Workshop

Towards harmonised implementation of the ICH M10 Guideline

Chapter 8 – Documentation

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on behalf of the EBF

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Flow of the session

- Short introduction on what is new or what has changed
- List of top ten themes/questions selected from the EBF survey
- Panel discussion, building on pre-submitted questions
- Discussion on any additional questions/comments raised in the panel discussion
- Proposals for harmonized implementation

Chapter 8 – Documentation

what is new or what has changed

Synopsis overview of methods

– History/evolution of methods to be available only at the analytical site (not in reports).

Critical reagents

– more information requested (conc. if applicable)

Stability

– working solution stability now requested

Calibration standards and QCs:

– batch number, preparation dates and stability period to be included in validation reports

Standard Operating Procedures:

– A list of procedures/analytical protocols used for the method has to be included in the BA report

Chapter 8 – Documentation

what is new or what has changed

Sample Tracking:

- Storage location of QCs and Cals is no longer required in validation reports
- Number of samples/shipment should be indicated in the BA report
- Subject Ids should be added to BA reports for BA/BE studies

Chapter 8 – documentation

what is new or what has changed

Analysis (new requirements):

- **Validation reports:**
  - Table of Calibration Standard Concentration and response function of all accepted runs with accuracy and precision
  - Instrument ID for each run for BA/BE studies
  - 100% summary table of accepted and failed runs for BA/BE studies

- **Bioanalytical reports:**
  - Table of reinjected runs with results from reinjected runs and reason(s) for reinjection
  - Instrument ID for each run for BA/BE studies
  - 100% summary table of accepted and failed runs for BA/BE studies
  - List of subjects to be indicated for BA/BE studies
  - ISTD plots requested for BA/BE studies

Chapter 8 – documentation

what is new or what has changed

Chromatograms and reintegration:

- 100% Chroms for all runs in Validation report for BA/BE studies
- 100% Chroms for all runs in Bioanalytical report for BA/BE studies

Reanalysis/Repeat analysis:

- Re-analysis SOP no longer needed in BA report
- Values from rejected runs to be included in a separate table for BA/BE studies

ISR:

- SOP for ISR no longer needed in BA report

Chapter 8 – documentation

what is new or what has changed

Audits and inspections:

- For BA/BE, list of regulatory site inspections including dates and outcomes for each analytical site if conducted over last 3 years and one year up to study completion

Documentation/Communication:

- Relevant documentation includes, but is not limited to, source data, protocols and reports, records supporting procedural, operational, and environmental concerns and correspondence records between all involved parties

Themes/questions discussed today

1. **Synopsis overview of methods:** History/evolution of methods to be available only at the analytical site (not in reports). The info is still needed in the summary table in the CTD module so it would be good to have it in the reports to facilitate the compilation of the CTD.
2. **Validation reports**: for BA/BE studies, Instrument IDs for each run, 100% summary tables of accepted and failed runs, 100% chroms from all runs are requested. These requirements should apply to Bioanalytical Reports and not to Validation Reports.
3. **Bioanalytical reports:** Instrument ID for each run for BA/BE studies (should this include ancillary equipment?).
4. **Bioanalytical reports:** table of reinjected runs with results from reinjected runs. Not clear, in case a reinjected run is accepted the results should already be in the report.
5. **Standard Operating Procedures:** a list of procedures/analytical protocols used for the method should be provided. Are these SOPs or Method Descriptions?
6. **Sample Tracking:** analytical site storage location: what does this mean? Is it freezer temp (e.g. -20°C) or freezer ID and address of the lab?
7. **Analysis:** Instrument use logs including dates of analysis for each run at analytical site: are separate instrument logbooks needed or can this information be included in the run summary tables?
8. **Chromatograms and reintegration:** sentence after Mode of reintegration does not make any sense. Information to include in the run summary tables is not defined. Typo?
9. **Reanalysis/Repeat analysis**: values from rejected runs to be included in a separate table for BA/BE studies: not clear, as original runs may have no reportable concentration data.
10. **Audits and inspections:** for BA/BE, list of regulatory site inspections including dates and outcomes for each analytical site if conducted over last 3 years and one year up to study completion

Theme n.1: Synopsis overview of methods

- A summary table of all the relevant Validation Reports should be provided for each analyte, including Partial Validation and Cross Validation Reports. The table should include the method identification code, the type of method, the reason for the new method or additional validation (e.g., to lower the limit of quantification). Changes made to the method should be clearly identified.

