

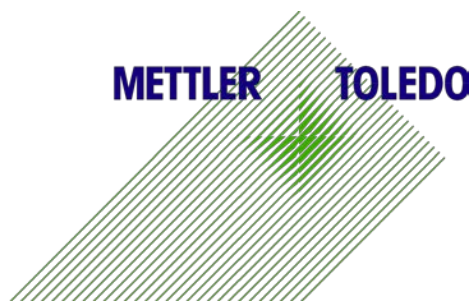
USP General Chapter <41>

by Denis LOUVEL, Mettler-Toledo Sales international, GmbH



Location: SOFITEL, Cairo
Date: November 18th, 2015

denis.louvel@mt.com



Review of the
application domain
of this general
chapter

USP GC 41 – Scope

New version	Old version
<p>This chapter states the requirements for balances used for materials that must be accurately weighed (see <i>General Notices, 8.20</i>).</p>	<p>Pharmacopeial tests and assays require balances that vary in capacity, sensitivity, and reproducibility.</p>

Comment

General notices (8.20) provide details for the application domain

Content of General Notices

8.20. About

If the measurement is stated to be "accurately measured" or "**accurately weighed**," follow the statements in the general chapters *Volumetric Apparatus* <31> and *Balances* <41>, *USP37* respectively.

- Have a look in the USP monographs when these 2 key-words "**accurately weighed**" are indicated

- Any balance used according a USP article where the 2 key words "**accurately weighed**" are indicated, must comply to GC <41>.

General notices USP 37 - 6.50.20. Solutions

- *Unless otherwise specified, all solutions shall be prepared with Purified Water. Solutions for quantitative measures shall be prepared using **accurately weighed** or accurately measured analytes.*

General notices USP 37 - 6.60.10.

Tablets

- *Where the procedure of a Tablet monograph directs to weigh and finely powder not fewer than a given number of Tablets, a counted number of Tablets shall be weighed and reduced to a powder. The portion of the powdered Tablets taken shall be representative of the whole Tablets and shall, in turn, be **weighed accurately**.*

USP GC 41 – Example 3

General notices USP 37 - 6.60.20. Capsules

- Where the procedure of a Capsule monograph gives direction to remove, as completely as possible, the contents of not fewer than a given number of the Capsules, a counted number of Capsules shall be carefully opened and the contents quantitatively removed, combined, mixed, and **weighed accurately**. The portion of mixed Capsules contents taken shall be representative of the contents of the Capsules and shall, in turn, be **weighed accurately**.

- Don't waste your time for this research
- Test all the balances of your lab against GC <41>.

USP GC 41 – Scope (1)

New version	Old version
<p>Unless otherwise specified, when substances must be “accurately weighed”, the weighing shall be performed using a balance that is calibrated over the operating range and meets the requirements defined for repeatability and accuracy.</p>	<p>Unless otherwise specified, when substances are to be “accurately weighed” for Assay, the weighing is to be performed with a weighing device whose measurement uncertainty (random plus systematic error) does not exceed 0.1% of the reading.</p>

Comment

The scope is **no more** limited to "Assay", it is extended to almost all weighing processes.
Two tests are clearly required : Repeatability and Accuracy (also called trueness)

USP GC 41 – Accuracy

Sensitivity, linearity, and eccentricity all account for systematic deviations; i.e., they limit the **accuracy** of the balance (based on the definition of accuracy in *Validation of Compendial Procedures* 1225 and ICH Q2). In the International Vocabulary of Metrology (VIM) and documents of the International Organization for Standardization, this concept is referred to as trueness.

- An additional test (accuracy) is required
- This accuracy test is the same as the one applied in house.

USP GC 41 – Scope (2)

New version	Old version
<p>For balances used for other applications, the balance repeatability and accuracy should be commensurate with the requirements for its use.</p>	<p><i>No detail</i></p>
<p>Comment</p>	
<p>Same tests for other applications only the specifications change.</p>	

- Identify the weighing requirements for the other applications.

