Email address:
jogarao.gobburu@fda.hhs.gov

Population Analyses Software Validation: Good Practices

Joga Gobburu

Team Leader, Pharmacometrics,

OCPB/CDER/FDA

The views expressed in this article are those of the authors and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended or should be inferred.

FDA uses pop analyses for regulatory decisions

- Labeling
  - Risperidone, Oxacarbazepine, Sotalol, Gabapentin, Amphotericin, Antihemophilic Factor, Dolasetron, Levofloxacin,Zometa
- Guidances
  - Exposure-Response, Pop PK

Why do we need validation?

- Software packages may affect public health decisions. Reliability and reproducibility of software packages essential.

- FDA and Sponsors face the same challenges.

Why do we need validation?

- To provide adequate confidence in interpreting the results from population analyses
  - Sound scientific practice
  - Currently population analyses are used for supportive evidence and to substantiate labeling statements.
  - Use of these analyses is increasing

Why care?

- CFR Part 11 mandates software validation, FDA issued Guidances
  - Most current activity pertains to devices
  - Vendors are seriously considering these regulatory expectations

Why care?

- Review Process
  - Sponsors' analyses are reproduced by the FDA reviewers
  - Failure to reproduce is an unnecessary burden for both FDA and Sponsor
    - Focussing on applying models to make drug development decisions is a better use of time
  - FDA attempts to develop models irrespective of whether sponsors do so
    - Sponsors might want to reproduce FDA models

Why care?

- Review Process
  - FDA's Critical Path initiatives call for model based analyses. Important to solve the software validation quandary.

- Compatability between sponsor sites

Validation Types

- Vendor
  - Should perform rigorous tests to qualify the software for intended purposes, during the design and development stages
- User (and Vendor)
  - Should qualify installation
  - Should periodically test

Vendor Validation

- Ideally
  - Should test how different modules function and interact with others
  - Should test the limits of the software capacity
- Practically
  - Impossible to test all scenarios before release

Vendor Validation

- Ideally
  - Should test how different modules function and interact with others
  - Should test the limits of the software capacity
- Practically
  - Impossible to test all scenarios before release

Good Software Practices

- Installation
  - Restricted privileges
  - Qualify
    - Physical
    - Functional
- Maintenance
  - Revision controls (audit trials)
  - Updates (vendor)

Installation: Restricted Privileges

- Organizations should identify ‘system administrators’ for installing and maintaining population analyses software, to ensure consistency
- Why?
  - Software packages might behave differently depending on how they were installed

Installation: Qualify

- Physical
  - The total number of lines of code in the installation media (e.g.: disks) and on the user machine should be compared after every installation
    - To ensure ‘physical’ similarity. Of course, this assumes that the installation kit is up to date, for e.g.: in terms of patches.
    - Automatic programs can be developed to do this, that could be used by both FDA and Sponsors

Installation: Qualify

- Functional (software+system)
  - Good installation kit should be available.
    - NIST has reference data sets that are used by statistical software vendors for qualifying the performance of different procedures or modules (e.g.: ANOVA). Similarly pop data sets can be made available
  - A library of data sets should be centrally available to FDA and Sponsors to perform identical qualification tests
  - Installation qualification should be one command away and generate a log

Maintenance: Revision Controls

- Depending on the need, a user could install a program differently. It is possible that this change might affect some other user in an unknown manner.

- System administrators should be the only personnel to re-install software. A log of different installs should be maintained.

Maintenance: Updates

- When a fresh bug or glitch is detected, the user should be responsible for communicating that to the vendor
  - Associated data sets should also be available
- Vendors should have a transparent protocol for handling bugs
  - By default the users should be notified
  - Depending on the seriousness different actions might be taken
  - Users should insist on reviewing that protocol

Installation: Qualify

- Reference Data Sets
  - For the installation to be qualified with respect to the current patches, we need data sets that could identify the lack thereof
  - It is useful to understand the interactions between software and system
    - Eventually that might lead to rational choice of software and system combination

Installation: Qualify

- Reference Data Sets
  - FDA does not own any data, so the Sponsors should come forward in sharing data sets (blinded)
  - PhArma should make this a priority and coordinate a working group

Proposal: Summary

- Physical
  - Match installed and vendor provided program verbatim line by line
- Functional
  - Procure up to date list of bugs and the respective patches
  - Procure data sets that could detect if these patches were not installed
  - Automate install qualification and generate log

Proposal: Summary

- Maintenance
  - Restricted personnel to install, modify programs
  - Automatic audit trails
- All pop analyses to regulatory agencies might also eventually need
  - Audit trails at the time of analyses
  - Results of the installation qualification

Good Software Practices

Email address:
jogarao.gobburu@fda.hhs.gov

- Is the proposal practically achievable?
- Would you be interested in supporting (time,data,use) such an initiative?
- How should we go about it?

Acknowledgement

- Pharmacometrics Team
  - Dr. Beasley and Dr. Booth

- ECPAG Organizers