

- *„A **workflow** consists of an **orchestrated** and **repeatable pattern** of business activity enabled by the **systematic organization of resources into processes** that transform materials, provide services, or **process information**. It can be depicted as a **sequence of operations**, declared as work of a person or group, an organization of staff, or one or more simple or complex mechanisms.”*

https://en.wikipedia.org/wiki/Workflow

Applicable to Pharmacometric modeling?

henning.schmidt@intiquan.com

Discussion and application of a workflow approach to Population PK modeling

J Pharmacokinet Pharmacodyn
DOI 10.1007/s10928-014-9370-4

ORIGINAL PAPER

Enhancing population pharmacokinetic modeling efficiency and quality using an integrated workflow

Henning Schmidt · Andrijana Radivojevic

http://web.intiquan.com/Material/PopPK_Workflow/schmidt_radivojevic_2014.pdf

Fully Documented Example for a PopPK Workflow Performed with SBPOP – Supplementary to the paper

Supplementary Material

http://web.intiquan.com/Material/PopPK_Workflow/index.html

Article

- Enhancing population pharmacokinetic modeling efficiency and quality using an integrated workflow

Journal

- Journal of Pharmacokinetics and Pharmacodynamics

Authors

- Henning Schmidt, Novartis Pharma AG, Basel, Switzerland
- Andrijana Radivojevic, Novartis Pharma AG, Basel, Switzerland

Information

The supplementary material is made available as a ZIP file organized as:

- **Supplementary Material.html**: HTML (this) page that documents the popPK model building process, using an integrated workflow and associated workflow tools, as discussed in the paper. This document should be opened in a web-browser. All results for the popPK example have already been generated and are available through the HTML page by clicking on embedded links.
- **PopPK Example**: Folder containing the scripts/models/output/data for the complete popPK example. The main script file (SCRIPT_01_popPK.m), which performs the whole popPK is at the same time the source for the HTML page.
- **Original Data**: Folder containing the simulated data that is used in this example and information on the individual subjects' PK parameters that were used in the simulation. At the end of this example, original data will be used for comparison with model predictions.

Enhancing population pharmacokinetic modeling efficiency and quality using an integrated workflow, Journal of Pharmacokinetics and Pharmacodynamics, doi:10.1007/s10928-014-9370-4, 2014.

henning.schmidt@intiquan.com

IntiQuan

What does a Workflow Approach bring?

- Structure
- Systematic analysis
- Consistent quality across an organization
- Less inter-modeler variability and thus in average higher quality

- Workflow approaches are applicable on small scale
  - General dataset specification => Data Checking, Data Exploration, Data Conversion
  - NLME model generation, run, creation of typical GoF plots and tables
  - Etc.
- Workflow approaches are applicable on larger scale
  - Generation of a model subspace of interest
  - Running all these models (including creation of GoF plots, etc.)

Data => Generalized standard dataset format

- **Imagine** you could represent all the clinically relevant data in a humanly understandable and reusable (for many different purposes) form

USUBJID	COMPOUND	STUDY_DESCRIPTION	CENTER	SUBJECT	INDICATION_NAME	TRT_NAME	VISIT	VISIT_NAME	BASE	SCREEN	DATE_DAY	DATE_TIME	DURATION	NOMINAL_TIME	TIME	TIME_UNIT	TYPE_NAME	NAME	VALUE	VALUE_TEXT	UNIT	LLOQ
Theo_1	Theophylline	Old Theophylline data	1	1	Healthy Volunteers	400mg Single Dose	1	Visit 1	1	1	01-01-1970	00:00	0	0	0	Hours	Demographics	Gender	1	Male		
Theo_1	Theophylline	Old Theophylline data	1	1	Healthy Volunteers	400mg Single Dose	1	Visit 1	1	1	01-01-1970	00:00	0	0	0	Hours	Body	Weight	79.6		kg	
Theo_1	Theophylline	Old Theophylline data	1	1	Healthy Volunteers	400mg Single Dose	1	Visit 1	0	0	01-01-1970	00:00	0	0	0	Hours	DOSE	Theophylline Dose	400		mg	
Theo_1	Theophylline	Old Theophylline data	1	1	Healthy Volunteers	400mg Single Dose	2	Visit 2	0	0	01-01-1970	00:00	0	0.25	0.25	Hours	PK	Theophylline Concentration	2.84		ug/ml	
Theo_1	Theophylline	Old Theophylline data	1	1	Healthy Volunteers	400mg Single Dose	3	Visit 3	0	0	01-01-1970	00:00	0	0.57	0.57	Hours	PK	Theophylline Concentration	6.57		ug/ml	
Theo_1	Theophylline	Old Theophylline data	1	1	Healthy Volunteers	400mg Single Dose	4	Visit 4	0	0	01-01-1970	00:00	0	1	1.12	Hours	PK	Theophylline Concentration	10.5		ug/ml	
Theo_1	Theophylline	Old Theophylline data	1	1	Healthy Volunteers	400mg Single Dose	5	Visit 5	0	0	01-01-1970	00:00	0	2	2.02	Hours	PK	Theophylline Concentration	9.66		ug/ml	
Theo_1	Theophylline	Old Theophylline data	1	1	Healthy Volunteers	400mg Single Dose	6	Visit 6	0	0	01-01-1970	00:00	0	3.75	3.82	Hours	PK	Theophylline Concentration	8.58		ug/ml	
Theo_1	Theophylline	Old Theophylline data	1	1	Healthy Volunteers	400mg Single Dose	7	Visit 7	0	0	01-01-1970	00:00	0	5	5.1	Hours	PK	Theophylline Concentration	8.36		ug/ml	
Theo_1	Theophylline	Old Theophylline data	1	1	Healthy Volunteers	400mg Single Dose	8	Visit 8	0	0	01-01-1970	00:00	0	7	7.03	Hours	PK	Theophylline Concentration	7.47		ug/ml	

Self explaining content, informative, useful

ID	TIME	AMT	Y	CENS	wt	sex
1	0	15.07	.	.	60.3	1
1	0.5	.	15.2	0	60.3	1
1	3	.	19.3	0	60.3	1
1	6	.	15.3	0	60.3	1
1	8	.	16.4	0	60.3	1
1	12	.	7.7	0	60.3	1
1	18	.	5	1	60.3	1
1	24	.	5	1	60.3	1
2	0	20.39	.	.	81.6	1
2	0.5	.	8.85	0	81.6	1
2	3	.	20.5	0	81.6	1

???

