Brief/Technical Note

Theme: Best Practices for Bioanalytical Methods: Recommendations from the Global Bioanalysis Consortium
Guest Editors: Binodh DeSilva and Philip Timmerman

Recommendations from the Global Bioanalysis Consortium Team A8: Documentation

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Abstract. The A8 Global Harmonization Team focused on the documentation needed to support both small and large molecule bioanalysis. Current regulatory requirements were compiled and compared. The scope of the team's discussions included the validation report, the bioanalytical report, study plans, raw data, and bioanalytical summaries for the common technical document (CTD). A common high-level table of contents for method validation and sample analysis reports is proposed. Suggestions have been made as to how the CTD can be standardized to improve usability and review. Additional comments have been made on reports of failure investigations, study plans, and raw data documentation. The recommendation is that no prescriptive guidelines are required in these areas but should be led by good scientific practices subject to particular circumstances.

KEY WORDS: A8; documentation; GBC; reports.

INTRODUCTION

The A8 Global Harmonization Team focused on the documentation needed to support both small and large

molecule bioanalysis. To initiate the discussion, the current regulatory requirements listed in the Food and Drug Administration (FDA) (1), European Medicines Agency (EMA) (2), PDMA/MHW (3,4), State Food and Drug Administration (SFDA) (5), Agência Nacional de Vigilância Sanitária (ANVISA) (6,7), Therapeutic Goods Administration (TGA) (8), and Health Canada (9) guidances were compiled and compared. Although current publications are quite detailed on the subject (see for instance also the conference report on the third AAPS/FDA bioanalytical workshop (10)) the team felt some topics would benefit from further clarification. In general, it is clear to the bioanalytical community what should be documented during conduct of a bioanalytical study. In essence, the documentation should enable reconstructability of the reported data. The discussions in the team were therefore mainly focused on what information needs to be archived in the raw data (but should be readily retrievable upon request) and what information needs to end up in the final report.

The scope of the team's discussions included the validation report, the bioanalytical report, study plans, raw data (both paper and electronic records) and bioanalytical summaries as part of the common technical document (CTD).

Documentation on method development was considered to be out of the team's scope as only certain organizations choose to formally document this aspect of bioanalysis in a report. The team does not recommend writing reports on method development as a regular practice. Nevertheless, the team does recommend that any critical experiments performed during assay development be verified during validation and results included in the validation report. An example could be special assay needs discovered during development

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ABBREVIATIONS: GBC, Global bioanalysis consortium; FDA, Food and Drug Administration; EMA, European Medicines Agency; MHW, Ministry of Health and Welfare; SFDA, State Food and Drug Administration; ANVISA, Agência Nacional de Vigilância Sanitária; TGA, Therapeutic Goods Administration; CTD, Common technical document; SOP, Standard operating procedure; GLP, Good laboratory practice; PDF, Portable document format; GCP, Good clinical practice; MRD, Minimum required dilution; LLOQ, Lower limit of quantitation; ULOQ, Upper limit of quantitation; LBA, Ligand binding assay; LIMS, Laboratory information management system; QC, Quality control sample.

(e.g., particular sample stabilization requirements). Documentation on biomarkers was also not considered within scope of the team.

CONTENT OF THE VALIDATION AND BIOANALYTICAL STUDY REPORT

A considerable amount of the team's effort was focused on the two main report types that are produced by the bioanalytical lab: the validation report which documents the validity of the method prior to sample analysis and the bioanalytical report which summarizes the acceptability of the analytical results found during study sample analysis. The team is not recommending nor has it designed a template for these report types, rather has proposed suggested table of contents for these documents. Standardizing the way these reports are built should facilitate the review by regulatory authorities. The outcome of these discussions is reflected in [Appendix 1](#) for the validation report and [Appendix 2](#) for the bioanalytical report. The reader is deferred to these appendices for recommendations for each of the sections of these reports.

STUDY PLAN

For study sample analysis conducted at the sponsor's own bioanalytical lab, we suggest that a dedicated bioanalytical study plan should be optional. Pre-analytical work (*i.e.*, sample collection) is and must be, specified in the preclinical or clinical study protocol or in a separate pharmacokinetics (PK) sample collection instruction manual.

It is good practice to develop a study plan for outsourced studies, especially when the sponsor requests procedures to be followed which deviate from the contract lab's SOPs.

For method validations, a study plan may be mandatory, certainly if the company chooses to perform validations of preclinical assays according to good laboratory practice (GLP). The wording in the recent EMA guidance (2) on the need to perform method validations under GLP is somewhat ambiguous. Within this global bioanalysis consortium (GBC) team, there was no consensus on the need to perform validations under GLP.