ICH M10
section 8.1

Table 1: Documentation and Reporting

Items	Documentation at the Analytical Site	Validation Report*	Bioanalytical Report*
Chromatographic System Suitability	• Dates, times, and samples used for suitability testing	• Not applicable	• Not applicable
Synopsis Overview of Method Evolution	• History/evolution of methods (e.g., to explain revisions, unique aspects with supportive data, if available)	• Not applicable	• Not applicable

ICH M10
table 1

Table 2. Documentation and Reporting (refer to sections III.B and VI for additional information)

Items	Documentation at the Analytical Site	Validation Report*	Analytical Study Report*
System Suitability	• Dates, times, QCs or samples used for suitability testing	• Not applicable	• Not applicable
Synopsis	• Not applicable	• Synopsis of method development (e.g., evolution of methods with multiple revisions, unique aspects)	• Not applicable
		• Overall summary information	

FDA 2018

Theme n.1: Synopsis overview of methods

- This information should be included in Section 2.6.4/2.7.1 of the Common Technical Document (CTD; or electronic CTD, eCTD) or reports.
- History/evolution of methods should be available only at the analytical site (not in reports).
- Would it be good to have it in validation reports to facilitate the compilation of the CTD?

Questions to the panelists/audience: What is your interpretation of this requirement? Would you support the proposal to always include the history/evolution of methods in Validation reports?

Theme n.2: Validation reports

Table 1 continued: Documentation and Reporting

Items	Documentation at the Analytical Site	Validation Report*	Bioanalytical Report*

Analysis	• Documentation and data for system suitability checks for chromatography
	• Instrument use log, including dates of analysis for each run
	• Sample extraction logs including documentation of processing of calibration standards, QCs, and study samples for each run, including dates of extraction
	• Identity of QCs and calibration standard lots, and study samples in each run
	• Documentation of instrument settings and maintenance
	• Laboratory information management system (LIMS)
	• Validation information, including documentation and data for:
	  ○ Selectivity, specificity, sensitivity, precision and accuracy, carry-over, dilution, recovery, matrix effect
	  ○ Bench-top, freeze-thaw, long-term, extract, and stock solution stability
	  ○ Cross/partial validations, if applicable
		For All Studies:
		• Table of all runs (including failed runs), and analysis dates
		• Table of calibration standard concentration and response functions results (calibration curve parameters) of all accepted runs with accuracy and precision.
		• Table of within- and between- run QC results and calibration standards (from accuracy and precision runs). Values outside the acceptance criteria should be clearly marked.
		• Include total error for LBA methods
		• Data on selectivity, specificity, dilution linearity and sensitivity (LLOQ), carry-over, recovery. Bench-top, freeze-thaw, long-term, extract, and stock solution stability
		• Partial/cross-validation, if applicable
		• Append separate report for additional validation, if any
		Additionally, for Comparative BA/BE Studies also include:
		• Instrument ID for each run in comparative BA/BE studies †
		• 100% of run summary table of accepted and failed runs
			For All Studies:
			• Table of all runs, status (accepted and failed), reason for failure, and analysis dates.
			• Table of calibration standard concentration and response function results (calibration curve parameters) of all accepted runs with accuracy and precision.
			• Table of QCs results of all accepted runs with overall (between-run) accuracy and precision results of the QCs and between-run accuracy and precision results from accepted runs.
			• Table of reinjected runs with results from reinjected runs and reason(s) for reinjection
			• QCs graphs trend analysis encouraged
			• Study concentration results table.
			Additionally, for Comparative BA/BE Studies also include:
			• Instrument ID for each run in comparative BA/BE studies†
			• IS response plots for each analytical run, including failed runs
			• 100% of run summary table of accepted and failed runs

† May append or link from Validation Report.

Theme n.2: Validation reports

For BA/BE studies, Instrument IDs for each run, 100% summary tables of accepted and failed runs, 100% chroms from all runs are requested. Possible interpretations:

1. These requirements apply to the Validation Reports for BA methods used to support BA/BE studies.
   - The requirements may apply to all validation reports if it is not known in advance whether a method will be used to support BA/BE or not.
   - In case it is not known whether the assay would be used for BA/BE, the additional information could be added in a new amended version of the original validation report.

