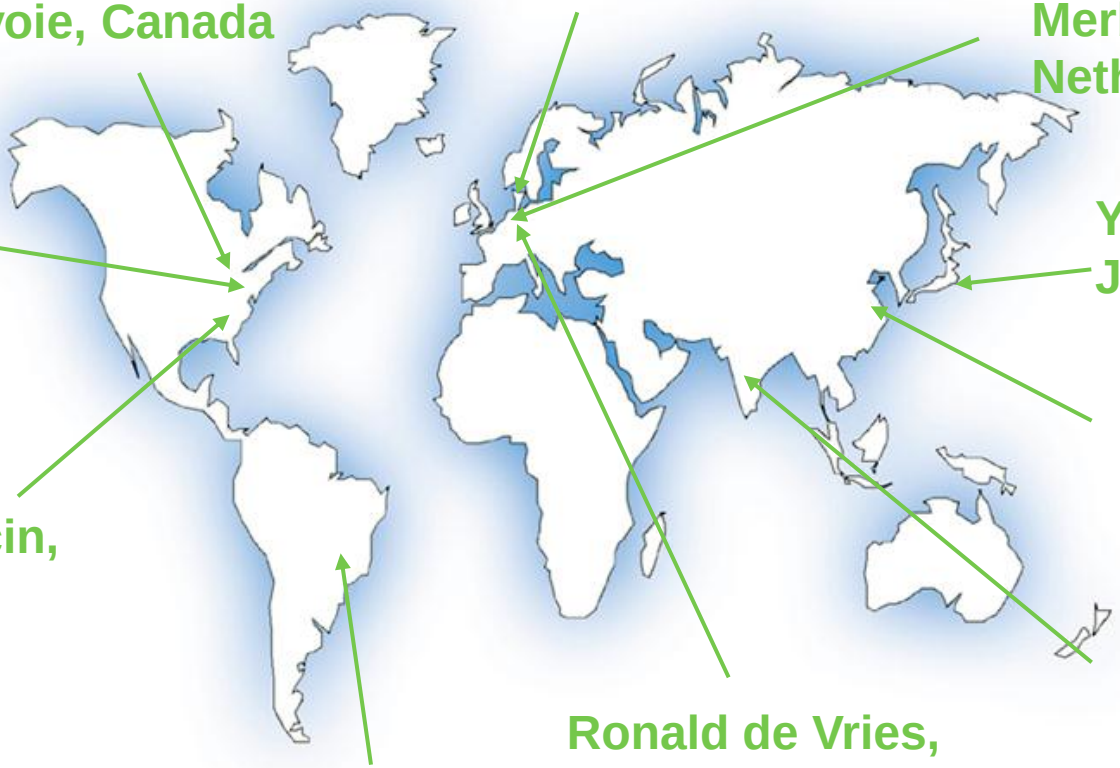
HARMONIZATION TEAM A6 (STABILITY) UPDATE

Nico van de Merbel

16 November 2011

Harmonization team A6



Morten Kall, Denmark

Nico van de Merbel, Netherlands

Natasha Savoie, Canada

Joleen White, USA

Yoshiaki Ohtsu, Japan

Kelly Dong, China

Julie Diancin, USA

Manish Yadav, India

Ronald de Vries, Belgium

Francesca Riocci, Brazil

Activities

Building of team: **May/June 2011**

Start: **June 2011**

Definition of scope: **July 2011**

Summarizing stability requirements in relevant guidelines, white papers etc: **August/September 2011**

Evaluation of stability requirements and definition of high-, medium- and low-priority issues: **October 2011**

Discussion of high-priority issues and preparation of recommendations: **ongoing**

Scope

Spiked samples (biological and surrogate) and extracts
Incurred samples and extracts

Normal matrices (blood, plasma/serum, urine, tissue)
Special matrices (hemolyzed, lipidemic etc)

Presence of co-formulated and co-administered drugs, metabolites

Stock and standard solutions, reagents

Stability during sample collection and transport
Stability during extraction and analysis

Scope

Definitions and nomenclature:

- -70 vs -80 °C
- room temperature
- degradation vs stability vs solubility loss vs absorptive loss
- fresh vs stored