But typical PMX dataset

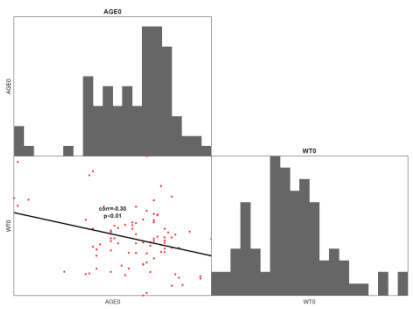
- That is independent of a single person
- That is independent of a single analysis
- That does not require cumbersome manual reformatting

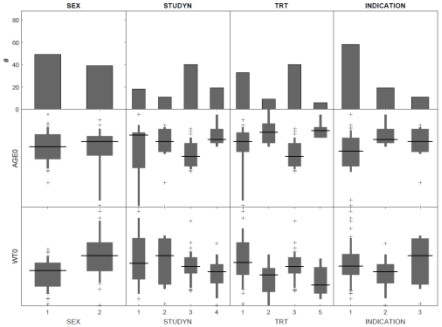
henning.schmidt@intiquan.com

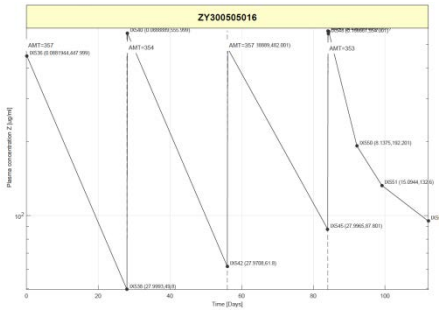
IntiQuan

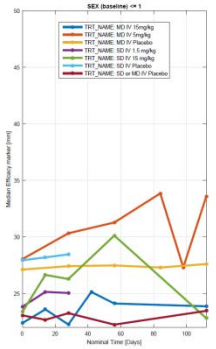
Data Exploration

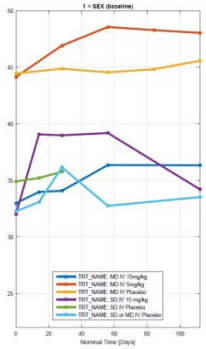
- **Imagine** you could quickly explore your PK and PD data by generation of the typical plots that everyone always would like to see (but might forget about it)











- **Imagine** axes labels would already have the correct names and units
- **Imagine** you could prepare tables that need to be shown in all modeling reports, just from the general dataset format

Study	Study Description	Treatment Groups	N subjects	N Active Doses (Dose Z)	N Observations (Efficacy marker)	Nominal Time Observ
Y1	FIH HV Study (Healthy volunteers)	SD IV 1.5 mg/kg	6	iv (min/median/max: 1/1/1)	min/median/max: 3/3/3	0,14,28
		SD IV 15 mg/kg	12	iv (min/median/max: 1/1/1)	min/median/max: 0/1.5/3	0,14,28
		SD IV Placebo	6	No active doses	min/median/max: 0/3/3	0,14,28
Y10	PoC Study Indication 2 (Indication 2)	SD IV 15 mg/kg	14	iv (min/median/max: 0/1/1)	min/median/max: 1/2/2	0,112
Y3	Profiling Study 1 (Healthy volunteers)	MD IV 5mg/kg	47	iv (min/median/max: 1/4/4)	min/median/max: 1/5/5	0,28,56,84,98,112
		MD IV Placebo	45	No active doses	min/median/max: 2/5/5	0,28,56,84,112
Y8	PoC Study Indication 1 (Indication 1)	MD IV 15mg/kg	9	iv (min/median/max: 2/2/2)	min/median/max: 3/5/5	0,14,28,42,56,112
		SD IV 15 mg/kg	10	iv (min/median/max: 1/1/1)	min/median/max: 1/4/5	0,14,28,56,112
		SD or MD IV Placebo	21	No active doses	min/median/max: 1/5/5	0,14,28,56,112

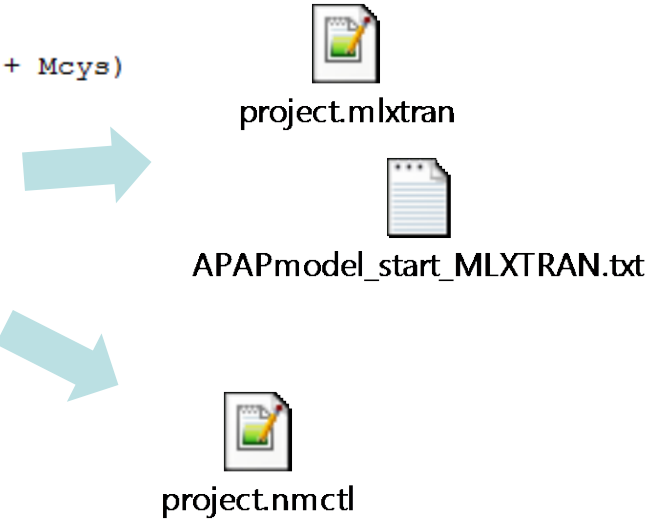
henning.schmidt@intiquan.com

IntiQuan

General (population) modeling

- **Imagine** you could simply convert your desired mathematical model into the NLME software of your choice

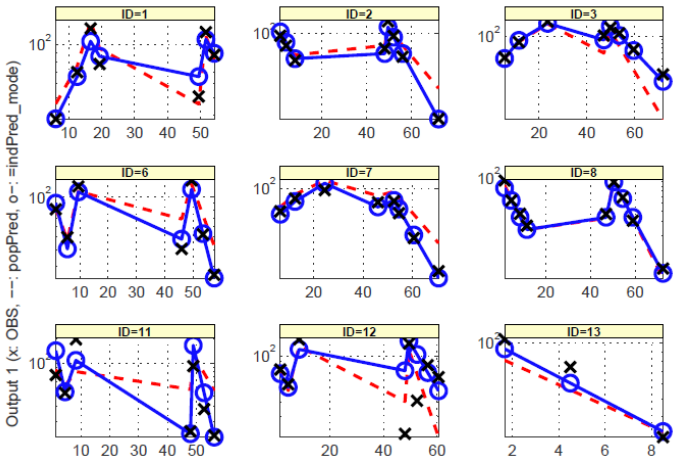
```
d/dt(Ap)        = INPUT1 - Ap/Vp*(CLp + Mgluc + Msulf + Mnac + Mcys)
d/dt(Apgluc)    = Mgluc/Vp*Ap - CLpgluc/Vpgluc*Apgluc
d/dt(Apsulf)    = Msulf/Vp*Ap - CLpsulf/Vpsulf*Apsulf
d/dt(Apnac)     = Mnac/Vp*Ap  - CLpnac/Vpnac*Apnac
d/dt(Apcys)     = Mcys/Vp*Ap  - CLpcys/Vpcys*Apcys
```