- Test **Repeatability** and **Accuracy** as defined in GC <41>
- Replace **0,10%** by your own criterion for each application

USP GC 41 – Application domain – end

New version	Old version
<p>For a discussion of the theoretical basis of these requirements, see general information chapter <i>Weighing on an Analytical Balance</i> <1251>, which may be a helpful – but not mandatory – resource.</p>	<p><i>No detail</i></p>
<p>Comment</p>	
<p>Additional & important information; understand the contents of GC <1251> is necessary.</p>	

USP GC 41 – Consequence

- GC <1251> is not mandatory, but contains valuable and sensitive information showing the advanced knowledge of the FDA since the first regulation.
- Ignore the content of GC <1251> is very risky.

- End of the review for the application domain

- Review of the requirements for the repeatability assessment

Repeatability – Specification

New version	Old version
<p>Repeatability is assessed by weighing one test weight NLT 10 times.</p>	<p>Measurement uncertainty is satisfactory if three times the standard deviation of not less than ten replicate weighings divided by the amount weighed, does not exceed 0.001.</p>
<p>Comment</p>	
<p>Always 10 weighing results</p>	

- Only **one** weight for this control.

Repeatability – Test weight (1)

New version	Old version
<p>[Note - The test weight must be within the balance's operating range, but the weight need not be calibrated.</p>	<p><i>No detail</i></p>

Comment

The weight selection is free as long it is within the measuring range of the balance.
It is no more related to the size of the sample.
No calibration certificate required.

Repeatability – Test weight

New version	Old version
<p>Because the standard deviation is virtually independent of sample mass within the balance's capacity, use of a small test weight, which may be difficult to handle, is not required.]</p>	<p><i>No detail</i></p>
<p>Comment</p>	
<p>The standard deviation is not related to the load. Using a large weight is easier than a small weight.</p>	

Repeatability – Consequence

- With <GC 41>, the definition of the load value is very large.
- The load value is more specific in table 1 of GC <1251> :
 - *10 replicate weighings (using a test weight that is a few percent of the nominal capacity of the balance).*

Repeatability – Consequence

- Don't test the minimum weight of the balance
- Repeatability is constant over the whole measuring range.
- Each manufacturer provides the balance repeatability with one standard deviation.

Repeatability – Assessment (1)

New version	Old version
<p>Repeatability is satisfactory if two times the standard deviation of the weighed value, divided by the desired smallest net weight (i.e., smallest net weight that the users plan to use on that balance), does not exceed 0.10%.</p>	<p>Measurement uncertainty is satisfactory if three times the standard deviation of not less than ten replicate weighings divided by the amount weighed, does not exceed 0.001.</p>

Comment

USP follows the mathematical rounding rules.
The less strict expansion factor is compensated by a more strict accuracy requirement.

USP rounding rules

- This table shows the rounding rules defined by the USP (rounding by excess).

Relative error needed	Rounding \Rightarrow Result
1%	1.49% = 1% \Rightarrow Pass
	1.50% = 2% \Rightarrow Fail
0.1%	0.149% = 0.1% \Rightarrow Pass
	0.150% = 0.2% \Rightarrow Fail
0.10%	0.1049% = 0.10% \Rightarrow Pass
	0.1050% = 0.11% \Rightarrow Fail

Repeatability – Consequence

- The expansion factor change from 3 to 2 reduces the minimum weight by 30%.
- The change from 0.1% to 0.10% increases the minimum weight by 30%.
- Theoretically, these changes have no consequence on your current minimum weight

Repeatability – Condition

New version	Old version
<p>If the standard deviation is less than $0.41d$ (d is the scale interval) replace this standard deviation with $0.41d$.</p> <p>In this case, repeatability is satisfactory if two times $0.41d$, divided by the desired smallest net weight does not exceed 0.10%.</p>	<p><i>No detail</i></p>

Comment

The rounding of a digital indication limiting the weighing result, is taken into account.

