Documentation and reporting: best practices proposed by the GBC

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Focus Workshop

(*In collaboration with the AAPS and JBF*)

Industry input into ICH M10: Experimental data as the cornerstone for a science driven bioanalytical guideline

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Problem statement

- Current guidelines on documentation from different regions are pretty much in agreement at a high level…
- …however every region does have its own special requirements: *e.g.* separate CS-BE document for Health Canada, very detailed information on reference standards and IS for Anvisa…
- ICH harmonization is opportunity to standardize documentation wish list from different authorities avoiding delays in the review process.
- Try to move away from country specific documentation requests

The work done by GBC Team A8

- Discussions held in 2011-2013
- Only minor differences between requirements in regulatory guidelines:
  - FDA 2001 & CC III
  - EMA 2012
  - CFDA 2005
  - Anvisa 2003/2012
  - TGA 2004
- Team proposed table of contents for validation report and bioanalytical report
- Team proposed separate section in CTD dedicated to clinical bioanalysis named: “Summary of bioanalytical methods” as an alternative to 2.7.1.
  - Currently section 2.7.1. is on “Summary of Biopharmaceutic Studies and Associated Analytical Methods” which only covers part of the clinical studies

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TOC validation report

SIGNATURE PAGE

STATEMENT OF REGULATORY COMPLIANCE

METHOD VALIDATION SUMMARY TABLE

KEY STUDY INFORMATION (STUDY DATES, PERSONNEL, ARCHIVING)

1. INTRODUCTION

2. METHODS AND MATERIALS
- 2.1. Reference compounds
- 2.2. Calibration standards and QCs
- 2.3. Materials and apparatus
- 2.4. Data acquisition and processing
- 2.5. Calculations

3. VALIDATION EXPERIMENTS AND RESULTS
- 3.1. Regression model
- 3.2. Lower and upper limits of quantification (LLOQ and ULOQ)
- 3.3. Accuracy (% bias) and Precision (% CV) (Include total error for LBA's)
- 3.4. Carry-over
- 3.5. Selectivity
- 3.6. Matrix effect (Specificity in case of LBA's)
- 3.8. Dilution of samples (dilutional linearity and hook effect in case of LBA's)
- 3.9. Extraction recovery
- 3.10. Incurred Sample Reproducibility (ISR) (if applicable)

4. STABILITY
- 4.1. Stability in stock solutions and working solutions
- 4.2. Processed sample stability (PSS)
- 4.3. Stability in matrix

5. CONCLUSIONS

6. TABLES

1. analytical batch overview (table of runs and analysis dates, passed or failed, link with Watson run number)
2. back calculated values calibration curves
3. calibration curve parameters
4. accuracy and precision from QCs
5. evaluation of carry-over
6. evaluation of selectivity
7. matrix effect
8. dilution of samples
9. extraction recovery
10. ISR
11. stability data

7. ADDENDA

Addendum 1:Chemical structures (for small molecule assays)
Addendum 2:Certificates of analysis
Addendum 3:Assay description
Addendum 4:Chromatograms

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TOC bioanalytical report

TABLE OF CONTENTS ANALYTICAL REPORT

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What to document where ?

- CC III paper[1] contains a very detailed table on what information should be:
  - Stored in the raw data
  - Documented in the assay validation report
  - Documented in the bioanalytical report
- Recommendation: Propose this table serve as a starting point for ICH M10 discussions

1. C.T. Viswanathan *et al.*, Pharmaceutical Research 24, 1962-1973 (2007)

Table 1. Details of Documentation Desirable at the Analytical Site and in Validation and Analytical Reports

Items	Analytical Site	Validation Report	Validation Report Appendix	Analytical Report	Analytical Report Appendix
Standard	• Certificate of analysis, purity, stability for analyte. • Record of receipt and storage. • Lack of interference between IS and analyte.	• Batch/Lot #, purity and manufacturer. • Stability at time of use.		• Batch/Lot #, Purity and Manufacturer • Stability at time of use	
Stock solution preparation	• Records of preparation. • Storage location and condition.				
Calibrators and QCs preparation	• Records of preparation. • Freezer log (sample ingress/egress, temperature).	• Preparation dates. • Storage conditions.		• Storage conditions.	
Run acceptance criteria	• SOP* for calibrators, QCs and chromatographic interferences.	• Short description.	• SOP (optional).	• Short description.	• SOP (optional).
Assay procedure	• SOP for the method.	• Brief description of method of extraction, and analysis.	• SOP (optional).	• Brief description.	• SOP (optional).
Sample tracking	• Study sample receipt, condition on receipt and location of storage. • Tracking of QC, calibrators and study samples. • Freezer logs.	• Storage condition and location.		• Dates of receipt of shipments and contents. • Sample condition on receipt. • Storage location and condition.	
Analysis	• Dates of extraction and analysis and instrument ID for each run. • Identity of QCs, calibrators, and study samples • Documentation of processing of calibrators, QCs, and study samples for each run. • Documentation of instrument settings and maintenance. • Run summary sheets. • 100% chromatograms. • LIMS and mode of integration. • Extraction dates.	• Table of runs, instrument ID, and analysis dates. • Table of calibrator results of all runs with accuracy and precision. • Tables of within and between run QC results (accuracy and precision). • Bench-top, freeze-thaw, long-term and post-preparative and stock solution stability data. • Extraction recovery and matrix effect.	• Representative chromatograms. • Cross-validation, if applicable. • Additional validation, if any. • Long-term stability appended or written in a separate report.	• Table of all runs, and analysis dates. • Table of calibrator results of all passed runs with mean and % CV. • Tables of QC results of all passed runs with accuracy and precision. OK to include QC results of the failed runs.	• Chromatograms from 5%-20% of subjects for ANDA and representative chromatograms for NDA submissions.

