

# Predictive Modelling Environment – Infrastructure and functionality for pharmacometric activities in R&D

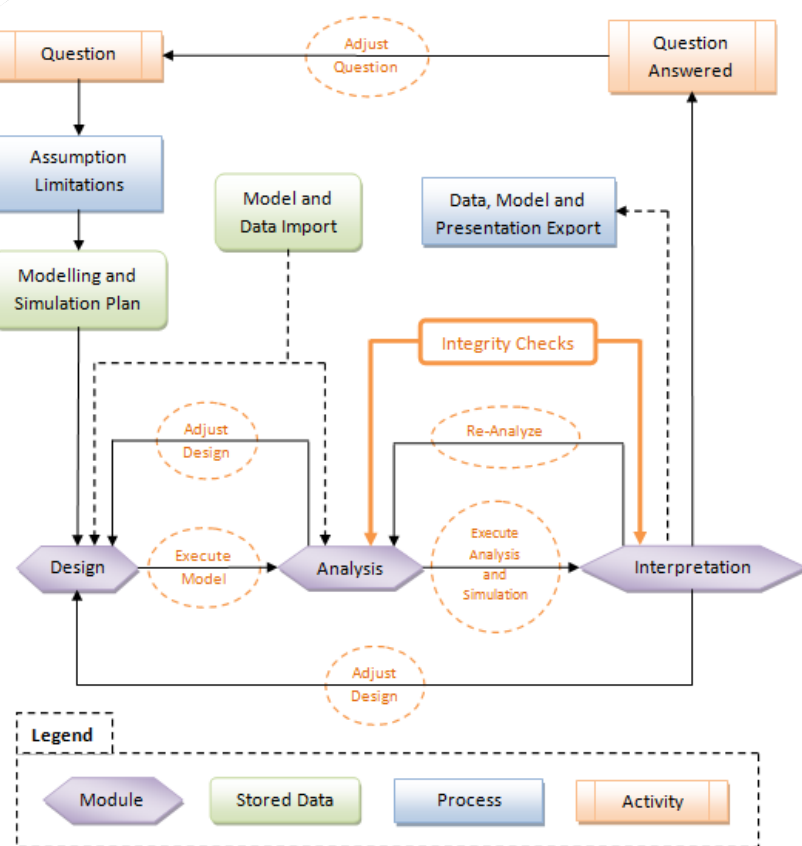


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## Introduction

The Predictive Modelling Environment (PME) supports Clinical Pharmacology Modelling & Simulation, enabling the implementation of M&S activities which are used to facilitate decision making within GSK. The system architecture has been developed taking into account a pre-defined workflow and the interaction between software packages such as R and NONMEM 7.2. Here we describe how a server-based tool has been implemented within the regulated R&D environment. Moreover, we show how workflow and software functionalities are integrated to meet the needs of a continuously growing pharmacometric community.



## Modelling & Simulation Workflow

### PME Workflow

The modelling and simulation workflow has been implemented in the PME web application by dedicated components. Every step of the workflow is recorded and made fully reproducible. Projects and sub-projects represent the units of analysis in PME.

#### DCP – Data Collection Plan

PME provides a central database for storage and re-use of data. The DCP is a wizard tool that helps the user to plan the data collection from one or multiple studies into the database for a specific PME Project. The input data files are normally in CSV format and data manipulation is performed in R.

#### DEP – Data Extraction Plan

The DEP is the second step of the PME workflow and consists of a more advanced wizard tool aimed to extract the data previously collected and format it into a NONMEM-ready dataset. The original data are not modified. A record of all the steps required to extract the data are kept in the PME database.