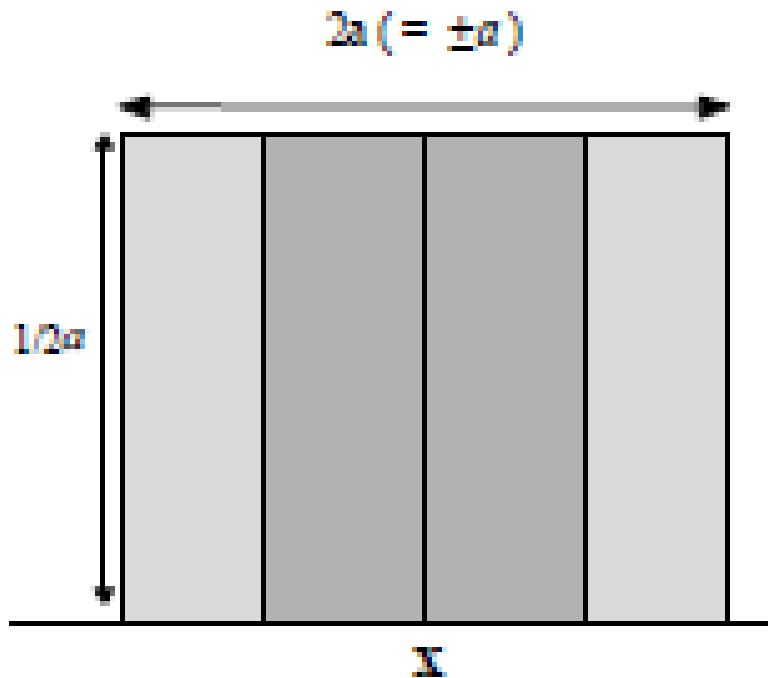
$\sqrt{2}$ takes into account the two readings (at zero and on load) during the test.

USP GC41 implements a special safety and corrects here an issue detected with the repeatability test :

What to do when the standard deviation = 0 ?

Repeatability – Why $0.41 d$?

- With the rectangular distribution, an estimate of the standard uncertainty related to the indication rounding, can be calculated.



$$u(x) = \frac{a}{\sqrt{3}}$$

Repeatability – Why $0.41d$?

- For a balance $a = d / 2$

$$u(x) = \frac{a}{\sqrt{3}} = \frac{d}{2\sqrt{3}} \gg \frac{d^2}{12} \gg \frac{d}{\sqrt{12}}$$

- One weighing means 2 measurements (at zero and on load)

$$\begin{aligned} u(x) &= \sqrt{2 \times \frac{d^2}{12}} = \sqrt{2} \frac{d}{\sqrt{12}} = \frac{d}{\sqrt{6}} \\ &= \mathbf{0.41d} \end{aligned}$$

- There is now a lower limit to the standard deviation.

Repeatability – Lower limit

- Formula for the conformity:

$$2 \times s / dsnw < 0.10\%$$

- The formula for the minimum weight comes from the conformity formula:

$$2 \times s / dsnw < 0.10\%$$

$$dsnw = 2 \times s / \text{required weighing tolerance}$$

$$m_{min} = 2 \times s / \text{required weighing tolerance}$$

Repeatability – Lower limit

- Formula for the minimum weight:

$$m_{min} = 2 \times s / \text{Required weighing tolerance}$$

- For a tolerance of 0.10%:

$$m_{min} = 2 \times s / 0.10\%$$

$$m_{min} = 2 \times s \times 1000$$

$$m_{min} = 2000 \times s$$

- When $s = 0.41 d$:

$$m_{min} = 2000 \times 0.41 d$$

$$m_{min} = 820 \times d$$

Repeatability – Lower limit

- This table shows the smallest minimum weight when a standard deviation is replaced by $0.41 d$: $m_{min} = 2000 \times s = 820 \times d$

Increment d	$s = 0.41 d$	Smallest minimum weight
1000 mg	410 mg	820 g
100 mg	41 mg	82 g
10 mg	4.1 mg	8.2 g
1 mg	0.41 mg	0.82 g
0.1 mg	0.041 mg	82 mg
0.01 mg	0.0041 mg	8.2 mg
0.001 mg	0.00041 mg	0.82 mg