Experimental design:

- t=0 vs nominal
- fresh vs frozen standards
- number of replicates
- concentrations and time-points
- ultra-low temperature for reference
- stability in whole blood
- instrument response vs concentrations

Acceptance criteria: fixed or statistical approach

Transferability of results

- between labs
- between methods

Out of scope

Stability of reference standards (team A4)

Stability of reagents for macromolecules (team L4)

Guidelines

US FDA Guidance for Industry Bioanalytical Method Validation (2001)

Brazil ANVISA Guide for Validation of Analytical and Bioanalytical Methods (2003, 2011)

EMA Guideline on Bioanalytical Method Validation (2011)

China SFDA Guidelines on non-clinical and clinical PK studies and BA and BE studies for chemical drugs (2005)

Japan PMDA, ongoing discussions

White papers

Viswanathan et al. Conference Report – Quantitative Bioanalytical Methods Validation and Implementation … (2007)

Nowatzke and Woolf. Best Practices During Bioanalytical Method Validation for the Characterization of Assay Reagents and the Evaluation of Analyte Stability … (2007)

Findlay et al. Validation of Immunoassays for Bioanalysis… (2000)

DeSilva et al. Recommendations for the Bioanalytical Method Validation of Ligand Binding Assays… (2003)

GCC: Recommendations on Internal Standard Criteria, Stability, ISR… (2011)

EBF: Blood Stability Testing (2011)

Evaluation

Priority for discussion: stability issues for which there is

- no guidance
- conflicting guidance or
- guidance with no or unclear scientific basis

and

- large impact on bioanalytical community

Examples

Illustration of our approach

Work in progress!

High priority

Incurred sample stability

Stability in presence of co-administered drugs

Transferability of stability results

Medium priority

Comparison to nominal or t=0

Incurred sample stability

Limited detail in current guidelines

"For compounds with potentially labile metabolites, the stability of analyte in matrix of dosed subjects should be confirmed" (FDA)

"Study samples may be used for assessment of LTS in addition to QC samples" (EMA)

"Ideally, study sample stability would be evaluated using freshly collected matrix from a test subject, but this approach is often impractical" (Nowatzke and Woolf)

Incurred sample stability

Scientifically, it is a potentially important issue, which may influence reliability of results, when not properly controlled

Practically, it has many difficult aspects, with respect to timing (difficult to perform prior to clinical phase), availability and ownership of samples, etc

Good opportunity for bioanalytical community to propose more concrete guidance

See separate session tomorrow 11:00 – 12:30

Stability in presence of co-administered or co-formulated drugs

Currently, no formal guidance, but regulatory observations on several occasions

Scientifically questionable, how can the presence of another drug induce instability of an otherwise stable compound?

Practically, it has a relatively large impact

All stability assessments?
All co-administered compounds?
Metabolites of co-administered compounds?

Stability in presence of co-administered or co-formulated drugs

GCC (Global CRO Council) survey early 2011

Results on over 100 non-proprietary and over 60 proprietary compounds were evaluated

No cases seen where there was instability due to the co-administered drug

Bioanalysis (2011) 3(12): 1323-1332

Transferability of stability results

Currently, no formal guidance, conflicting regulatory observations

Scientifically, (in)stability is determined by physico-chemical parameters (temperature, time, matrix composition, exposure to light)

Results are universally valid if storage conditions can be exactly reproduced

Practically, it has a relatively large impact if stability has to be re-assessed at all bioanalytical labs involved

in particular long-term stability

Transferability of stability results

Because of possible differences in temperature between labs, a bracketing approach might be useful for **bench-top stability** assessment

What is the added value of repeating **long-term stability**, if samples are stored at different locations

- in the same matrix
- in the same tubes
- at the same temperature
- for the same time
- protected from light

Note: by definition **whole blood stability** is assessed at a different location (lab) than where the samples are taken (clinic)

Compare to nominal or t=0

Conflicting guidance, although mostly reference to nominal

"Acceptance/rejection criteria for spiked, matrix-based calibration standards and validation QC samples should be based on the nominal (theoretical) concentration of analytes" (FDA)

