Temperature Stability Testing, Are both -20°C and -70°C required?

Presenter: Timothy Sangster
on behalf of EBF

Focus Workshop

(*In collaboration with the AAPS and JBF*)

What should be the scope of the guideline and why.

including discussion on studies, development phases or analytes in/out of scope

The Altis Grand Hotel Lisbon,
Portugal September 24-26, 2017

Problem statement

- Although fundamental physicochemical laws are clear, industry continues to over-validate long term storage stability testing, by repeating successful long term storage at -20°C at -70/80°C at increased cost and no added value.

Temperature stability testing, are both -20°C and -70°C needed?

We currently generate frozen stability data at all conditions that samples at stored at. It is possible to generate frozen stability at -20°C and then storage at a lower temperatures (-70°C or -80°C) is considered acceptable?

Current Regulatory Guidance

- EMA Guideline on bioanalytical method validation. 2011
  - 4.1.9. Stability

    ‘….and after the applied storage conditions that are to be evaluated.’

    ‘Stability studies should investigate the different storage conditions over time….’

    ‘Long term stability of the analyte in matrix stored in the freezer.’

    ‘The QC samples should be stored in the freezer under the same storage conditions and at least for the same duration as the study sample.’

Current Regulatory Guidance

- FDA Guidance for Industry – Bioanalytical Method Validation – 2001
  - D. Stability

    '…after long-term (frozen at the intended storage temperature)….'

What would be required?

- As for any stability testing, LTS experiments should cover the required exposure of the samples
- Unlike other stability testing, there may be confusion:
  - Samples are frequently shipped/stored at temperature which are lower than the docuemnted LTS (during shipment on dry ice, at -70°/-80° for a variety of practical reasons
  - This stimulates labs to also document these lower temperatures, even though there is no scientific rationale

Current Industry Practice

- Stability is done at the temperature of storage
- Some labs do -20°C and -70/80°C temperatures
- -20°C samples shipped on Dry Ice – is stability covered?

Scientific Principles

Definition of Arrhenius equation

- an equation describing the mathematical relationship between temperature and the rate of a chemical reaction.

NOTE: The Arrhenius equation is sometimes expressed as k = Ae-E/RT where *k* is the rate of chemical reaction, *A* is a constant depending on the chemicals involved, *E* is the activation energy, *R* is the universal gas constant, and *T* is the temperature.

https://www.merriam-webster.com/dictionary/Arrhenius%20equation

Survey Results - Chromatography Assays

- Per year

-20°C tested	644
-20°C failed	35
-70/80°C tested	503
-70/80°C failed	8

Examples of both temperatures tested: 343

1 example where -20°C did not match

Survey Results - Ligand Binding Assay

- Per year

-20°C tested	212
-20°C failed	14
-70/80°C tested	287
-70/80°C failed	12

Examples of both temperatures tested: 192

0 examples where -20°C did not match

Recommendation

The generation of frozen storage stability at one temperature would validate the use of lower temperatures for storage.

- Example 1

  -20°C storage stability validated and site stores samples at -80°C.

- Example 2

  -20°C Storage stability and samples stuck in transit on dry ice for 5 days.

Acknowledgement

- Thank you to all companies that took the time and responded to the survey

- Many thanks for your attention

Acknowledgment

- EBF community
- AAPS/JBF bioanalytical leadership

Contact: info@europeanbioanalysisforum.eu

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