Implementation of a NONMEM cluster and add-ons within UCB

C. Castelain[1], A. Dalis[1], X. Deflorenne[1], M. Destrée[1], B.D. Lacroix[2], M.L. Sargentini-Maier[2]

[1] IT department, UCB, Belgium; [2] Pharmacometrics, Global Exploratory Development, UCB, Belgium

RATIONALE

- NONMEM is the reference platform used by pharmacometricians to develop various types of models, such as pharmacokinetics/pharmacodynamics, disease progression, compliance...
- NONMEM is used extensively within UCB Pharmacometrics, in exploratory research and for supporting regulatory submissions
- Regulatory agencies increasingly require drug development to be supported by M&S.
- M&S tasks are highly time-consuming and require intensive computer power. Automation is crucial to provide pharmacometricians with an integrated environment where they can focus on model design and scientific tasks.
- The environment within which NONMEM was running at UCB required several major improvements:
  - — Insufficient processing power
  - — Multiple copies of NONMEM on independent multiprocessor workstations
  - — No automation tool
  - — Manual traceability between results and software versions
  - — No (procedure for) implementation of bug fixes

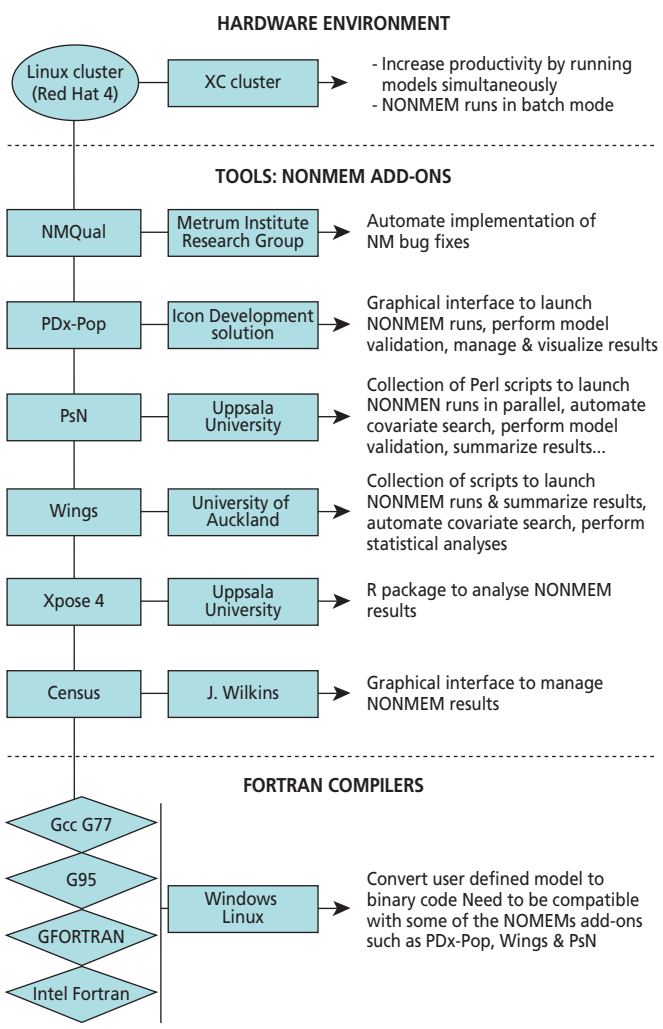
OBJECTIVES

- **Performance:** Provide a robust hardware infrastructure
- **Productivity:** Test and implement adequate software/freeware packages
- **Compliance:** Ensure traceability between modeling results and software version. Maintain the different NONMEM versions in a secure environment.

METHODS

- **Investigation phase** to define the appropriate hardware environment and to select the right combination of NONMEM related tools (***Figure 1***).

Figure 1 – Hardware environment and tools tested during the investigation phase

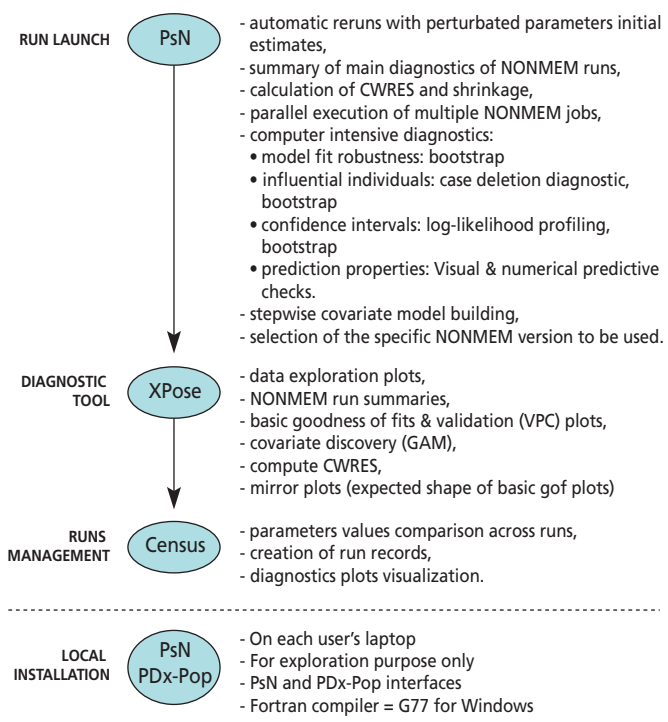


- **Computerized systems validation:** risk assessment approach (NONMEM cluster and related tools)
  - — Installation qualification for all hardware and software components.
  - — Focus on reproducing the NONMEM reference run results (non-regression testing).
  - — For PsN and R/Xpose, key functionalities such as the bootstrap, jackknife, stepwise covariate model and conditional weighted residuals were tested. These tests focused on the consistency of the outputs as it is barely impossible to check numeric results for which we rely on a modeler peer review.
  - — Cluster stress tests: queues management, CPU intensive methods.