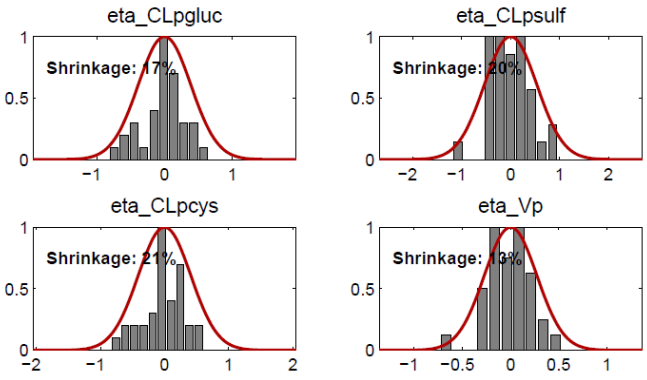


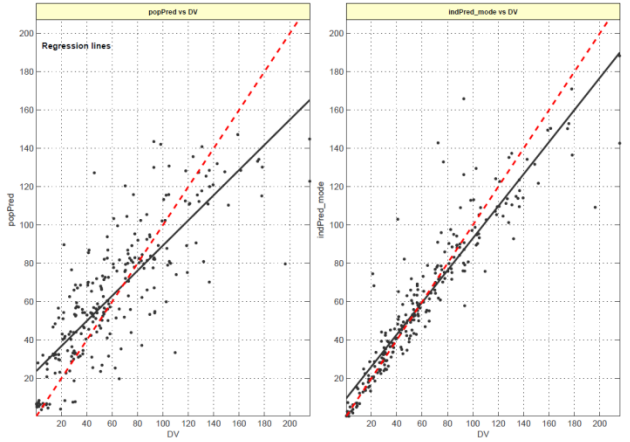
- **Imagine** you could automatically prepare your NLME modeling dataset from the standard dataset and use this across different NLME modeling tools (NONMEM and MONOLIX)

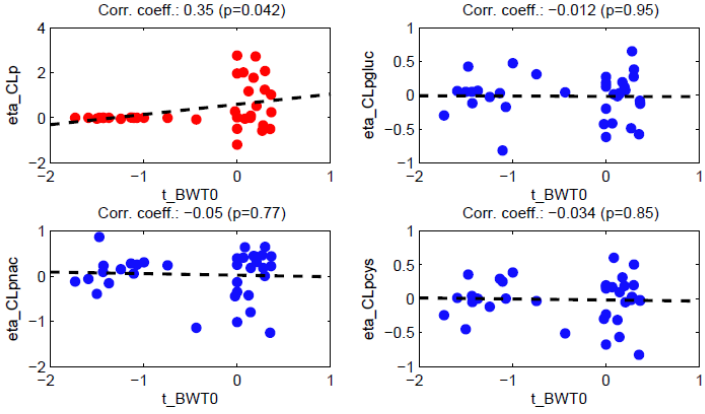
General (population) modeling

- **Imagine** each run of a model would immediately also produce the standard goodness of fit assessments, enabling you to quickly assess the model









henning.schmidt@intiquan.com

IntiQuan

General (population) modeling

- **Imagine** the output of NONMEM would be transformed to something that is humanly readable and contains the same information as the MONOLIX output

```
================================================================================
    Summary results
    Project: MODEL_01
================================================================================

--------------------------------------------------------------------------------
Termination information (Method(s): SAEM,IMP)
--------------------------------------------------------------------------------
    STOCHASTIC PORTION NOT COMPLETED
    REDUCED STOCHASTIC PORTION COMPLETED

    OPTIMIZATION NOT COMPLETED

--------------------------------------------------------------------------------
Name                              Value          stderr         RSE (%)
--------------------------------------------------------------------------------
CLp                             0.06733          0.1775*          263.6*
Vp                                2.634          0.9709*          36.86*
Mgluc                           0.04044         0.01986*          49.12*
                                      (*approximation by sampling)

omega(CLp)                        0.795          0.1686           21.2
omega(Vp)                        0.3028         0.03458          11.42
omega(Mgluc)                     0.4875         0.07423          15.23

error_ADD1                        1.969           1.334          67.76
error_PROP1                      0.2173          0.0239             11

--------------------------------------------------------------------------------
Objective function (IMP)
--------------------------------------------------------------------------------
OFV:    5891.45
AIC:    5971.45
BIC:    6186.46
```

Imagine you could just focus on the right model, rather than on cumbersome data and tool issues ...

henning.schmidt@intiquan.com

General clinical trial simulation

- **Imagine** you would not need to recode your model in Berkeley Madonna or other software for simulation

```
model      = IQMmodel('model.txt');
dosing     = IQMcreateDOSING('INFUSION',DOSE,DOSINGTIMES,INFUSION_TIME);
results    = IQMsimdosing(model,dosing,SIMULATION_TIME);
```

- **Imagine** you would NOT need to create cumbersome datasets for simulation
- **Imagine** you could sample population parameters and/or individual parameters (with or without covariate effects) directly from MONOLIX and NONMEM projects

```
parameters  = IQMsampleNLMEfitParam(NLMEproject,TYPE,NSAMPLES,COVARIATES);
```

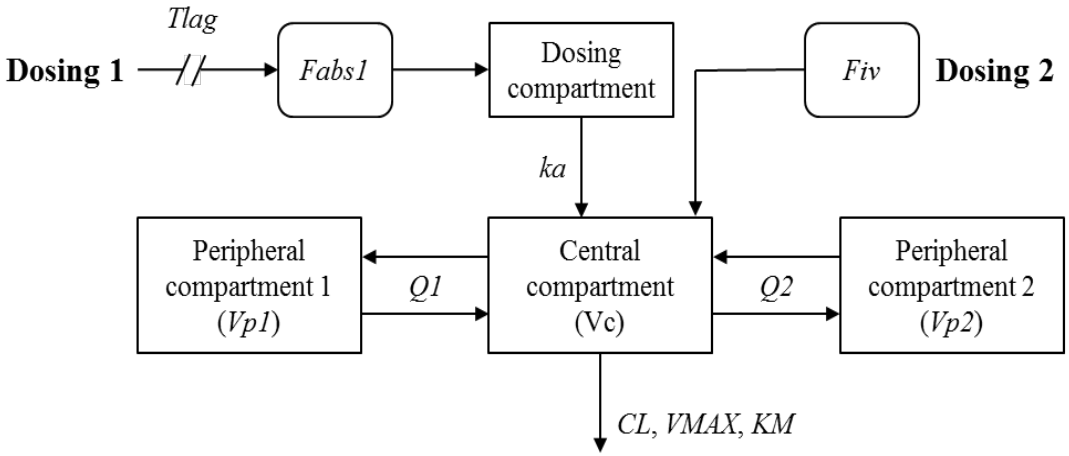
- **Imagine** even VERY complex clinical trial simulations are just a couple of for-loops away

```
Loop over trial
    Loop over treatment arm
        Loop over individual patient
            Simulate
            Store results
        Process results
    Process results
Process results
Display results
```

henning.schmidt@intiquan.com

Workflow approach to popPK modeling

- An internal review at Novartis revealed that >85% of all generated popPK models can be represented by the following „general popPK model structure“:



