Workshop on ICH M10

C5 - Stock and working solutions stability

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(table moderator: Tom verhaeghe)

14 November 2023 – Barcelona, Spain

From the guideline

- **3. Chromatography**
- ***3.1. Reference standards***
- Stock and working solutions should only be prepared from reference standards that are within the stability period as documented in the CoA (either expiration date or the retest date).

From the guideline

3.2. Validation

3.2.8. Stability

3. Stability of the analyte and IS in stock and working solutions

The stability of the stock and working solutions of the analyte and IS should be determined under the storage conditions used during the analysis of study samples by using the lowest and the highest concentrations of these solutions. They should be assessed using the response of the detector. Stability of the stock and working solutions should be tested with an appropriate dilution, taking into consideration the linearity and measuring range of the detector. If the stability varies with concentration, then the stability of all concentrations of the stock and working solutions needs to be assessed. If no isotopic exchange occurs for the stable isotopically-labelled IS under the same storage conditions as the analyte for which the stability is demonstrated, then no additional stability determinations for the IS are necessary. If the reference standard expires, or it is past the retest date, the stability of the stock solutions made previously with this lot of reference standard are defined by the expiration or retest date established for the stock solution. The practice of making stock and working solutions from reference standards solely for extending the expiry date for the use of the reference standard is not acceptable.

Pre-meeting survey

	the question	Yes	No
Q1	When do you perform stock and working solutions stability validation?		
Q2	What criteria do you apply for this assessment?		
Q3	How do you handle IS that have different concentrations and solvents than the analyte?		
Q4	Do you think it is possible/accepted to perform stability assessment of the unlabeled analyte in the solvent and concentration of the IS (as most of the time the IS is the limiting factor)?	12	1
free text			

Key message from the pre-meeting survey comments

- When do you perform stock and working solutions stability validation?
  - Stock solution: Before-during-after MV, after 1-3-6-12 months
  - Working solution: when needed (if not prepared daily)
- What criteria do you apply for this assessment?
  - Bias 5-10-15% *vs* fresh solution; “same as in ICHM10”
  - Depends on the technique UV = 10%; MS = 15%
  - %CV 10-15%
- How do you handle IS that have different concentrations and solvents than the analyte?
  - Try to use same solvent, then no need to test; conc. covered by low-high of analyte WS
  - Always test IS solution stability; test if analyte is unstable
- Do you think it is possible/accepted to perform stability assessment of the unlabeled analyte in the solvent and concentration of the IS (as most of the time the IS is the limiting factor)?
  - Yes (if the salt is the same, if the storage period is covered by the stability of the analyte)

Key message from the round tables

Q1 When do you do Stock and Working Solution Stability

- All conduct the stability assessment in Validation
- Most have an idea of stability from the Method Development
- Working solution stability is regularly done in CROs
- Those who make working solutions and discard on the day don't always do bench top stability

Q2 What criteria do you apply for stability assessment?

- Mixture of criteria's across all workshops group
- Mainly using 5% for stocks but some are going up to 10%
- 15% is sometimes used for protein LCMS
- Most use the same criteria regardless of platform

Q3 what about Internal Standard Stock and Working Solution?

- Nobody really cares about the Internal Standard Stability however it is in the guidance
- For stable labels using the analyte stability, if in the same solution and storage conditions is also common place. If needs to be extended, suggestion is to extend analyte stability rather than using up your IS stock material.
- Some apply a 1 year expiry and use the batch to batch assessment to provide scientific justification for no formal assessment. This can include analogue IS.
- Many don’t see why we need to do stability on IS when we don’t need a certificate of analysis?
- Maybe more discussion needed?

Raw data from the pre-meeting survey comments

- In the next slides we provide the unredacted details from 56 survey files reaching us prior to the deadline.
- Surveys that have arrived after the deadline could not be included anymore, for logistic reasons. Please speak up if your comment wasn't already captured in the other 56 files

On Q1: When do you perform stock and working solutions stability validation?,

- During validation for a short period and later on for a longer period
- In validation
- During first validation a "new" solution is used
- First Full validation
- Beginning of project
- At the discretion of the Validation Study Director
- Always x5
- Stock solution stab prior to BMV and not as part of BMV.
- After 1, 3 and/or 6 -12 months of storage. We do not do working solution unless they can not be prepared freshly In the validation study
- at the 1 month timepoint

On Q1: When do you perform stock and working solutions stability validation?, cntd

- Stock: Always, Working: When stored
- stock solution stability : done once for one analyte (in the first validation study for exempla) / working solution stability : almost never
- Every validation where stock and working solutions are used Fist validation
- part of the method validation
- During core validation
- "Stock solution: when it is prepared from a powder
- Working solution : when a storage is needed"
- If stocks are stored
- during method validation
- depends, sometimes after the validation

On Q1: When do you perform stock and working solutions stability validation?, cntd

- at the end of the development step and before the validation is possible otherwise at the end of the validation
- With the main BA validation
- At the end of validation and study samples analysis
- During method validation
- During validation activity The last test in the method validation.
- As part of the validation, normally after the 1 month stability period has passed
- During validation
- When data are needed to cover study sample analysis and to support regulated studies
- Both in method development and in method validation
- Always if not performed in previous validations as per guidelines

On Q2: What criteria do you apply for this assessment?