RESULTS

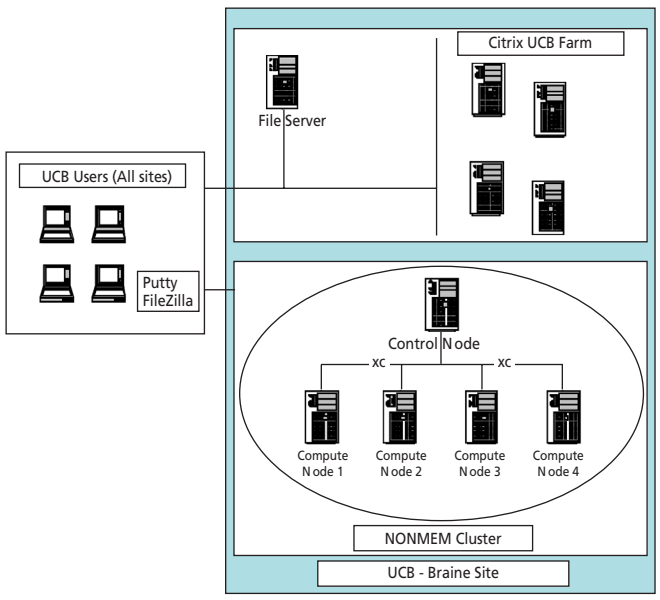
- **Selected productivity tools (*Figure 2*)**

Figure 2 – Selected productivity tools



- **Performance objective - NONMEM cluster**
  - — Cluster of HP servers including one head node and 4 computes nodes (***Figure 3***).
  - — Head node configuration:
    - • HP ProLiant DL385 G2 Base – Red Hat 4
    - • AMD Second-Generation Opteron 2218 2.6 GHz dual –core
    - • 2 GB RAM
    - • 72 GB for OS (X2 for mirroring) + 3 X 146 GB for data (raid 5)
  - — Compute node configuration:
    - • HP ProLiant DL385 G2 High Performance – Red Hat 4
    - • 2 X AMD Second-Generation Opteron 2218 2.6 GHz dual –core
    - • 2 GB RAM
    - • 72 GB (X 2 for mirroring)
  - — XC package supplied by HP
    - • Operating system
    - • Cluster program Load Sharing Facilities (LSF)
    - • Fortran compiler gcc G77 – compatible with PsN and PDxPop
  - — Connection to the cluster
    - • SSH protocol: freeware package Putty
    - • 10 GB of disk space by user
    - • File exchanges to cluster: FileZilla software (FTP protocol)
  - — Prioritization
    - • LSF queues (normal, short, night…) + "priority" queue

Figure 3 – NONMEM system architecture



- **Compliance objective:**
  - — Subversion configuration management tool.
  - — UCB specific change to source code: the hardware / OS configuration, version release date, installation status (development, acceptance or production) and user identification reported in NONMEM result files.
  - — Production of a release note at each code modification to ensure traceability and reproducibility.
  - — Maintenance of former NONMEM versions to be able to reproduce a former run in the exact same conditions.
  - — New versions tested against NONMEM reference runs published by Icon to detect any discrepancy.
  - — Internal procedure for management of NONMEM source code.
  - — Internal Users guides were produced. All users were trained to NONMEM cluster and PsN.

CONCLUSIONS

- The implemented system is used by about 15 users located on 3 sites.
- Some of the M&S work and most of the computer intensive model validation procedures recently performed and submitted would not have been possible without the cluster implementation because of insufficiencies in processing power and time limitations. The capability to run several models simultaneously provided huge improvement.
- The integration of several NONMEM related productivity tools such as PsN, Census and R/Xpose allowed not only saving time, but also facilitated performing some new tasks, such as the computation of CWRES, shrinkage or production of mirror plots.
- The compliance to computerized systems regulations was markedly improved thanks to the central NONMEM installation and a version control system.
- The NONMEM cluster implementation presented here has been achieved with standard software and hardware components which have proven their compatibilities and robustness. Its implementation does not require excessive costs and is easily expandable.

REFERENCES

(1) NONMEM and PdxPOP software: Icon Development Solutions - http://www.icondevsolutions.com/nonmem.htm
(2) NMQual: Metrum Institute - http://www.metruminstitute.org/index.shtml
(3) PsN: Lars Lindbom, Mats Karlsson, Niclas Jonsson and Andrew Hooker - Uppsala University - http://psn.sourceforge.net/
(4) Wings for NONMEM: Nick Holford - University of Auckland - http://wfn.sourceforge.net/
(5) R : http://www.r-project.org/
(6) Xpose4: Andrew Hooker, Justin Wilkins, Mats Karlsson and Niclas Jonsson http://xpose.sourceforge.net/
(7) Census: Justin Wilkins - http://census.sourceforge.net/
(8) HP XC System Software: http://h20311.www2.hp.com/HPC/cache/275435-0-0-0-121.html
(9) Putty: Simon Tatham: http://www.chiark.greenend.org.uk/~sgtatham/putty/
(10) FileZilla: http://filezilla-project.org/
(11) Subversion: http://subversion.tigris.org/