Repeatability – Lower limit

- It is impossible to weigh a sample lower than the smallest net weight.
- Easy to check for a FDA inspector

Repeatability – Lower limit

- Formula for the minimum weight:

$$m_{min} = 2 \times s / \text{Required weighing tolerance}$$

- For a tolerance of 1%:

$$m_{min} = 2 \times s / 1\%$$

$$m_{min} = 2 \times s \times 100$$

$$m_{min} = 200 \times s$$

- When $s = 0.41 d$:

$$m_{min} = 200 \times 0.41 d$$

$$m_{min} = 82 \times d$$

Repeatability – Lower limit

This table shows the smallest minimum weight when a standard deviation is replaced by $0.41 d$: $m_{min} = 200 \times s = 82 \times d$ (1%)

Increment d	$s = 0.41 d$	Smallest minimum weight
1000 g	410 g	82 kg
100 g	41 g	8.2 kg
10 g	4.1 g	820 g
1 g	0.41 g	82 g
0.1 g	41 mg	8.2 g
0.01 g	4.1 mg	820 mg
0.001 g	0.41 mg	82 mg

- End of the review
for the repeatability
assessment

- Review of the requirements for the accuracy assessment

Accuracy – Specification

New version	Old version
<p>The accuracy of a balance is satisfactory if its weighing value, when tested with a suitable weight(s), is within 0.10% of the test weight value.</p>	<p>A weight class is chosen so that the tolerance of the weights used does not exceed 0.1% of the amount weighed.</p>

Comment

Same modification for the relative value as the repeatability test.

- The requirement level is far from the one currently applied.
- A daily control is no more necessary.

Accuracy – Test Weight

New version	Old version
<p>A test weight is suitable if it has a mass between 5 % and 100 % of the balance's capacity.</p>	<p>Generally, class 2 may be used for quantities greater than 20 mg, class 3 for quantities of greater than 50 mg, and class 4 for quantities of greater than 100 mg.</p>

Comment

Test weight depends on the balance capacity, no more on the sample amount

Accuracy – Consequence

- At least **one** weight for this control.
- A daily control is no more necessary with such tolerance level.
- Enable **FACT** for all of your balances !

Accuracy – Consequence

- CarePac for balance assessment



Accuracy – Test Weight

New version	Old version
<p>The test weight's maximum permissible error (mpe), or alternatively its calibration uncertainty, shall be NMT one-third of the applied test limit of the accuracy test.</p>	<p>Weights should be calibrated periodically, preferably against an absolute standard weight.</p>

Comment

NMT one-third corresponds to OIML references as R76
The weights are still traceable to national or international standards.

The calibration periodicity still depends on the use interval.

Accuracy – Test Weight

New version	Old version
Applicable standards are the following: ASTM E617 and OIML R 111	American National Standard ANSI/ASTM E617

Comment

OIML R111 weights are now listed, as ASTM weights not allowed in Europe.

- End of the review for the accuracy assessment

- The text shown in most of the next slides is a copy/paste of GC <1251>.

Minimum weight (1)

- The minimum weight is explained in GC 1251
- The minimum net sample weight, m_{min} , of a balance is expressed by the equation:
 - $m_{min} = k \times s / \text{required weighing tolerance}$, with
 - k , the coverage factor (usually 2 or larger)
 - s , the standard deviation
- The minimum weight describes the lower limit of the balance below which the required weighing tolerance is not adhered to.

