A8: Documentation

Team members:

Team lead

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Other members

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- Hollie Barton PPD NA
- Marian Kelley Mkelley Consulting NA
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- Richard Hucker Pfizer EU
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Interdependencies with other teams – if any

- Dilution factor/ULOQ: S1
- IS evaluation: S1/S2/S3
- Carry-over: S1/S2
- Validation under GLP?: A1

In scope

- Definitions of different report types
- Method Validation reports
- Study protocol / plan
- Study reports
- Failure investigation and documentation
- Documentation at analytical site (including data generation, handling and reporting)
- Raw data definitions (electronic and paper) including chain of custody for samples and reference, standards, notebook records, instrument use, maintenance, system validation, freezer records etc
- Archiving and retrieval of data, storage period for data
- Bioanalytical summary documents ie CTD sections 2.7.1. and 2.6.5.
- Technology platforms for reports

Out of scope

- Clinical study reports
- Documentation of method development
- Harmonized template for validation and study reports

Strategy

- Checked current requirements from different guidelines: FDA, EMA, ANVISA, Health Canada, SFDA(China), PMDA(Japan), TGA (Australia), no specific guidance for India (relies mainly on FDA)
- Highlight significant differences between guidelines
- Extra attention to ANVISA guidelines which are very detailed and confusing
- Highlight overlaps with other teams
- Highlight areas of non-consensus within the team
- The philosophy is not to dictate a restricted format but to discuss the content of the reports. The team feels that this could obviate the need for specialized docs like CSBE for Canada or the detailed requirements from Anvisa.
- Should the team propose a TOC?
- Following things have been discussed: analytical report, validation report, failure investigations, study plan, raw data

Analytical report

- Dates of shipments: only include dates of first and last shipment; include statement that LTS data cover the age of the samples and include longest period of sample storage (from sample taken to analysis)
- Storage location for samples, QCs and calibrators: in a freezer/ ultrafreezer with set temperature
- Dates of subject sample analysis: Anvisa requests clock times of first and last injection for each run; advise: list runs where analysis was interrupted due to technical issues
- Define grouping of subjects' samples in run: advise not to include by default; can be deduced from chromatograms in report
- Date of preparation of QCs: add general statement that QCs were used within proven LTS term
- Limit of quantitation: should the dilution factor be mentioned or conc. of highest dilution QC? Check with team S1

Analytical report

- Repeat analyses: only list repeated samples that are part of accepted batches Canada, Brazil and now also EMA request number of repeats as % of total number of samples. No consensus on what we should include: only PK repeats, or also repeats for analytical reasons and over the curve or over diluted samples? % of failed batches might be better way to assess ruggedness of assay
- Chromatograms: Do the selection *a priori* :first 5 or 20% of subjects with corresponding standards and QCs
- IS evaluation: depends on the outcome of team S1
- Table with the results: usually in specific format that fits database; contains a lot of information which might make difficult to read
- QA statement: note on clinical studies; a proposed wording could be: ” Report XXX and related raw data were inspected and verified for compliance to applicable governmental regulations and implemented internal standard operating procedures by the XXXX unit of XXX. We can reasonably confirm that the report reflects the raw data and the procedures of the project.”

Analytical report

- SOPs: ANVISA requires some SOPs attached to the report; the team advises against that, SOPs are available on request

Validation Report

- Most comments made for the analytical report also apply to validation reports
- Summary table of experimental data considered very useful in facilitating the review; A template is available in EMA guidance CPMP/EWP/QWP/1401/98 (see next slide)
- Carry-over: align the verbiage with the recommendations of team S2