Proposed at YEMM

2. These requirements should apply only to Bioanalytical Reports and not to Validation Reports.

Question to the panelists/audience: what is your interpretation of this requirement?

† May append or link from Validation Report.

Theme n.3: Bioanalytical reports

Bioanalytical Report*

For All Studies:

- Table of all runs, status (accepted and failed), reason for failure, and analysis dates.
- Table of calibration standard concentration and response function results (calibration curve parameters) of all accepted runs with accuracy and precision.
- Table of QCs results of all accepted runs with overall (between-run) accuracy and precision results of the QCs and between-run accuracy and precision results from accepted runs.
- Table of reinjected runs with results from reinjected runs and reason(s) for reinjection
- QCs graphs trend analysis encouraged
- Study concentration results table.

Additionally, for Comparative BA/BE Studies also include:

- Instrument ID for each run in comparative BA/BE studies†
- IS response plots for each analytical run, including failed runs
- 100% of run summary table of accepted and failed runs

The Instrument ID for each run should be included in the BA report for BA/BE studies.

Possible interpretations:

1. Include instrument used for data acquisition only (e.g. LC-MS xyz)
2. As in 1. + all its connected components (LC pumps, autosampler)
3. As in 2. + its connected components (LC pumps, autosampler) + ancillary equipment (e.g. centrifuges, RSPs)

Question to the panelists/audience:

what is your interpretation of this requirement?

Theme n.4: Bioanalytical reports

Bioanalytical Report*

For All Studies:

- Table of all runs, status (accepted and failed), reason for failure, and analysis dates.
- Table of calibration standard concentration and response function results (calibration curve parameters) of all accepted runs with accuracy and precision.
- Table of QCs results of all accepted runs with overall (between-run) accuracy and precision results of the QCs and between-run accuracy and precision results from accepted runs.
- Table of reinjected runs with results from reinjected runs and reason(s) for reinjection
- QCs graphs trend analysis encouraged
- Study concentration results table.

Additionally, for Comparative BA/BE Studies also include:

- Instrument ID for each run in comparative BA/BE studies†
- IS response plots for each analytical run, including failed runs
- 100% of run summary table of accepted and failed runs

This requirement is not clear: in case a run is reinjected and accepted, the accepted results are already in the report.

Possible interpretations:

- Report the tabulated data as requested, and document the reason
- Do not report these tables

} Proposed at YEMM

Question to the panelists/audience:
what is your interpretation of this requirement?

Theme n.5: Standard Operative Procedures

Table 1 continued: Documentation and Reporting

Items	Documentation at the Analytical Site	Validation Report*	Bioanalytical Report*
Standard Operating Procedures (SOPs; Procedures)	Procedures for all aspects of analysis, such as: • Method/procedure (validation/analytical) • Acceptance criteria (e.g., run, calibration curve, QCs) • Instrumentation • Reanalysis • ISR • Record of changes to SOP (change, date, reason, etc.)	• A detailed description of the method procedures	• A list of procedures/analytical protocols used for the method

The list of procedures/analytical protocols used for the method should be included in the Bioanalytical Report. This requirement is unclear.

Possible interpretations:

1. All SOPs followed to perform the analysis should be included in the list.
2. The list of procedures corresponds to the Bioanalytical Method Description, which may be included as an appendix. No additional SOPs should be listed.

Question to the panelists/audience: what is your interpretation of this requirement?

Theme n.6: Sample Tracking

Sample Tracking	• Study sample receipt, and condition on receipt • Records that indicate how samples were transported and received. Sample inventory and reasons for missing samples • Location of storage (e.g., freezer unit) • Tracking logs of QCs, calibration standards, and study samples • Freezer logs for QCs, calibration standards, and study samples entry and exit	• Not applicable	**For All Studies** • Dates of receipt of shipments number of samples • Sample condition on receipt • Analytical site storage condition and location • Storage: total duration from sample collection to analysis • List of any deviations from planned storage conditions, and potential impact **Additionally, for Comparative BA/BE Studies also include:** • The subject ID

The analytical storage conditions and location should be included in the Bioanalytical Report. This requirement is unclear.