"*Although the traditional approach of comparing analytical results for stored samples with those for freshly prepared samples has been referred to in this guidance, other statistical approaches […] can be used" (FDA)*

"The obtained concentrations are compared to the nominal concentrations" (EMA)

Compare to nominal or t=0

"The concentrations of all the stability samples must be compared to the average of the values previously calculated for the samples on the first day of the test" (ANVISA 2003)

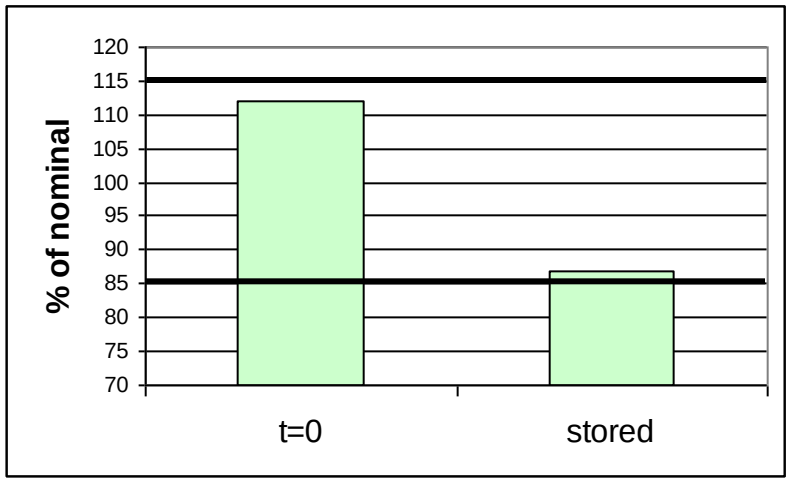
"Stability is showed when deviation higher than 15% (fifteen percent) of the average of the obtained concentrations in relation to the nominal value is not observed" (ANVISA 2011)

"Intended (nominal) concentrations should be used for comparison purposes. Additionally, […] a comparison with the initial day 0 or day 1 samples is recommended" (Viswanathan et al.)

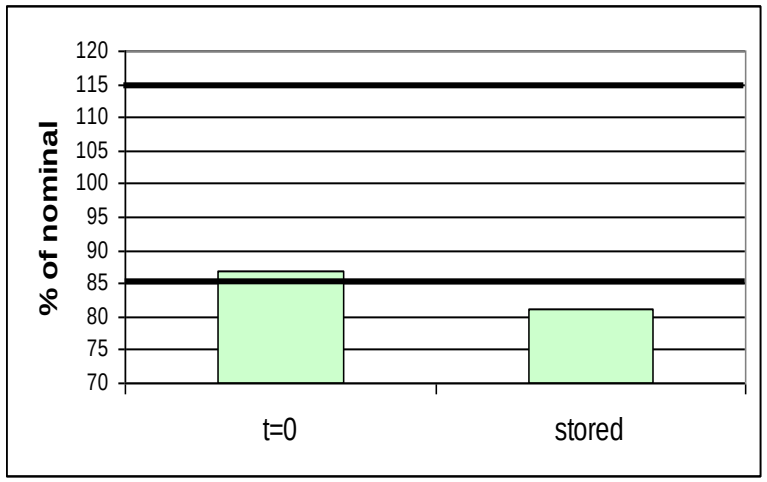
"It is recommended that the measured mean concentrations derived from the initial analysis […] be within ~5 to 7% of the nominal concentrations" (Nowatzke and Woolf)

Compare to nominal or t=0

Comparison to nominal is industry standard, but caution is needed



25% decrease



6% decrease

Other topics

Analyte stability in **tissues**
- no detailed guidance

Analyte stability in **whole blood**
- no detailed guidance

Analyte stability in **extracted samples**
- better distinction needed between
  - extract stability
  - autosampler stability
  - re-injection reproducibility

Analyte stability in **stocks and standards**
- acceptance criteria?

Future

Continue discussions within team and interact with other teams

Interaction with BA community, through regional organizations

Preparation of science-based proposals for all items on the scope list

Remember

We represent you!