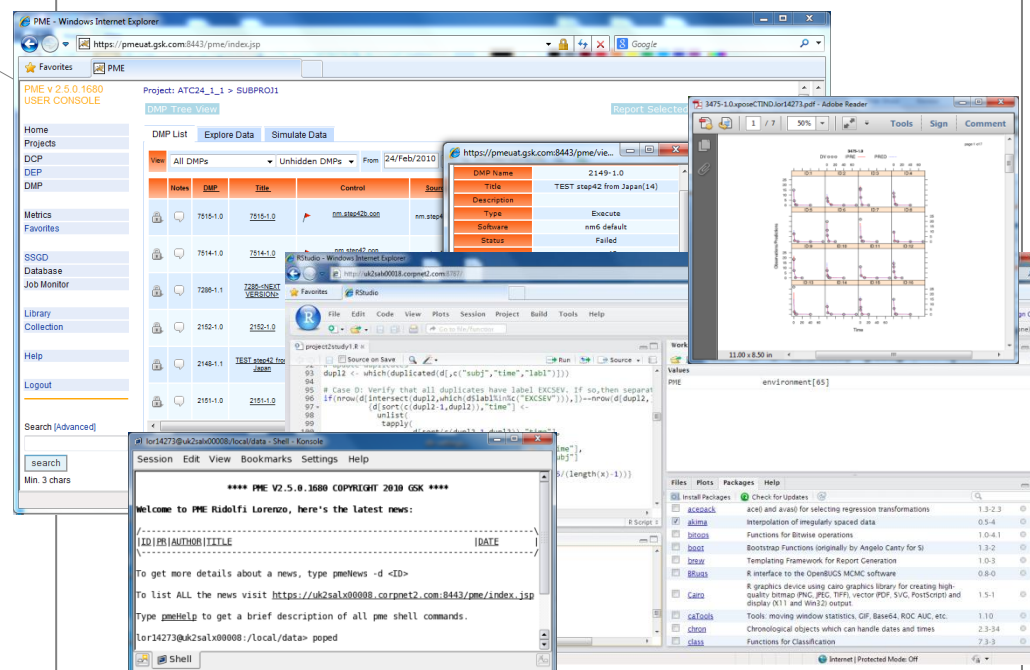
#### DMP – Data Modelling Plan

It is the core of PME, responsible for the development and execution of the NONMEM runs. Different options allow for model execution, VPC, NPC, SCM and bootstrap runs. The output files produced by a DMP run are archived and stored in the database along with the input control stream and dataset.

#### Reporting Suite

It is a tool that enables the creation of graphical post-processing reports. The suite provides the basis for integrity checks and model interpretation. It also supports the creation of the documentation required for regulatory submissions. Reports can be executed against complete DMP runs

## PME 2.5 Overview



### PME 2.5 GUI

### Three Interfaces

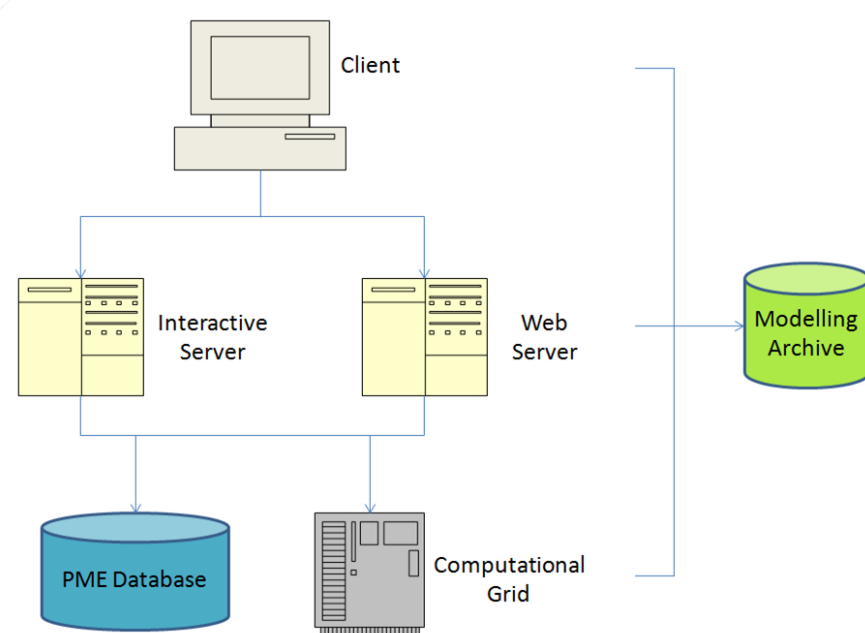
- Web Interface (PME web application)
- Command Line Interface (Oracle SGD)
- Windows Fileshare (Samba)