Minimum weight (2)

- For materials that must be accurately weighed, GC <41> stipulates that repeatability is satisfactory if 2 times the standard deviation of the weighed value, divided by **desired smallest net weight**, does not exceed 0.10%.
- With this criterion the equation simplifies to:

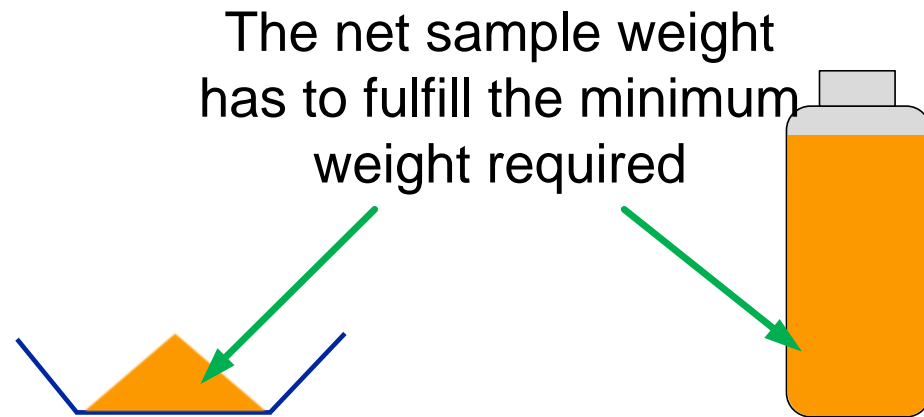
$$m_{min} = 2000 \times s$$

- As the standard deviation can not be lower than $0.41 \cdot d$, the smallest net minimum weight is :

$$m_{min} = 820 \times d$$

Sample weight

- The minimum weight applies to the sample weight, not to the tare or gross weight.



- A tare vessel cannot be taken into account to fulfill the respective minimum weight criterion.
- USP explicitly states in the new version the scientific fact that the minimum weight always refers to the net sample weight.

Standard deviation variability (1)

- Factors that can influence repeatability while the balance is in use include:
 - The performance of the balance and thus the minimum weight can vary over time because of changing environmental conditions.
 - Different operators may weigh differently on the balance – i.e., the minimum weight determined by different operators may be different.

Standard deviation variability (2)

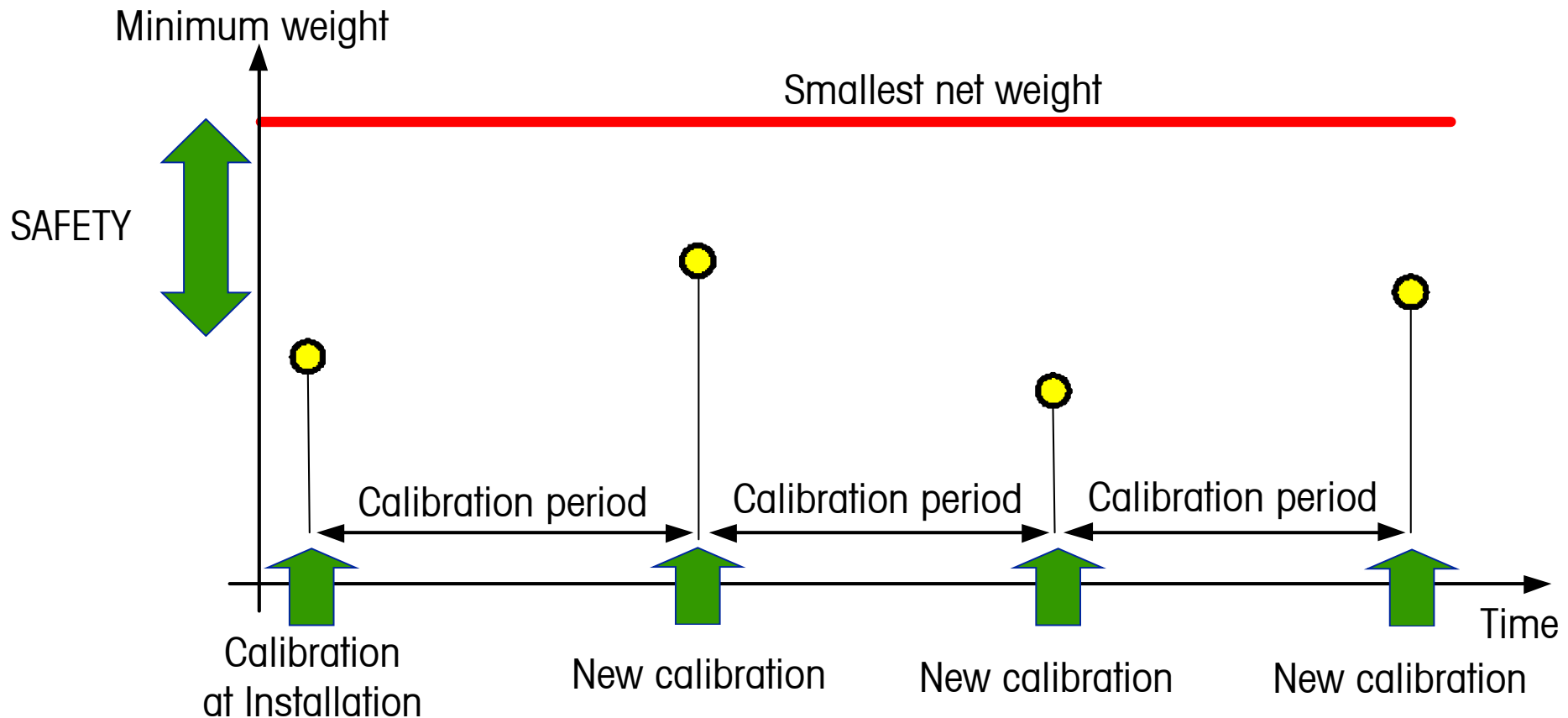
- The standard deviation of a finite number of replicate weighings is only an estimation of the true standard deviation, which is unknown.
 - The determination of the minimum weight with a test weight may not be completely representative for the weighing application.
 - The tare vessel also may influence minimum weight because of the interaction of the environment with the surface of the tare vessel.
- For these reasons, when possible, weighings should be made at larger values than the minimum weight.