- And this structure is likely to support >95% of all clinically relevant questions with respect to the dose/concentration relationship

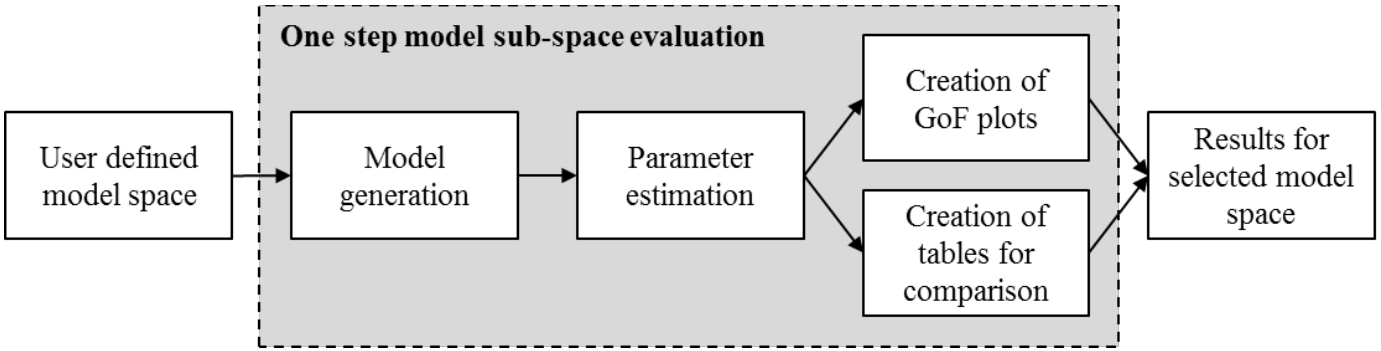
henning.schmidt@intiquan.com

IntiQuan

PopPK modeling workflow

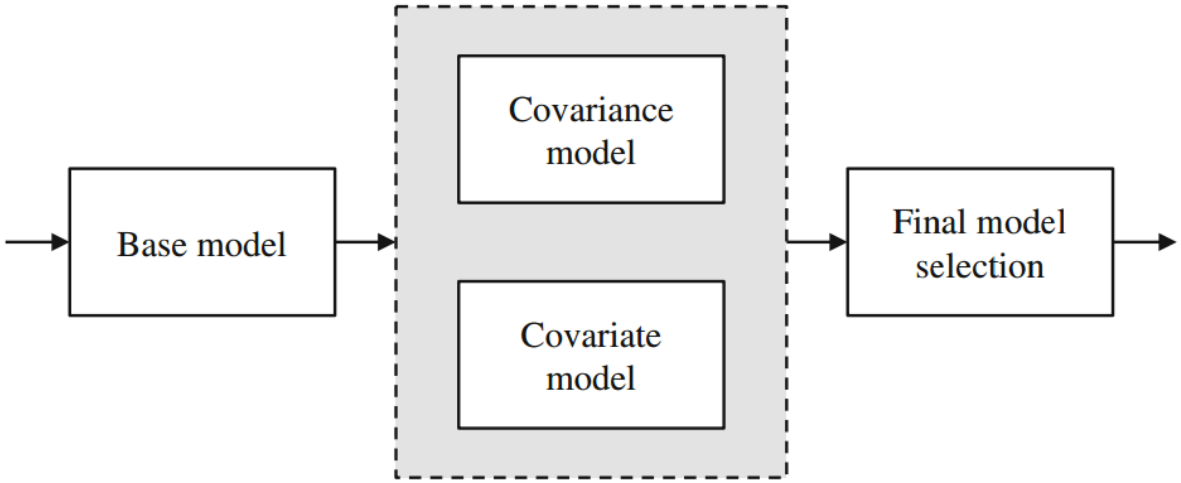
- **Imagine** you only need to describe the models that you are interested in evaluating and the workflow tools would do the rest

```
input1.stepIdentifier:        MODEL_BRUTE_FORCE
input2.nrCompartments:        1,2,3
input2.errorModels:           additive,additive+proportional,exponential
input2.elimination:           linear,linear+saturable
input2.lagTime:               no,yes

input2.parameters:            All fixed and random effects estimated
                              No random effect on Q1
                              No random effect on Vp1
                              No random effect on Q1 and Vp1

input2.covariate:             NONE
                              {CL,Weight,Age,Gender},{Vc,Weight,Age,Gender}
                              {CL,Weight,Gender},{Vc,Weight,Gender}
                              {CL,Weight},{Vc,Weight}

input2.covariance:            DIAGONAL
                              {CL,Vc,Vp1}
                              {CL,Vc}

PopPKModelSpace(input1,input2)
```



PopPK modeling workflow

- **Imagine** a structure popPK workflow template supports you in doing the typical activities during popPK model building



- **Imagine** the typical analyses are just a click away
  - Stepwise covariate search
  - Bootstrap
  - VPC
  - Etc.