### Available Tools

- NONMEM 5 – 6 – 7.1 – 7.2
- PsN 3.4.2
- R 2.13.1
- Wide selection of R packages
- Rstudio Server
- OpenBUGS
- Matlab
- PopED
- FACTS

### Benefits

- Validated workflow and environment
- Use of a remote grid
  - freeing up local resources
  - parallel executions
  - better performance
- Reduced costs as licenses are shared
- Data reuse/sharing
- Reproducible executions
- System modularity
  - easier to update or substitute single components
  - integration with third party tools



### PME Architecture

## Technical Infrastructure

Maintaining the underlying technical infrastructure has been one of the biggest challenges in the development of PME. The latest version of PME (2.5) introduces the use of a layered architecture to decouple the end user interfaces from the underlying software and hardware components.

### End-User

Includes the PME web interface and third party software (Rstudio, Matlab, PopED, OpenBUGS, ..)

### Tools

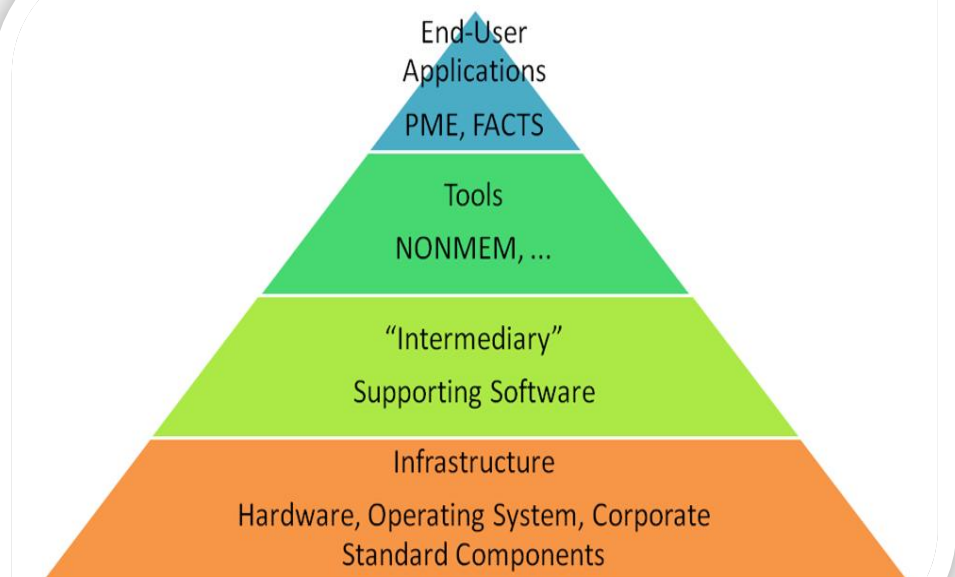
This layer includes the underlying tools used by the PME web interface (NONMEM, PsN, R, ..). These tools can be also accessed directly by the user from the command line interface

### Intermediary Tier

Software framework shared by all the user applications. These include the Sun Grid Engine to manage the execution of runs in the computational grid; Oracle Secure Global Desktop to provide users with a command line interface; Samba as a tool to access the server file system used as the Modelling Archive.

### Infrastructure

The underlying hardware infrastructure, a group of Linux servers consisting of 1) a web node dedicated to the PME web application itself, 2) an interactive node dedicated to direct access to R, NONMEM and PsN from command line, and 3) a grid of nodes for the execution of runs (NONMEM, R, FACTS, ..).



## Architecture - Layers

### Gaps

GSK commitment to the DDMoRe initiative has been beneficial in the development of this platform. PME has been used as an example and a starting point for the discussions on the modelling framework that DDMoRe is expected to deliver. At the same time the outcome of these discussions have been fed back into PME and some of the gaps have been closed to ensure that the PME environment is compatible with the long-term changes promoted by DDMoRe.

### Conclusions

PME 2.5 is the result of years of internal and external development where the users' needs have been balanced with the industry standards, taking into account the requirements for an integrated workflow. Many of the technical challenges arising from the development and upgrade of modelling and simulation environment are due to differences in the expectation and expertise within the user community, which impose flexibility and consensus on workflows. System modularity, standard processes and grid computing are essential to ensure that M&S tools can be upgraded in a rapidly evolving field.