Standard deviation variability (3)

- As a consequence, use a safety factor, showing that the smallest net sample weight is always larger than the minimum weight determined at a particular time by a particular person.

Standard deviation variability (4)

- The figure below shows the variability of the minimum weight calibration after calibration.



Protocol – Calibration conditions

- In situations when the balance is located near equipment or systems that induce vibration, drafts, electromagnetic radiation, magnetic fields, or changes in temperature or humidity, the assessment is conducted with those systems operating in order to duplicate a worst-case scenario.
- As a minimum, the power is turned on and the balance is allowed to equilibrate according to the manufacturer's instructions (1 – 24 h, depending on the type of balance) before use.
- The tests should be recorded in such a manner that the data can be used to easily track balance performance and to assist in laboratory investigations as needed.

Protocol – Test conditions

- The same load-sharing on the balance pan receptor is preserved during each application, in order to not generate off centre load error.
- The display is set to zero at the beginning of the test and if necessary, between each load placed on the receptor.
- With each load, the repetition of measurements takes place during a short period of time and without interruption.
- The respective duration of application of the same load is virtually identical.

SOP – Preload

- As repeatability depends on the size and surface area of the weighed object, large or heavy receivers introduce a deviation from the conditions under which the repeatability was determined without considering the receivers.
- Therefore, either receivers of a low mass and small surface are used (especially in cases when specimens of low weight are being measured) or the repeatability test is performed with the receiver placed on the weighing pan as a preload.
- Receivers are used at ambient temperature in order to prevent the formation of air currents within the weighing chamber.

SOP – Repeatability (1)

- Value of the test load
 - Few percent of the balance maximal capacity (e.g. 5% as MT)
- Value to record
 - Only stable displayed values are recorded
- Number of weighing results
 - Repeatability is assessed by weighing one test weight NLT 10 times

SOP – Repeatability (2) : Test operation

- 1) Place the receiver (e.g. flask) usually used with the sample on the pan
- 2) Reset to zero the balance display. The display must indicate "0.00000 g"
- 3) Place the test weight on the balance pan. Caution: handle it with adequate manner (i.e. glove, clip, tweezers...)
- 4) Record the displayed value after stabilization
- 5) Transfer the data to the printer
- 6) Remove the load of the pan
- 7) Repeat 9 times from point 2
- 8) Assess the measuring data
- 9) Repeat the test with an other receiver (e.g. weighing boat)