- internal criteria, 10%
- 15%
- Assay acceptance criteria (+/- 15%)
- ±15% of freshly prepared solution used as reference
- comparing to fresh Calibratiors ; spiked in plasma
- 5-10% compared to freshly prepared solution
- 10% for MS assays
- 10%
- For determination of stability of stock solutions, the relative deviation between the mean of the 3 measurements of the stored stock solution and the reference value must not exceed 5%.
- 5%
- Stocks within 5% solutions within 10%SOP
- same than all stability criteria
- bias <5%, precision <10%
- 5% when injecting dilutions, or measuring using spectrophotometry

On Q2: What criteria do you apply for this assessment?

- The acceptance criteria will be increased to ±15.0% (and ±20.0% at LLOQ level) when stock/spike solutions will be tested in biological matrix like freshly prepared calibrators
- 5/10%
- Same as in ICH M10
- Bias and CV 10%
- 5%
- Within 10%
- 10% 5%
- Within 5% from qualified stock
- Area comparison and variation <15%
- 10% change, 15% CV
- Depends on the platform of assessment, if UV (quite often) or fluorescence detection is used, the criteria are 10 % and 90-110%. For MS it is 15 % and 85-115%

On Q2: What criteria do you apply for this assessment?, cntd

- within 5 % if uv detector or within 10% for LCMS
- No in-house BA, I work with CROs and normally use what they propose
- The mean Percentage response of stability and comparison solution for drug and IS: it Should be ±10%
- Bias within 5% between ref and CV <5%
- mean results: deviation from freshly prepared solution (+/- 5 % and/or +/- 10 %)
- The % mean solution stability should be in the range of 90-110,. % CV for stability and comparison samples should be within 10% 10% for stock stabilities.
- resulting QCs /Cals need to pass
- 10% change, 15% CV
- T=0 At the defined conc. Vs sample stored at working temperature
- within 10% (GBC paper 2014)
- usually 10% percentage difference if in solvent, depends on vendor's SOP

On Q3: How do you handle IS that have different concentrations and solvents than the analyte?

- We only use Sil and therefore same solvents as analyte
- Own stability tests
- Solution stability performed (analogue only)
- For SIL-IS, no stability is explicitely determined
- Concentration of IS is in the range od concentration of the analyte, avoid different Reagents. If not avoidable verify
- under discussion
- The same as the analyte. Dilute till it's on range and compare old vs new stock.
- "A structural analogue internal standard can be given 12 months stability provided one month stability of the stock solution of the corresponding analyte has been shown. SILIS stab = proven stab for Analyte, providing ""SILIS test "" conducted pre- validation.
- Focus on ZERO samples post validation, in-study "
- We performed the IS stability only for not stable labelled compound
- still infer stability if isotopically labelled
- Considered no stability is tested on deuterated IS, only verify if area ratio are correct for unlabelled IS
- a separate stability test is done
- Ignore by definition

On Q3: How do you handle IS that have different concentrations and solvents than the analyte?, cntd

- As long A/P is OK why worry about IS stability?
- IS SL stability performed in addition, if CoA is available Stability have to be done
- Current procedure-no stability investigation for stable labelled IS separate assessment IS concentration is always bracketed by the analyte high and low concentration We often dilute the internal standard working solution in plasma/serum (same matrix as validated for) in order to being able to use the extensive number of matrix stability data
- Stability need to be demonstrated
- IS stability is performed when solvents id different
- try to avoid
- We perform all solution stabilities as in the case of drug stock and dilution
- According to validation.
- We have not done IS stability before due to the interpretation of page 5, a COA is not required for the IS as long as the suitability for use is demonstrated. As part of the ICH M10 section stability(3) have only start doing it in this year. A bit of ambiguity here. IS concentration is always bracketted by the analyte high and low concentration
- Istd is handled considering the analyte solubility, sample prep. And extraction are adapted consequently
- at least short-term stability should be determine

On Q4: Do you think it is possible/accepted to perform stability assessment of the unlabeled analyte in the solvent and concentration of the IS (as most of the time the IS is the limiting factor)?

- Yes, but I think it is not necessary as long as no isotope exchange occurs
- is stability assessment at the concentration really needed. The objective for a ISTD is to have stability over the batch run (constant response) and no unlabelled analyte.
- No, we have been challenged by ANVISA; we proved stability for the analyte in solution for 6 months but use the solution of the STIL IS for longer period because of scarce material and they want us to cover the use of the IS solution with stability data; is probably not related to ICM10 as they have not yet adopted it.
- Yes, only if analyte conc is included in the IS conc range
- Is the stability of internal standard a valid assessment? We tend not to use analogues, but believe demonstration of a consistent level and without presence of analyte is sufficient (zero)
- Y (provided that the salt form is identical due to solubility differences)
- Y, possible if IS is the stable label of analyte
- Do not understand the question It is acceptable but very complicated to handle Yes, should be accepted. Then will work on the area ration and compensate for injection variability
- N, but in case we evaluate the chemical properties of the unlabeled analyte before assessing the stability
- if you can demonstrate no isotopic exchange occurs, yes

Free text

- Can stock and working solutions be completed on HPLC\PDA for MS studies and what will the acceptance criteria look like?
- Stock solution stability - what is your common practice on assessing stock solution stability? Do you prepare the primary stock and then use this one throughout the validation and then test after final validation run (excl Long-term stability), but within e.g. 2 weeks? Or do you establish stock solution stability as one of the first parameters prior to the start of the validation?