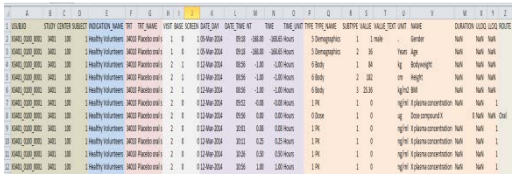
You then could focus on the „science of modeling“ and „providing timely input for decision making“ rather than on the „art of working around tool issues“

henning.schmidt@intiquan.com

IntiQuan

PopPK modeling workflow:
From data standards to standard outputs

Standard dataset format covering all pharmacometric analyses



Automatic checking of dataset integrity

⇒ Fewer iterations, higher quality

NONMEM dataset

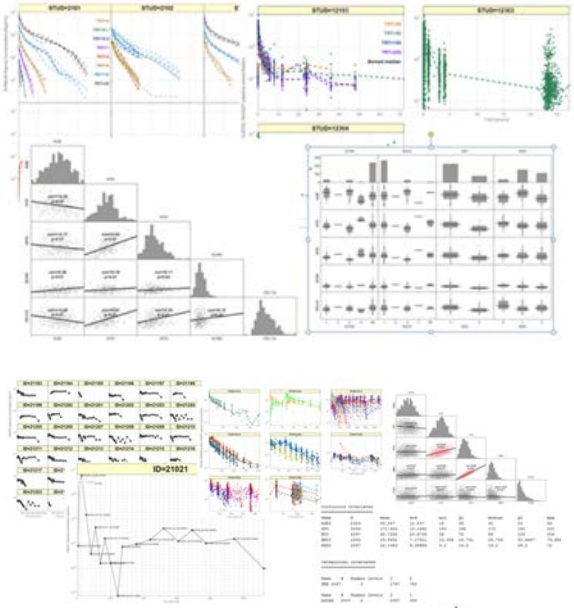
MONOLIX dataset

Required formats adapted to subsequent modeling workflow

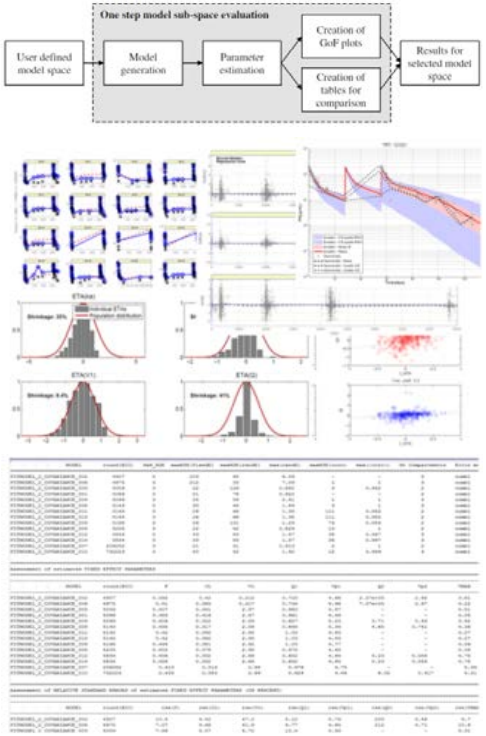
⇒ Fewer data mistakes

⇒ Higher quality

Automatic generation of typical data exploratory analyses



Automatic generation of models of interest and GoF assessments, etc.



New associates get up-to-speed quicker
Less mistakes
Faster turn-around of analyses
Higher and more consistent quality

henning.schmidt@intiquan.com

IntiQuan

Summary

- Customizable workflow approaches allow to perform similar analyses in the same manner, leading to more consistent results across individual modelers and higher quality
- **General modeling tools, used in the workflow approaches, allow to step-out of workflow approaches at any point in time and do model and modeling customizations as desired**
- Good tools and workflow approaches allow to structure data, models, outputs and scripts in a humanly understandable form that is suitable for peer-review, validation, transition to another person

Tutorial Outline

- General introduction to the IQM Tools Suite
- General introduction PMX Workflow Approaches
- **General Dataset Specification**
- Hands on PopPK Workflow Example (classroom possible)
- Hands on PopPK+PD Workflow Example (self study only)

henning.schmidt@intiquan.com

General standard dataset

- Capturing clinically relevant information
- Reuse of the data for many purposes (across line functions – DMPK, PMX, STATS)
- Collection of data in databases
- Efficient data preparation
- Efficient data checking => higher quality data
- Efficient standard analyses
- Easy integration in workflow approaches

General standard dataset – is it feasible?

Datasets for pharmacometric analyses: internal review and standardization efforts

Andrijana Radivojevic[1)], Henning Schmidt[2)]

Pharmacometrics Modeling & Simulation, [1)]Novartis Pharmaceuticals Corporation, East Hanover, USA, [2)]Novartis Pharma AG, Basel, Switzerland

NOVARTIS

Background & Objective

Analysis datasets for the conduct of pharmacometric (PMX) analyses are usually prepared by the modeler him/herself or requested from a supporting programming group. The content and the structure of such datasets are defined in a dataset specification. There are currently no standards in this regards, and therefore the dataset structure typically depends on the modeling activity, the modeling tool, the models to be assessed, and even on the modeler. This kind of *freedom* is directly translated into lower efficiency in dataset preparation process, multiple iterations between modelers and programmers, and compromised quality of the of delivered analysis dataset.

Standards, however, could considerably improve the process of dataset specification, preparation, and allow for automated dataset quality checks. The goal of this work is to analyze the typical content of PMX datasets, reasons for their variability, and to assess if and how standardization in this context might be feasible.

Methods

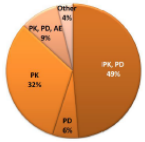
Extensive review of historical and existing data requests within the Novartis PMX Modeling & Simulation (M&S) department was performed. This included 384 different data requests, spanning the period 1999–2015. Those data requests were directly linked with corresponding PMX tasks related to support of drug development programs across various Novartis business units and disease areas, e.g. immunology, dermatology, primary care, critical care, neuroscience, ophthalmology, biosimilars and oncology.

The exercise provided solid statistics on dataset structure and data content of analysis datasets for PMX deliverables. Inter-modeler variability considering styles, preferences, analysis platforms, modeling methods, disease area specific requirements and more, was captured as well.

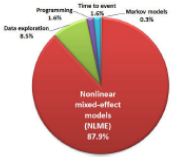
Results

Clinical Questions, Data Content and Analysis Types

- Characterization of dose-exposure-response relationships has been, and still is, the main *leitmotif* in all PMX activities. It is then not surprising that the majority of requested datasets are tailored to enable those kinds of analyses and answer related clinical questions.



- Consequently, pharmacokinetic (PK), pharmacodynamic (PD) and adverse event (AD) information are captured in datasets, with the main focus on describing and/or predicting drug efficacy and safety.
- Nonlinear mixed-effects (NLME) modeling remains the predominant methodology used to analyze this data, with only rare occurrence of alternative approaches.
- Given that data exploration is, and should be, a subset task of any modeling activity, there is no need to differentiate it in a separate analysis category.



