Stability Assessments (including Co-dosed Medication, Blood Stability, and Tube Number)

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Stability tests in regulations

Biological samples

- Bench-top stability
- Freeze-thaw stability
- Long-term frozen stability
- (Whole blood stability)

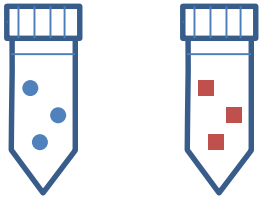
Extracts

Stock and working solutions

- Bench-top stability
- Storage stability (typically in a refrigerator)

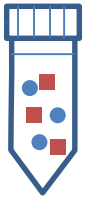
Stability in the presence of co-medication

Validation study



Differences?

Study samples



Situations include:

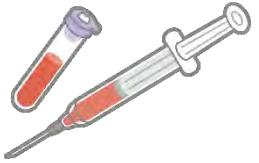
- Co-formulation
- Fixed combination

Survey by GCC (2012) and AAPS (2017):

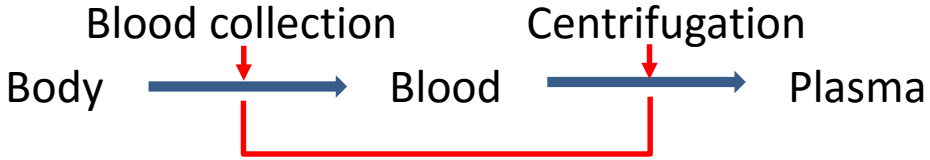
Stability differences were rarely observed.

Industry perspective (ref 1-6):
The risk that stability is compromised in the presence of co-medication is low.

Whole blood stability (1/3)



When plasma samples are analyzed

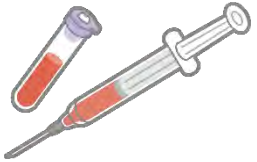


EMA GL: “A demonstration of this stability may be needed on a case-by-case basis, depending on the structure of the analyte.”

FDA/MHLW GL: Not explicitly require.

Currently, many pharmaceutical companies routinely conduct whole blood stability tests in validation studies and discuss the tests extensively (ref 1, 2, 7-9).

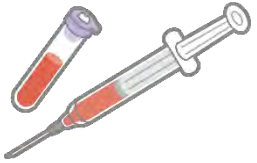
Whole blood stability (2/3)



Good to know:

- In AAPS survey (2017), 25% of responders answered “yes” to the question “Have you observed different stability conclusions between plasma and whole blood, except when the analyte is not stable in plasma or the analyte is a *N*-oxide or hydroxamic acid?”.
- Considering current industry practice, differences in stability between plasma and blood can be ascribed to
  - Faster degradation in red blood cells (RBC)
  - Slow or temperature-dependent distribution to RBC
  - Gap between “aged plasma” and “relatively fresh blood”

Whole blood stability (3/3)



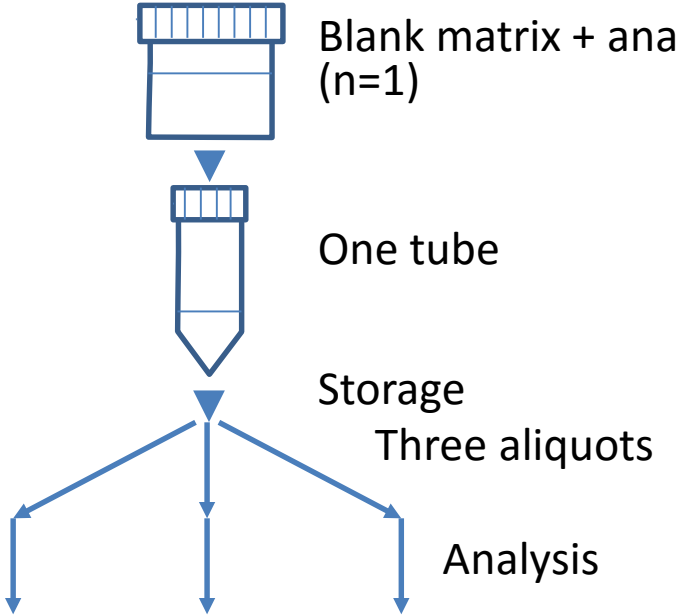
Discussion for industry scientists:

- Validation or “method development with sufficient documentation”
- Study design (matrix to be measured, temperature, equilibrium at t=0)
- Freshness and donors of whole blood

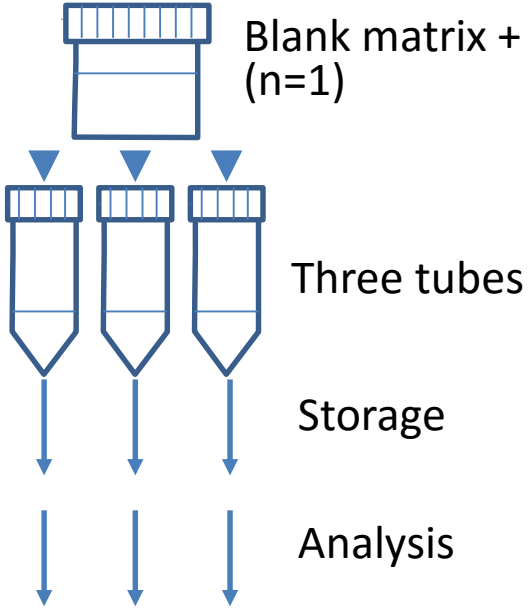
Industry perspective for ICH M10 (ref 6, 10):

Whole blood stability should not be required as a routine method validation item.