4. Bioanalytics

Table 4.1 Bioanalytical method validation

Analytical Validation Report Location(s)	< Study Code > <vol/page, link>	
This analytical method was used in the following studies:	<Study IDs>	
Short description of the method	<e.g. HPLC/MS/MS, GC/MS, Ligand binding>	
Biological matrix	< e.g. Plasma, Whole Blood, Urine>	
Analyte Location of product certificate	<Name>, <vol/page, link)>	
Internal standard (IS)[1] Location of product certificate	<Name> <vol/page, link>	
Calibration range (Units)		
Lower limit of quantification (Units)	<LLOQ>, <Accuracy%>, <Precision%>	
Standard curve range (Units)		
QC concentrations (Units) Location	<vol/page, link>	
Between-run accuracy	<Range or by QC>	
Between-run precision	<Range or by QC>	
Within-run accuracy	<Range or by QC>	
Within-run precision	<Range or by QC>	
Matrix Factor (MF) (all QC)[1] IS normalized MF (all QC)[1] C.V.% of IS normalized MF (all QC)[1] % of QCs with >85% and <115% n.v.[1,4] % matrix lots with mean <80% or>120% n.v[1,4]	Low QC <Mean> <Mean> <C.V.%> <%> <%>	High QC <Mean> <Mean> <C.V.%> <%> <%>
Long term stability of the stock solution and working solutions[2] (Observed change %),	Confirmed up to <Time> at <°C> < %, Range or by QC>	
Short term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %)	Confirmed up to <Time> <%, Range or by QC>	
Long term stability in biological matrix (Observed change %) Location	Confirmed up to <Time> at < °C> <%, Range or by QC> <vol/page, link>	
Autosampler storage stability (Observed change %)	Confirmed up to <Time> <%, Range or by QC>	
Post-preparative stability (Observed change %)	Confirmed up to <Time> <%, Range or by QC>	
Freeze and thaw stability (Observed change %)	<-Temperature °C, # cycles, > <Range or by QC>	
Dilution integrity	Concentration diluted <X-fold> Accuracy <%> Precision <%>	
Partial validation[3] Location(s)	<Describe shortly the reason of revalidation(s)> <vol/page, link>	
Cross validation(s) [3] Location(s)	<Describe shortly the reason of cross-validations> <vol/page, link>	

[1]Might not be applicable for the given analytical method
[2] Report short term stability results if no long term stability on stock and working solution are available
[3] These rows are optional. Report any validation study which was completed after the initial validation study,
[4] n.v. = nominal value

Instruction

Many entries in Table 4.1 are applicable only for chromatographic and not ligand binding methods. Denote with NA if an entry is not relevant for the given assay. Fill out Table 4.1 for each relevant analyte.

Failure investigation and documentation

- No need for separate report for every failed run or experiment. If straightforward document in analytical or validation report
- If more extensive separate report could be valuable; document a priori which experiments will be conducted
- Important to have an SOP
- Team will not propose a list of topics that should trigger investigation

Study plan

- Good practice for outsourced studies; not needed for internal studies
- Some discussion on need for study plan for validations in view of new EMA guidance; not sure if these should be conducted under GLP which would require a study plan
- Team will not build a template for the study plan

Raw data

- All data need to be retrievable to allow reconstruction of the study.
- In the future, more data will be stored electronically; special attention to archiving and retrieval of these data as instrument platforms and software change over time. A decommissioning plan should be in place.
- With increased use of electronic document management systems in the labs electronic copies should be considered of equal value as paper copies (eg in chain of custody information of patient samples)
- Some regulators request temperature loggers for shipment monitoring; we propose not to go down that route; although some companies use it for BE studies
- Lots of requests around documentation of storage conditions at clinical sites; Agree that BA group is responsible for educating the sites regarding storage conditions, but general agreement that BA group is not responsible for confirming site conditions. Sites are under GCP and storage conditions at sites should be documented in a GCP compliant manner.
- For authority inspections we recommend 48 hours advance notice so we can gather the data which is often stored offsite.
- The lab should define in SOP which are the raw data (paper or electronic); in case of chromatographic assays the electronic data are generally considered the raw data.

CTD

- Lack of standardization may increase review time
- No uniformity on where bioanalysis is documented: some document in 2.7.1., others in 5.3. because of the limitations in 2.7.1.
- Advise to report on the history of the assay: explain rationale for changing the method
- Assay descriptions should be very high level and focused on the compound being submitted; in case of fixed dose combinations better to discuss assays for all analytes
- For interacting drugs a reference to the validation report should be sufficient. For proprietary assays often limited detail is available in the report which may trigger questions.
- Metabolites and urine assays only briefly touched upon. Unless these data are used to back-up safety decisions.
- Some companies only include detail on the “mature” assays and not on the assays used in the early stages of development.

Next steps

- Finalize discussions on feedback from San Antonio, ACBio and today's EBF meeting: e-archiving procedures and documentation of sample age–LT stability data
- Finalize discussion on technology platforms for reports
- Touch base with other teams to finalize some open items
- Write down our proposal in a recommendation document

The A8 Team

Global Bioanalysis Consortium
On harmonization of bioanalytical guidance