Heterogeneity in data specification

- Despite the aim of answering similar questions, capturing similar information and analyzing data using similar methodology, the content and structure of analysis datasets still largely depend on the modeling activity, the modeling tool, the model to be assessed, and the modeler.
- Our survey gives some insight on major sources of variability:
  - Non-unified nomenclature: same variables are named differently, e.g., REGIMEN, ARM, TRT, COHORT.
  - Non-mnemonic nomenclature: variable names are not possible to be associated with the entity they represent e.g., FLAG1, FLAG2, ..., FLAG30.
  - Different programming abilities among modelers: basic data manipulations are part of data specifications, thus increasing the dataset preparation time.
  - Extent of requested information: directly influencing the size of analysis dataset, e.g., from < 1MB – 800MB (when including time points for simulation).
  - Modeling platform: NONMEM vs. MONOLIX, R vs. MATLAB.
- All these differences significantly compromise the efficiency and quality of PMX deliverables and directly impact:
  - Resources for data preparation: each data request is a new data request, with different structure and different content.
  - Project takeover: datasets almost never contain names of observations or units, but only compartment numbers which are linked with their meaning in other documents – making it more complicated for a naïve modeler to onboard.
  - Fluent usage of various software tools: datasets are adapted to one software tool (mostly NONMEM) only.
  - Reusability and Reproducibility: datasets are adopted to the individual code of one modeler performing the analysis. If another modeler has his/her own set of scripts, then another matching dataset needs to be created, containing the same information but in a different structure.

Discussion

- As presented in [1], the concept of a generalized dataset and its automatic transformation into an analysis specific dataset offers a robust solution that overcomes the aforementioned issues.

- The notion of generalized dataset resembles the idea of a master dataset for clinical projects. It consists of a broad collection of clinical information in a well-defined structure that is independent of the project (typically standard within a therapeutic area), of the modeling activity to be performed, and of the modeling tool to be used.
- The standardized structure allows for more efficient and less error-prone preparation of datasets, automatic data consistency checks, pooling across studies, easier understanding and re-use of the data, automatic generation of common graphical exploration plots, automatic conversion to modeling activity and tool dependent modeling datasets.
- This approach directly contributes to improved efficiency and quality of PMX deliverables, and a proof-of-concept was demonstrated by implementation in [2].

- Recognizing the advantages of data standardization, Novartis PMX M&S is on its way towards the successful organization-wide implementation of the concepts discussed here:
  - The existing generalized dataset described in [1] was updated to cover ≥ 95% of the identified needs in a diverse PMX group.
  - Proof-of-principle has been demonstrated in multiple clinical projects.
  - It is a collaborative effort between modelers and programmers, who work in parallel on improving related processes and background infrastructure, and developing tools.

Conclusion

Underestimation of the time needed for preparation of high quality modeling datasets is a common oversight, and lack of data standards and supporting tools can have direct implications on reproducibility and auditing of modeling work [3]. Therefore, a standardized dataset format within PMX organizations is a pivotal step toward efficient implementation of model-based drug development in a corporate setting. All this should be taken within a broader context of streamlined workflows and industrialization efforts. Global alignment on this topic would further advance the field of Pharmacometrics.

References:

[1] Schmidt, Radivojevic (2014) Enhancing population pharmacokinetic modeling efficiency and quality using an integrated workflow. J Pharmacokinet Pharmacodynam. DOI 10.1007/s10928-014-9370-4

[2] Schmidt (2013) SBPOP Package: Efficient support for model based drug development – from mechanistic models to complex trial simulation. PAGE www.sbtoolbox2.org

[3] Jönsson, Jonsson (2007) Timing and efficiency in population pharmacokinetic/pharmacodynamic data analysis projects. Pharmacometrics: The Science of Quantitative Pharmacology. Edited by E. Ette and P. J. Williams, John Wiley & Sons, Inc.

This study was supported by Novartis Pharma AG, Basel, Switzerland.

Poster presented at ACoP, October 4-7, 2015, Crystal City, VA, USA

Acknowledgments:
Didier Renard and Mick Looby for reviewing this poster.

Corresponding author: andrijana.radivojevic@novartis.com

It is not only feasible – it is absolutely necessary!

henning.schmidt@intiquan.com

IntiQuan

Documentation of General Standard Dataset used in IQM Tools

Column Name	Type	Description
IXGDF	numeric	Column containing numeric indices for each record (1,2,3,4,5, ...) to allow for matching records in case of post-processing the general dataset format
IGNORE	string	Reason/comment related to exclusion of the sample/observation from the analysis
USUBJID	string	Unique subject identifier
COMPOUND	string	Name of the investigational compound
STUDY	string	Study number
STUDYDES	string	Study description
PART	string	Part of study as defined per protocol (1 if only one part)
EXTENS	numeric	Extension of the core study (0 if not extension, 1 if extension)
CENTER	numeric	Center number
SUBJECT	string	Subject identifier (within a center - typically not unique across whole dataset)
INDNAME	string	Indication name
TRTNAME	string	Name of actual treatment given
TRTNAMER	string	Name of treatment to which individual was randomized
VISIT	numeric	Visit number
VISNAME	string	Visit name
BASE	numeric	Flag indicating assessments at baseline (=0 for non-baseline, =1 for first baseline, =2 for second baseline, etc.)
SCREEN	numeric	Flag indicating assessments at screening (=0 for non-screening, =1 for first screening, =2 for second screening, etc.)

henning.schmidt@intiquan.com

Documentation of General Standard Dataset used in IQM Tools

Column Name	Type	Description
DATEDAY	String	Start date of event ('01-JUL-2015')
DATETIME	string	Start time of event ('09:34')
DURATION	numeric	Duration of event in same time units as TIMEUNIT
NT	numeric	Planned time of event. Based on protocol, in the time unit defined in TIMEUNIT column
TIME	numeric	Actual time of event relative to first administration, in the time unit defined in TIMEUNIT column
TIMEUNIT	string	Unit of all numerical time definitions in the dataset ('hours','days','weeks','minutes')
TYPENAME	string	Unique type of event
NAME	string	Unique name for the event
VALUE	numeric	Value of the event, defined by NAME. E.g., the given dose, the observed PK concentration, or the value of other readouts. The values need to be in the units, defined in the UNIT column. Specific cases: - For concomitant medications the dose will be given - For BLOQ values, 0 will be used - Severity levels for adverse events - Should not be populated if VALUE_TEXT is populated
VALUETXT	string	Text version of value (if available and useful). Character value as given in the CRF. Should not be populated if VALUE is populated

henning.schmidt@intiquan.com

Documentation of General Standard Dataset used in IQM Tools

Column Name	Type	Description
UNIT	string	Unit of the value reported in the VALUE column. For same event the same unit has to be used across the dataset.
ULOQ	numeric	Upper limit of quantification of event defined by NAME
LLOQ	numeric	Lower limit of quantification of event defined by NAME
ROUTE	string	Route of administration (iv, subcut, intramuscular, intraarticular, oral, inhaled, topical, rectal)
INTERVAL	numeric	Interval of dosing, if single row should define multiple dosings
NRDOSES	numeric	Number of doses given with the specified interval, if single row should define multiple dosings
COMMENT	string	Additional information for the observation/event