Possible interpretations:

1. Include minimum info (e.g. -20°C freezer)
2. As in 1., plus freezer ID
3. As in 2., plus address of the lab?

Question to the panelists/audience: what is your interpretation of this requirement?

Theme n.7: Analysis - instrument use logs

Table 1 continued: Documentation and Reporting

Items	Documentation at the Analytical Site	Validation Report*	Bioanalytical Report*
Analysis	• Documentation and data for system suitability checks for chromatography • Instrument use log, including dates of analysis for each run	**For All Studies:** • Table of all runs (including failed runs), and analysis dates • Table of calibration standard	**For All Studies:** • Table of all runs, status (accepted and failed), reason for failure, and analysis dates.

Instrument use logs including dates of analysis for each run should be available at the analytical site. This requirement is unclear.

Possible interpretations:

1. Always use instrument logbooks
2. No instrument logbooks needed as the information is available in the run tables.

Question to the panelists/audience: what is your interpretation of this requirement?

Theme n.8: Chromatograms and reintegration

Table 1 continued: Documentation and Reporting

Items	Documentation at the Analytical Site
Chromatograms and Reintegration	• Electronic audit trail: • 100% e-chromatograms of original and reintegration from accepted and fail runs • Reason for reintegration • Mode of reintegration 100% of run summary tables of accepted and failed runs, including calibration curve, regression, weighting function, analyte and IS response and retention time, response ratio, integration type

This requirement is unclear.

Quite probably a typo, the wording after 'Mode of reintegration' should not be considered.

Proposed at YEMM

Question to the panelists/audience: what is your interpretation of this requirement?

Theme n.9: Reanalysis/Repeat analysis

Reanalysis/Repeat Analysis	• Procedures for conducting reanalysis/repeat analysis (define reasons for reanalysis, etc.) • Retain 100% of repeat/reanalysed data • Contemporaneous records of reason for repeats	• Not applicable	**For All Studies:** • Table of sample IDs, reason for repeat analysis, original and repeat analysis values, reason for reported values, run IDs **Additionally, for Comparative BA/BE Studies also include** • For comparative BA/BE studies, values from rejected runs should be included in a separate table.

Possible interpretations:

- Report the tabulated data as requested, and in case of no reportable data from the rejected run, mark these as 'NR' and explain the reason

} Proposed at YEMM

- Do not report these tables because data from rejected runs are meaningless by definition

Question to the panelists/audience: what is your interpretation of this requirement?

Theme n.10: Audits and inspections

8.1 Summary Information

Summary information should include the following items in Section 2.6.4/2.7.1 of the Common Technical Document (CTD; or electronic CTD, eCTD)) or reports:

- For comparative BA/BE studies, a list of regulatory site inspections including dates and outcomes for each analytical site if conducted over the last three years, and one year post study completion.

This requirement is unclear.
E.g. if the study was completed in 2016, should the inspections performed in the period 2019-2022 and 2016-2017 be included?

Question to the panelists/audience: what is your interpretation of this requirement?

LBA Documentation Clarified

Critical reagent documentation specifically clarified:

Retest/expiry dates of critical reagents should be included in all reports.

“The applicant is expected to maintain data at the analytical site to support summary data submitted in validation and bioanalytical reports. validation and bioanalytical reports should be submitted in the application.”

EBF: Critical Reagents handled at site level, could be a memo, partial validation, etc.

Bioanalysis 2018:

EBF recommendation on practical management of critical reagents for PK ligand-binding assays

Susanne Pihl[1], Barry WA van der Strate[2], Michaela Golob[3], Laurent Vermet[4], Birgit Jaitner[5], Joanne Goodman[6], Marianne Scheel Fjording[7] & Philip Timmerman[8]

LBA Documentation Clarified

List of **all SOPs included in report**?

EBF proposal for implementation:

Only methods that are study-specific, relevant analysis done – not full lists of the entire facility.

QC graphs of trend analysis?

EBF proposal for implementation:

Trending analysis of QCs is a good best practice but not for inclusion in reports.

LBA Documentation Clarified

Analysis section:
Instrument ID: Should this also be applied for other equipment e.g ELISA washer?

EBF proposal for implementation:
Only for **data-generating instruments** in the Validation and Bioanalysis Reports when required by M10 **BA/BE studies.**

Actions - recommendations

- …
- …
- …

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