Tube numbers in stability tests (1/2)



Three measured values



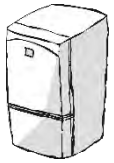
Three measured values

Tube numbers in stability tests (2/2)

- This requirement is specific to Canada
- “Drug stability in a biological fluid is a function of the storage conditions, the physicochemical properties of the drug, the matrix, and the container system” (the FDA draft guidance 2013)

Industry perspective (ref 11):
Increased tube numbers in stability tests appear to be associated with increased cost but not data quality.

Stability at −70ºC vs −20ºC



Both −20ºC and −70ºC freezers are used in clinical studies.

According to Arrhenius law, analytes are more stable at −70ºC than −20ºC.

Industry perspective (ref 6 and 12):
Demonstration of stability at −20ºC is sufficient for storage of study samples at −20ºC and −70ºC for the same period.

Stability at high conc (>ULOQ) (1/2)

For biological samples

Typical analyte concentrations in stability tests: LQC and HQC
Stability at high conc is not explicitly required by FDA/EMA/MHLW GL.

(see also MHLW replies to public comment No. 69)

Analytes are usually more stable at higher concentrations

- Lower adsorption to containers and endogenous insoluble components
- Lower efficiency of enzymatic degradation

Stability at high conc (>ULOQ) (2/2)

For biological samples

Exceptions include

- Expected high frequency of >ULOQ samples

AND

- "Urine sample of analytes with low aqueous solubility (risk of precipitation)" or "concentration-dependent stability between LQC and HQC"

AAPS survey (2017): 1/3 responders conduct LTS using dilution QC samples.

Industry perspective (ref 6 and 13):
Stability tests at high conc. are needed on a case-by-case basis (not routinely).

Processed sample stability and reinjection reproducibility (1/3)

Chromatographic assays

Biological samples

IS addition

Extraction

Injection samples (extracts)

(Storage)

Injection

Two conditions of injection samples

Intact

(waiting for injection)

Pierced

(reinjection)

In addition, there are two types of storage (see next slide)

Processed sample stability and reinjection reproducibility (2/3)

Two types of storage

Separate from calibration samples
Calibration sample injection ↓ Storage period Study sample injection
Examples include • Original run without incidents • Partial batch injection after injection failure in the original run

Chromatographic assays

Together with calibration samples
Completion of extraction ↓ Storage period Start of injection of a whole batch
Examples include • Instrument failure before a whole batch injection (original injection) • Instrument failure during analysis (reinjection)

Processed sample stability and reinjection reproducibility (3/3)

Chromatographic assays

Conditions for stability tests should be in line with those for actual sample analysis studies (MHLW replies to public comment No. 67).

Currently, the following points vary across the industry

1. Type and number of experiments
2. Experimental design
3. Definition of storage duration

Industry perspective (ref 6, 7, 12, 14, 15):
Requirements for these stability tests should not be too prescriptive.

Stability of IS solutions

Topic 1

EMA GL does not require stability assessment of SIL-IS solutions. This is the common practice of EU and US industries. However, the JP industry conducts stability assessments due to fear of rejection from MHLW.

Topic 2

When IS solution stability is tested (e.g. analogue IS), we suggest monitoring the interference of zero samples (rather than checking the IS responses of neat solutions). This is in line with MHLW replies to public comment No. 11.
While FDA/EMA GL require IS solution stability data, they do not mention the test method or acceptance criteria.

Small differences in freezer temperature

Freezers

- Various acceptance ranges
- “−10ºC to −30ºC” or “Lower than −20ºC”

Deep freezers

- “−70ºC setting” or “−80ºC setting”

Industry perspective:

Small differences (such as 10ºC) in temperature do not compromise the stability of samples.

Summary (1/2)

Industry concerns

- Increased requests for stability data under various conditions, which do not seem scientifically necessary

- Being (too) prescriptive for study design and evaluation

Summary (2/2)

Major topics

- The risk that stability is compromised in the presence of co-medication is low.
- Whole blood stability should not be required as a routine method validation item.
- Increased tube numbers in stability tests appear to be associated with increased cost but not data quality.

Questions and Contact Information

Japan Bioanalysis Forum
http://bioanalysisforum.jp/en

Expectation on ICH M10 – from JBF's viewpoint -
http://bioanalysisforum.jp/images/2017_8thJBFS/022_Expectation_on_ICH_M10_from_JBF.pdf

Acknowledgements

- Responders to the AAPS survey
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