The general dataset format in IQM Tools covers >95% of the typical pharmacometric analyses. It is certainly not complete and perfect, but it is a start in the right direction. An industry wide agreement would be of tremendous interest.

henning.schmidt@intiquan.com

Documentation of General Standard Dataset used in IQM Tools

- Optional columns in the IQM Tools General Standard Dataset format
  - The general data format might also contain the following columns, which are numeric equivalents to some string columns. If not provided, then these are generated automatically in the post processing steps of the general dataset in IQM Tools

Column Name	Type	Description
IND	numeric	Numeric indication flag (unique for each entry in INDNAME)
STUDYN	numeric	Numeric study flag (unique for each entry in STUDY)
TRT	numeric	Numeric actual treatment flag (unique for each entry in TRTNAME)
TRTR	numeric	Numeric randomized treatment flag (unique for each entry in TRTNAMER)

henning.schmidt@intiquan.com

Example for a General Standard Dataset

- Provided as CSV file in this PPT
- Right-click on the dataset, and there will be some menu point which will allow you to open it in Excel ...
- Have a look at it

IXGDF	IGNORE	USUBJID	COMPOUT	STUDY	STUDYDES	PART	EXTENS	CENTER	SUBJECT	INDNAME	TRTNAME	TRTNAME	VISIT	VISNAME	BASE	SCREEN	DATEDAY	DATETIME	DURATIO
1	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	1	Screening	0	1	04-May-19	07:00	0
2	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	1	Screening	0	1	04-May-19	07:00	0
3	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	1	Screening	0	1	04-May-19	07:00	0
4	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	2	Baseline	1	0	16-May-19	12:38	0
5	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	2	Baseline	1	0	17-May-19	07:00	0
6	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	3	VISIT 03	1	0	29-May-19	06:19	0
7	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	3	VISIT 03	1	0	29-May-19	06:30	0.083333
8	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	3	VISIT 03	1	0	29-May-19	08:50	0
9	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	4	VISIT 04	1	0	30-May-19	06:30	0
10	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	5	VISIT 05	0	0	########	06:30	0
11	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	6	VISIT 06	0	0	########	06:30	0
12	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	6	VISIT 06	0	0	########	09:04	0
13	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	7	VISIT 07	0	0	########	06:30	0
14	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	8	VISIT 08	0	0	########	06:30	0
15	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	8	VISIT 08	0	0	########	10:30	0
16	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	9	VISIT 09	0	0	10- Jul 81	06:30	0
17	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	10	VISIT 10	0	0	24- Jul 81	06:30	0
18	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	11	VISIT 11	0	0	########	06:30	0
19	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1107	Healthy vi	SD IV 15 m	SD IV 15 m	12	VISIT 12	0	0	########	06:30	0
20	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1108	Healthy vi	SD IV Plac	SD IV Plac	1	Screening	0	1	04-May-19	07:00	0
21	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1108	Healthy vi	SD IV Plac	SD IV Plac	1	Screening	0	1	04-May-19	07:00	0
22	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1108	Healthy vi	SD IV Plac	SD IV Plac	1	Screening	0	1	04-May-19	07:00	0
23	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1108	Healthy vi	SD IV Plac	SD IV Plac	2	Baseline	1	0	20-May-19	07:00	0
24	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1108	Healthy vi	SD IV Plac	SD IV Plac	2	Baseline	1	0	23-May-19	15:53	0
25	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1108	Healthy vi	SD IV Plac	SD IV Plac	3	VISIT 03	1	0	29-May-19	07:00	0.083333
26	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1108	Healthy vi	SD IV Plac	SD IV Plac	6	VISIT 06	0	0	########	09:50	0
27	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1108	Healthy vi	SD IV Plac	SD IV Plac	8	VISIT 08	0	0	########	09:09	0
28	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	1	Screening	0	1	03-May-19	07:00	0
29	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	1	Screening	0	1	03-May-19	07:00	0
30	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	1	Screening	0	1	03-May-19	07:00	0
31	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	2	Baseline	1	0	20-May-19	07:00	0
32	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	2	Baseline	1	0	23-May-19	17:04	0
33	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	3	VISIT 03	1	0	29-May-19	07:15	0
34	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	3	VISIT 03	1	0	29-May-19	07:31	0.083333
35	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	3	VISIT 03	1	0	29-May-19	10:01	0
36	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	3	VISIT 03	1	0	29-May-19	11:30	0
37	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	4	VISIT 04	1	0	30-May-19	07:30	0
38	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	5	VISIT 05	0	0	########	07:30	0
39	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	6	VISIT 06	0	0	########	07:30	0
40	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	6	VISIT 06	0	0	########	10:13	0
41	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	7	VISIT 07	0	0	########	07:55	0
42	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	8	VISIT 08	0	0	########	08:02	0
43	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	8	VISIT 08	0	0	########	13:11	0
44	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	9	VISIT 09	0	0	10- Jul 81	07:42	0
45	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	10	VISIT 10	0	0	24- Jul 81	08:00	0
46	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	11	VISIT 11	0	0	########	08:23	0
47	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1109	Healthy vi	SD IV 15 m	SD IV 15 m	12	VISIT 12	0	0	########	07:30	0
48	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1110	Healthy vi	SD IV 15 m	SD IV 15 m	1	Screening	0	1	07-May-19	07:00	0
49	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1110	Healthy vi	SD IV 15 m	SD IV 15 m	1	Screening	0	1	07-May-19	07:00	0
50	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1110	Healthy vi	SD IV 15 m	SD IV 15 m	1	Screening	0	1	07-May-19	07:00	0
51	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1110	Healthy vi	SD IV 15 m	SD IV 15 m	2	Baseline	1	0	16-May-19	11:53	0
52	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1110	Healthy vi	SD IV 15 m	SD IV 15 m	2	Baseline	1	0	17-May-19	07:00	0
53	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1110	Healthy vi	SD IV 15 m	SD IV 15 m	3	VISIT 03	1	0	29-May-19	07:25	0
54	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1110	Healthy vi	SD IV 15 m	SD IV 15 m	3	VISIT 03	1	0	29-May-19	07:40	0.083333
55	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1110	Healthy vi	SD IV 15 m	SD IV 15 m	3	VISIT 03	1	0	29-May-19	09:53	0
56	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1110	Healthy vi	SD IV 15 m	SD IV 15 m	3	VISIT 03	1	0	29-May-19	11:40	0
57	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1110	Healthy vi	SD IV 15 m	SD IV 15 m	4	VISIT 04	1	0	30-May-19	07:40	0
58	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1110	Healthy vi	SD IV 15 m	SD IV 15 m	5	VISIT 05	0	0	########	07:40	0
59	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1110	Healthy vi	SD IV 15 m	SD IV 15 m	6	VISIT 06	0	0	########	07:40	0
60	NaN	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1110	Healthy vi	SD IV 15 m	SD IV 15 m	6	VISIT 06	0	0	########	13:05	0
61	Ignore exa	ZY1001011	Z	Y1	FIH HV Stu	1	0	1	1110	Healthy vi	SD IV 15 m	SD IV 15 m	7	VISIT 07	0	0	########	07:44	0