RAW DATA

All laboratory data needs to be readily retrievable for the reconstruction of the study. As technology is evolving, it is anticipated that electronic data storage will increase and the volume of paper records will decrease. The lab should define per standard operating procedure (SOP) what is to be considered the raw data: paper or electronic. In case of chromatographic assays, the electronic data are generally considered as the primary raw data. We should however be sensitive to the fact that different parts of the world are moving with new technologies at different speeds and that not every organization will be able to commit to the investment required to be fully electronic.

The use and maintenance of electronic records is laid out in the FDA guidance on electronic records and electronic signatures Title 21 CFR Part 11 (11). An important challenge in complying with this regulation is the readability of

electronic data as instrument platforms and software versions change over time.

With the increased use of electronic document management systems in the labs comes the challenge of combining paper raw data from systems that are not (yet) producing electronic records with data from systems that do produce electronic records. As a transitional measure, until all study records can be produced electronically, we therefore recommend considering an electronic copy of a paper-based document of equal value. As an example, the chain of custody information of patient samples shipment continues to be documented on paper but a PDF of the scanned documents could be retained and the paper version can be destroyed after verification. We acknowledge that this is not according to current GLP guidelines but the impact is minimal.

The discussion on raw data also stretches beyond the physical limits of the bioanalytical lab. Regulators are paying more attention to the integrity of the samples prior to their arrival at the doorstep of the bioanalytical lab. Some regulators request temperature loggers for shipment monitoring, but the A8 team is not recommending this. It should be sufficient to make use of a courier that is logistically equipped to replenish dry ice during transport, should this be required to guarantee the integrity of the samples during transport. Much attention is also paid to the documentation of storage conditions at the clinical sites. The personnel at the clinical site should be fully aware of the importance of strict adherence to the sample collection and storage procedures as outlined in the clinical protocol or PK sample collection manual to ensure integrity of the samples. Sites and central labs are operating under good clinical practice (GCP) and storage conditions at sites (and central labs if applicable) should be documented in a GCP compliant manner.

Retrieval of raw data is expected to be performed quickly and completely. However, regulators need to be aware that raw paper data may be stored at an offsite location which does increase the time to retrieve the data. Therefore, the team recommends that inspectors give 24-h advance notice to expedite the review process.

FAILURE INVESTIGATIONS

There is no need to write a separate report for every failed run or experiment. If the reason for a failed batch or failed experiment is straightforward, then this can be described in the analytical or validation report. If more extensive investigations were done involving experimental testing, then it might be useful to document this in a separate failure investigation report which can then be appended to the respective report. It is important to document *a priori* which experiments will be conducted (e.g., in a lab notebook). Also a SOP should be available which describes failure investigations and when these should be initiated. A list of topics that should trigger an investigation is beyond the scope of this team.

THE COMMON TECHNICAL DOCUMENT

A lack of standardization of the bioanalytical section of the CTD may increase the regulators' review time due to the

repeated requests for the location of specific information in the CTD. Bioanalytical information on the preclinical and clinical assays is located in different sections of the CTD: section 2.6.5 for preclinical and section 2.7.1 for clinical assays. The current expectation on what information should be contained in section 2.7.1 is somewhat ambiguous as this section is limited to studies conducted as part of the formulation development process (focused on bioavailability and bioequivalence studies) and its associated analytical methods. It is, however, not very clear if the analytical methods used for any other PK study should also be described in this section (or totally omitted). The team recommends that a separate subsection in the clinical overview named “summary of bioanalytical methods” where all information on the clinical bioanalytical assays is combined should be created or reserved. The section should describe a high-level history of the method(s) with rationale for the changes made to the assays during the development of the compound. The focus should be on the compound(s) being submitted. No details need to be provided on dosed co-medications analyzed as part of a drug-drug interaction trial. Metabolite and urine assays should only be described here if these data are used to support safety decisions.

The section should contain two main tables: one, summarizing the main validation parameters of the different assays and the other one, linking the different clinical studies to the corresponding assays, the validation report and the study report.

CONCLUSION

The A8 (documentation) team of the GBC considered the following to be within their scope:

- Review of current global and regional regulatory guidelines where reporting of bioanalytical data is considered or required;
- Documentation to support small and large molecule regulatory bioanalysis.

The A8 team is making the following broad recommendations and comments:

- The major regulatory bioanalytical guidelines have a high degree of commonality regarding reporting requirements. Some authorities have particular requirements reflecting their particular intent, for example, in the reporting of bioanalytical data from bioequivalence studies. Some comments have been made on these particular requirements in an attempt to deliver coherence and harmonization;
- The method validation report, the bioanalytical study sample analysis report, and the bioanalytical part of the common technical document are the key documents for regulatory bioanalysis;
- The team have concluded that a common high-level table of contents for method validation and sample analysis reports is the most detailed level of description of report content needed or desirable;
- Suggestions have been made as to how the CTD can be standardized to improve usability and review;
- Additional comments have been made on reports of failure investigations, study plans, and raw data documentation. In general, we recommend that no prescriptive guidelines are required in these areas but

should be led by good scientific practices subject to particular circumstances.