Table 1. *Continued*

Items	Analytical Site	Validation Report	Validation Report Appendix	Analytical Report	Analytical Report Appendix
Failed runs	• Same as in "Analysis."	• Identify runs, assay date, and reason for failure.		• Identify runs, assay dates, and reason for failure.	
Reintegration	• Audit trail: original and reintegration. • Reason for reintegration. • Mode of reintegration.				• SOP (optional).
Deviations from SOPs/Method	• Documentation of deviations and unexpected events. • Investigation of unexpected events. • Impact assessment.	• Description of deviations. • Impact on study results. • Description and supporting data of significant investigations.		• Description of deviations. • Impact on study results. • Description and supporting data of significant investigations.	
Reassay	• Refer to "Analysis." • SOP for reassay criteria.		• SOP (optional).	• Table of sample IDs, reason for reassay, original and reassay values and run Ids.	• SOP.
Communication	• Between Analytical site and clinical site/sponsor.				

SOP indicates standard operating procedures; IS, internal standard; QC, quality control; QCs, quality control samples; %CV, interbatch imprecision; ANDA, Abbreviated New Drug Application; NDA, New Drug Application, and LIMS, Laboratory Information Management Systems.

Beyond CC III

- draft FDA guidance issued in Sep 2013 contained some additional requirements on documentation
- Some of these requirements may need to be clarified or challenged

Concerns and recommendations (1)

- Method development data in the validation report (FDA)
  - Not recommended; unclear what/when exactly needed

- Step by step description of procedures for preparing QCs and calibrators in the reports
  - Recommendation: details in raw data, only high level in report

Concerns and recommendations (2)

- Sample identification, collection dates, storage prior to shipment, information on shipment batch and storage prior to analysis. Information should include dates, times and sample condition in the bioanalytical report.
  - Recommendation: keep the detail in the raw data; provide statement in the report that “all samples were analyzed within proven LTS period”

- Reasons for missing samples in the bioanalytical report
  - Recommendation: list only received samples in the report (eg in results table); not always feasible for BA lab to get hold of that information, esp. for multi-site studies

Concerns and recommendations (3)

- Storage conditions at the clinical sites in the bioanalytical report
  - difficult for the BA lab to be aware of all deviations from prescribed storage conditions especially for phase 2/3;
  - Recommendation: include statement like: “sites were instructed to store PK samples in a monitored freezer with a set temperature of -20 C”

- % of repeats (Anvisa, Health Canada)
  - Recommendation: assuming this information is requested to gauge assay robustness, # failed runs is a better measure; this information is already displayed in the overview of analytical batches

Concerns and recommendations (4)

- Information on re-integrated samples: chromatograms before/after re-integration, table with re-integrated samples, reason, results before/after (FDA)
  - Balance risk/benefit: including the information upfront might save time as opposed to digging up when request comes in
  - Recommendation: keep that information in the raw data; or alternatively only report for “studies of high importance to the filing” (ie BE/BA type studies)
- Harmonize on #chromatograms in the report
  - Recommendation: 5% (20% BE studies)

Summary

- GBC team A8 propose high level TOC for bioanalytical reports
- Recommendation to use the table from CC III paper as a starting point for ICH M10 discussions on documentation
- Avoid including very detailed information on sample collection/storage/unavailability in the report and keep in the raw data
- If this detail is really needed in the report propose to limit to BE/BA type studies
- Balance effort of putting very detailed information in the report *vs* digging it up when the request comes in
- No real hurdles on documentation for ICH M10 harmonization…
  …but harmonization can make the submission process more efficient preventing re-work to meet country specific wish lists

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