henning.schmidt@intiquan.com

IntiQuan

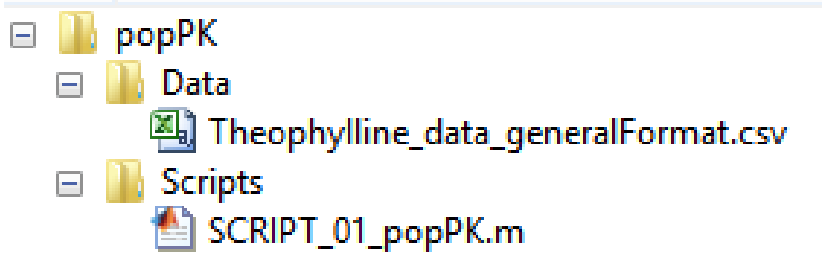
Tutorial Outline

- General introduction to the IQM Tools Suite
- General introduction PMX Workflow Approaches
- General Dataset Specification
- **Hands on PopPK Workflow Example (classroom possible)**
- Hands on PopPK+PD Workflow Example (self study only)

PopPK Hands-On Workflow Example

- Change into the **Example Files/popPK** folder
- You will find a complete PopPK Workflow example included

- The **Data** folder contains the example data in the general standard data format
- The **Scripts** folder contains a single script that walks you through this example popPK
- The script is well documented



- Please have a look at the scripts and data ...

henning.schmidt@intiquan.com

IntiQuan

PopPK Hands-On Workflow Example

- This example uses MONOLIX
- The same example is available with NONMEM on request

- In a classroom setting it is now time to switch to MATLAB and work through this example together.
- In a self study setting – please open MATLAB, change into the **Example Files/popPK/Scripts** folder, open the script and start reading, executing, etc.
- In any case, please change line number 30 in the script to define the location where you have IQM Tools installed

```
PATH_IQM              = 'D:\IntiQuan Modeling Tools\01 IQM Tools Suite';
```

- **Enjoy!**

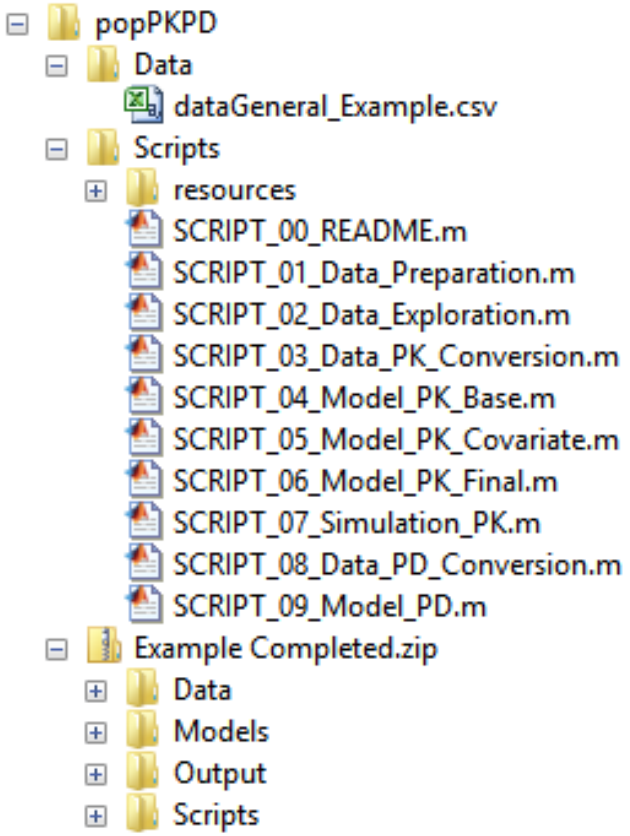
henning.schmidt@intiquan.com

Tutorial Outline

- General introduction to the IQM Tools Suite
- General introduction PMX Workflow Approaches
- General Dataset Specification
- Hands on PopPK Workflow Example (classroom possible)
- **Hands on PopPK+PD Workflow Example (self study only)**

PopPK+PD Hands-On Workflow Example

- Change into the **Example Files/popPKPD** folder
- You will find a complete PopPK+PD Workflow example included



- The **Data** folder contains the example data in the general standard data format
- The **Scripts** folder contains documented analysis scripts, numerically ordered as they should be executed
- Each script is highly documented
- The **Example Completed.zip** file contains the completed example as it looks when all scripts have run through **(This file is not available in the download version of the tutorial)**
- Please have a look at the scripts and data ...

henning.schmidt@intiquan.com

IntiQuan

PopPK+PD Hands-On Workflow Example

- This example uses MONOLIX and NONMEM – not for the same analyses, but for different purposes (e.g., stepwise covariate search is done using a gradient based method)

- This example is nothing for a classroom setting – the runtimes are not excessive but too long for not taking some long breaks inbetween
- In self study setting
  - Please open MATLAB, change into the **Example Files/popPKPD/Scripts** folder
  - Have a look at each script
  - Setup the correct path to IQM Tools in the header section of each script
  - Walk through step by step – it is highly documented and for once a pharmacometric analysis and its code is almost self explaining and transparent ;-)

- **Enjoy!**

henning.schmidt@intiquan.com

Tutorial Goal: „You should now be able to“

- **Understand the idea and power of PMX Workflow approaches**
- **Specify a general dataset format for your own projects**
- **Perform a PopPK using the IQM Tool PopPK Workflow**
  - Or at least customize the template code to own analyses
- **Perform a PopPKPD using IQM Tools**
  - Or at least customize the template code to own analyses

THE END

Thank you for your participation and interest!

The tutorial continues in Part 5 (IQM Tools Pro / Advanced Clinical Trial Simulations)

henning.schmidt@intiquan.com