APPENDIX 1: TABLE OF CONTENTS VALIDATION REPORT

Signature Page

Statement of Regulatory Compliance

For validations in preclinical species, if performed under GLP, the compliance statement is straightforward. However, for validations in man, one should refrain from claiming GLP. A proposed wording could be: “The report and related raw data were inspected and verified for compliance to applicable governmental regulations and implemented internal standard operating procedures.”

Method Validation Summary Table

This summary table is considered very useful in facilitating the review. A template for this table is available in the EMA guideline on the investigation of bioequivalence (12). This summary table could also be included as an addendum to the analytical report (addendum 5 in [Appendix 2](#)).

Key Study Information (experiment dates, personnel, archiving)

The start and end date of the experiments could be included here. However, more detailed information should be included in Table 6.1 at the end of the report.

For validations that are not carried out under GLP, the names of the responsible personnel are considered non-essential as the signature page indicates the key contributors to the study. However, for GLP validations this is essential. According to FDA GLP regulations (13), the name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study should be in the report.

The archiving location for the data cited should be documented in the report for GLP studies. For validations not conducted under GLP, the team recommends this be included as well to facilitate raw data retrieval.

1. Introduction

2. Methods and materials

2.1 Analytical Method Information

This section contains a high-level description of the assay (with a reference to a more detailed assay description in the addendum) and the regression model used. For large molecule bioanalysis, mention should be made of the platform employed, a high-level description of the ligand binding method, and the minimum required dilution (MRD).

2.2 Reference Compounds

2.3 Calibration Standards and QCs Preparation

2.4 Data Acquisition and Processing

A listing of the validated software that was used to acquire and process the data is necessary. A listing of calculations used may also be valuable in this section or can be described in the respective sections below.

2.5 Calculations

3. Validation Experiments and Results

3.1 Regression Model and Formula

3.2 Lower and Upper Limits of Quantification (LLOQ and ULOQ)

3.3 Accuracy (% Bias) and Precision (% CV) (including the formula used)

3.4 Carry-Over (if applicable)

3.5 Selectivity

3.6 Matrix Effect (specificity and MRD in case of LBAs)

3.7 Dilution of Samples (dilutional linearity and hook effect in case of LBAs)

3.8 Extraction Recovery (for chromatographic methods)

3.9 Incurred Sample Reproducibility (ISR) (if applicable)

4. Stability

4.1 Stability in Stock Solutions and Working Solutions

4.2 Processed Sample Stability

4.3 Stability in Matrix (short and long term, freeze/thaw)

5. Conclusions

6. Tables

6.1 Analytical Batch Overview (table of runs and analysis dates, passed or failed, link with Watson (or relevant LIMS) run number)

6.2 Back-Calculated Values Calibration Curves

6.3 Calibration Curve Parameters

6.4 Accuracy and Precision from QCs

6.5 Evaluation of Carry-Over

6.6 Evaluation of Selectivity

6.7 Matrix Effect

6.8 Dilution of Samples

6.9 Extraction Recovery

6.10 ISR

6.11 Stability Data

7. Addenda

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

The proposal is to include only a very limited number of chromatograms in the report: a blank, a zero, an LLOQ and a ULOQ standard.

APPENDIX 2: TABLE OF CONTENTS ANALYTICAL REPORT

Signature Page

Statement of Regulatory Compliance

For preclinical safety studies performed under GLP, the compliance statement is straightforward. However, for clinical studies, one should refrain from claiming GLP. A proposed wording could be: "The report and related raw data were inspected and verified for compliance to applicable governmental regulations and implemented internal standard operating procedures."

Key Study Information (sample receipt and analysis dates, personnel, archiving)

For sample receipt, especially when multiple shipments have occurred, only the date of the first and last sample reception should be sufficient (see also under 3.1.)

The start and end date of subject sample analysis could be included here. However, more detailed information should be included in the tables at the end of the report (see under 3.2)

For clinical study reports, the names of the responsible personnel are considered non-essential as the signature page indicates the key contributors to the study. However, for non-clinical GLP studies this is essential. According to FDA GLP regulations (13) the name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study should be part of the report of non-clinical laboratory study results.

The archiving location for the data cited should be documented in the report for GLP studies. For clinical studies the team recommends this be included as well to facilitate raw data retrieval.

