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		Homogeneity and stability
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Title: Homogeneity and stability

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1 Objective

Establish the criteria to considerate the material homogeneous and/or stable.

2 Scope

This document content applies to items used in PT. The items can be purchased or prepared by Mat Control.

3 Definitions

Not Applicable

4 Related Procedures

[PNT/MAT/005](#) - Labelling, packing and distributions of PT items

Homogeneity and Stability excel sheet.


5 Responsibilities

The technical responsible of Mat Control is responsible to elaborate the homogeneity and stability tests. The technician is responsible to run the tests.

6 References

This procedure considerates two main documents to run homogeneity and stability test:

- M. Thompson, Ellison, S. L. R., and Wood, R.. “The International Harmonised Protocol for the proficiency testing of chemistry analytical laboratories”, *Pure Appl. Chem.* 78, 145–196 (2006).
- International Organization for Standardization. ISO/FDIS 13528: Statistical methods for use in proficiency testing by interlaboratory comparisons.

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7 Instructions

7.1 *Homogeneity and stability*

The calculation is done in Excel sheet: MATCONTROL>> Homogeneity and stability.xls

Both documents suggest the same procedure to run homogeneity test. The difference is in the treatment of data. The Harmonised Protocol have a pre-procedure to compare the duplicates between them (Cochran test) and reject the pair in case of discrepancies. For this advance to detect analytical error between samples, the procedure to calculation is done according Harmonised Protocol.

While between-unit homogeneity is required to be sufficient, the participant should not assume that the distribution unit itself is sufficiently homogeneous for their particular analytical procedure. It is the responsibility of the participants to ensure that the test portion used for analysis is representative of the whole of the test material in the distribution unit.

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7.2 Annex A – Procedure to homogeneity test

Laboratory to carry out measurement	
Parameters:	
Procedures to measurement:	
Date:	Responsible

<i>Packing</i>	
Packing date:	Procedure:
Number of flasks packed:	Responsible:

Sampling

1. Select sample.

g (in ISO 13528) = m (in Harmonised Protocol) = number of samples

Choose randomly m samples among all lot that will be used in PT. m should be equal or bigger than 10.

$m =$ samples	$m \geq 10$
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Analyze

2. Homogenize the contents of each sample and take two test portions from each.

3. Analyze 2 test (k_1 and k_2) for each sample in a random order under repeatability conditions by the appropriate method.

Recommendation


The analytical method used must be sufficiently precise to allow a satisfactory estimation of s_{sam} . If possible, $\sigma_{an} < 0.5 \sigma_p$.

σ_{an} – standard deviation of analytical method

σ_p - standard deviation of all test

4. Report results:

m	Test portion k_1	Test portion k_2
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		

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Examine the data

5. First exam – Visual. Plot results vs. sample number

Trends or discontinuities	<input type="checkbox"/> yes <input type="checkbox"/> no
Nonrandom distribution of differences between first and second test results	<input type="checkbox"/> yes <input type="checkbox"/> no
Excessive rounding	<input type="checkbox"/> yes <input type="checkbox"/> no
Outlying results within samples	<input type="checkbox"/> yes <input type="checkbox"/> no

6. If any “yes” is marking in the table above, technical responsible takes decision about to exclude points.

7. Second exam – Statistical analyses.

Complete the excel sheet MATCONTROL>> Homogeneity and stability.xls:

B3:B14 with k1 values

C3:C14 with k2 values

B17 with standard deviation expected for all test

8. Look cells: H4 and I4, and verify the message

Duplicate - Outliers - 95%	
Good replicates	Verify and discard replicates

If H4 indicates “good replicates” – Go to step 9.

If I4 indicates “Verify and discard replicates” means that at least one pair of replicates is not good (Cochran test). Technical responsible shall takes the decision (visual) about witch pair discard.

Repeat step 8 until has message “good replicates” in H4.

DO NOT eliminate more than 3 pairs. If this happen, the test shall be cancel because there is evidence about big deviation in analytical method.


If H4 indicates “good replicates” – Go to step 9.

9. Look cells: H10 and I10, and verify the message

Homogeneity Check	
Homogeneous	No Homogeneous

If cell H10 has message “Homogeneous”, material follow to stability test.

If cell I10 has message “No Homogeneous”, technical responsible decides corrective actions to following the PT.

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7.3 Annex B – Procedure to stability test

Laboratory to carry out measurement	
Parameters:	
Procedures to measurement:	
Date:	Responsible

<i>Packing</i>	
Packing date:	
Number of flasks packed:	Responsible:

Basic stability tests involve a comparison of the apparent analyte levels between material subjected to likely decomposition conditions and material which has not been so treated. This usually requires a sample of the distribution units to be randomly divided into (at least) two equal subsets. The “experimental” subset is subjected to the appropriate treatment, while the “control” subset is kept under conditions of maximum stability, for example, at low temperatures and low oxygen tension.


Alternatively, and especially if stability for extended periods is of interest, the control subset may be kept under ambient conditions while the experimental subset is kept under conditions of accelerated decomposition (e.g., higher temperatures). The materials are then analyzed simultaneously, or if that is impossible, as a randomized block design.

Due the variability of type of material and conditions in each campaign, technical responsible shall establish and register the procedure for stability test according needs.

The following statistical treatment for data is for cases of repeatability conditions to analyze samples.

In the same excel sheet of Homogeneity test.

- Complete the excel sheet MATCONTROL>> Homogeneity and stability.xls:
B27:B31 with control values
C27:C31 with experimental values
- Ask in Data>Analyze of Data> T- test for two sample with same variance
- Select B27:B31 as interval 1
- Select C27:C31 as interval 2

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- Hypothesis of average difference = 0 (zero)
- Alfa = 0.05
- Interval to out : Select cell A33 ; Press “OK”
- Look cells: H27 and I27, and verify the message

Stability Check	
Stable	Unstable

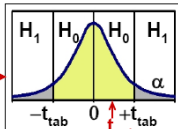
If cell H27 has message “Stable”, material is good to be distribute.

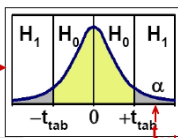
If cell I27 has message “Unstable”, technical responsible decides corrective actions to following the PT.

The one-way analysis of variance is done according:

COMPARING TWO MEANS (2 sides, σ not known and $s_1 = s_2$)

Hypothesis Criterion

$$H_0 : \bar{x}_1 = \bar{x}_2 \quad t_{\text{cal}} \leq t_{\text{tab}(\alpha, n_1+n_2-2 \text{ d.f.})} \rightarrow$$


$$H_1 : \bar{x}_1 \neq \bar{x}_2 \quad t_{\text{cal}} > t_{\text{tab}(\alpha, n_1+n_2-2 \text{ d.f.})} \rightarrow$$


$$t_{\text{cal}} = \frac{|\bar{x}_1 - \bar{x}_2|}{s \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}} \quad s = \sqrt{\frac{(n_1-1)s_1^2 + (n_2-1)s_2^2}{n_1+n_2-2}}$$

[Tables](#)