1. Introduction

2. Materials and Methods

2.1 Analytical Method Information

This section contains a high-level description of the assay (with a reference to a more detailed assay description in the addendum) and the regression model used. For large molecule bioanalysis, mention should be made of the platform employed, a high-level description of the ligand binding method, and the MRD,

2.2 Reference Compounds

2.3 Calibration Standards and QCs Preparation

The actual date of preparation of the QCs and standards need not be listed here but a statement should be added that QCs and standards were used within the proven long-term stability period.

2.4 Data Acquisition and Processing

A listing of the validated software that was used to acquire and process the data is necessary. A listing of calculations used may also be valuable in this section or can be described in the respective sections below.

3. Results

3.1 Sample Receipt and Storage

A general statement like “samples and QCs were stored in a monitored freezer with a set temperature of -20°C ” should be sufficient unless there were any deviations which should be documented here along with an evaluation of the impact on the study results. More specific information should be kept in the raw data. Care should be taken that all samples are analyzed within the window of demonstrated stabilities, *e.g.*, long-term storage stability. This can be documented by a statement that “long-term stability data cover the age of the samples and include the longest period of sample storage.”

3.2 Sample Analysis (batch overview, acceptance criteria)

Any laboratory information management system (LIMS) should be able to generate a tabular overview of all batches within a study, including the failed runs, along with the analysis date (refer to Table 5.1). This should help reviewers assess the quality of the method. The high-level reason for failure should also be described in the report, *e.g.*, “batch failed because too many QCs outside of acceptance criterion” is considered sufficiently detailed.

For chromatography methods, ANVISA is requesting clock times of first and last injection in each run but this seems excessive, since this will be in the raw data. However, we do recommend that a good scientific practice would be to identify those runs where the analysis was interrupted due to technical issues. Also, the grouping of the subjects' samples within the run is available in the raw data and should not be described in detail in the report.

The acceptance criteria can be described in the text or the specific SOP can be included as an attachment.

3.3 Linearity

Discussion on back-calculated values and regression parameters for calibration lines referring to Table 5.2 and 5.3.

3.4 Accuracy

Calculation of the within- and between-run QCs accuracy with reference to the data in Table 5.4.

3.5 Precision

Calculation of the within- and between-run QCs precision with reference to the data in Table 5.4.

3.6 IS evaluation (if applicable)

If an IS evaluation was done in the study the criteria should be listed here.

3.7 Repeat analysis

List the repeated samples in a table (Table 5.5) with the initial value, the reason for the repeat, the repeat value, and the reason for acceptance. This should only be done for samples that were part of accepted batches. Canada, Brazil, and the EMA request the number of repeats as a percentage of the total number of samples. There was no consensus on how exactly this number should be calculated nor on the need to include this in a report. If the purpose of this number is to assess the ruggedness of the assay, then we suggest using the percentage of failed batches as the value, although it can be argued that this is “*de facto*” obtained from the data in the report.

3.8 Incurred Sample Reproducibility (ISR) (if applicable)

If ISR was performed as part of the study the criteria should be listed here.

3.9 Failed Run Investigation (if applicable)

3.10 SOP/Assay Method Deviations (if applicable)

Include any deviation from the validated assay here and describe the impact on the study results.

4. Conclusions

5. Tables

5.1 Analytical Batch Overview

This is a table listing all of the analytical runs with corresponding analysis dates and indication if the run passed or failed

5.2 Back-Calculated Values Calibration Standards

5.3 Calibration Curve Parameters

These parameters include slope, intercept, and correlation coefficients. For large molecule bioanalysis, the asymptotes can also be included. Performing statistics on these parameters does not have added value and can be omitted.

5.4 Accuracy and Precision from QCs

The table should display the QC results from all accepted batches, outliers should be flagged and both intra- and inter-batch accuracy and precision should be calculated.

5.5 Reanalyzed Individual Samples

This table should trace the reanalyzed samples to a valid reported value, and include the reason for the failure.

5.6 ISR

6. Addenda

Addendum 1 Certificates of analysis for the analyte(s)
Addendum 2 Assay description
Addendum 3 Results Report

The final results are listed here in tabular format. However, results are usually listed in a specific format to fit with a database, especially in case of clinical studies. This often makes these tables very difficult to read and may therefore be of limited added value. It is therefore suggested to only list these columns in the table which allow identification of the sample along with the corresponding concentration.

Addendum 4 Chromatograms (for chromatographic methods)

Most regulators ask for 5 or 20% of the subjects with calibration samples and QCs from these runs, and only for clinical studies. It is best to define which chromatograms will be included in the report *a priori* in an SOP, *e.g.*, the first 5 (or 20)% of subjects analyzed to avoid cherry picking the best looking chromatograms.

Addendum 5 Method validation summary (from validation report); optional

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