SOP – Repeatability (3) : Assessment

- Repeatability is satisfactory if two times the standard deviation of the weighed value, divided by the **desired smallest net weight**, (e.g. 50 mg) does not exceed 0.10%:

$$\frac{2 \times s}{\text{Desired smallest net weight}} < 0.10\%$$

SOP – Repeatability (4) : Assessment

- If the test result has failed, the following actions may improve the results:

Enlarge *dsnw*

1. This reduces the relative error for the same repeatability
2. A larger minimum weight must be accepted by the analyst

Improve the repeatability

1. Place a draft shield (around the pan or around the balance)
2. Change the weighing settings
3. Select a better location, more stable
4. Chose a balance with a better readability

SOP – Repeatability (5) : Accessories



- **Value of the test load**

- Between 5 to 100 percent of the balance maximal capacity (e.g. 200 g)

- **Value to record**

- Only stable displayed value is recorded

SOP – Accuracy (2) : Test operation

- 1) Reset to zero the display; the display must indicate "0.00000 g"
- 2) Place the test weight on the balance pan. Caution: handle it with adequate manner (glove, clip, tweezers...)
- 3) Record the displayed value after stabilization
- 4) Issue a printout
- 5) Control if the indicated value is not larger than the defined tolerance. If the limit value is over, adjust the balance and restart the test.
- 6) If acceptable limit value is again over, the balance is switched off, and disconnect of the main power, (unplug the cable), inform the department Responsible its defective state and contact the service manufacturer.

SOP – Accuracy (3) : Assessment

- Accuracy is satisfactory if the error of indication does not exceed 0.05 % of the test load

Acceptance criteria (1)

- Deviations are largely independent from each other, it is not likely that all deviations occur simultaneously and have the same algebraic sign.
- The arithmetic addition of all individual deviations to assess the balance accuracy would constitute a rather conservative approach.

	Test limit	Deviation
Accuracy test	0.10 %	0.09 %
Repeatability test	0.10 %	0.09 %
Algebraic sum	0.20 %	0.18 %

Acceptance criteria (2)

- A quadratic addition of the individual deviations is a more realistic approach.
- By allocating 50% of the weighing tolerance budget to the acceptance criteria of the individual properties, analysts ensure adherence to the required weighing tolerance.
- These properties are taken to fulfill the accuracy requirement described in <41>.

	Test limit	Deviation
Accuracy test	0.05 %	0.04 %
Repeatability test	0.10 %	0.09 %
Quadratic sum	0.11 %	0.10 %

SOP – Test results

Nominal load value: **10 g** Tare load value: **50 g (100 ml flask)**

Desired smallest net weight, *dsnw*: **50 mg**

Weighing #	Reading	Assessment against repeatability requirement: Standard deviation > 0.41 <i>d</i> : Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> $\frac{2 \times 0.000011 \text{ g}}{0.05 \text{ g}} = 0.043\%$ Calculation of Minimum Weight, <i>MW</i> : $MW = 2000 \times s = 2000 \times 0.000011 \text{ g} =$ 0.022 g <i>MW</i> below <i>dsnw</i> : Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> The repeatability meets the requirement of 0.10 %. Repeatability complies: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
Weighing result 1	10.00000 g	
Weighing result 2	10.00000 g	
Weighing result 3	10.00001 g	
Weighing result 4	10.00003 g	
Weighing result 5	10.00002 g	
Weighing result 6	10.00000 g	
Weighing result 7	10.00000 g	
Weighing result 8	10.00000 g	
Weighing result 9	10.00000 g	
Weighing result 10	10.00000 g	
Standard deviation, <i>s</i>	0.000011 g	

	Certified value	Displayed value	Error	MPE	Pass/Fail
Load	200.00008 g	200.00011 g	0.00003 g	± 0.10000 g	Pass

Accuracy correct: **Yes** **No**

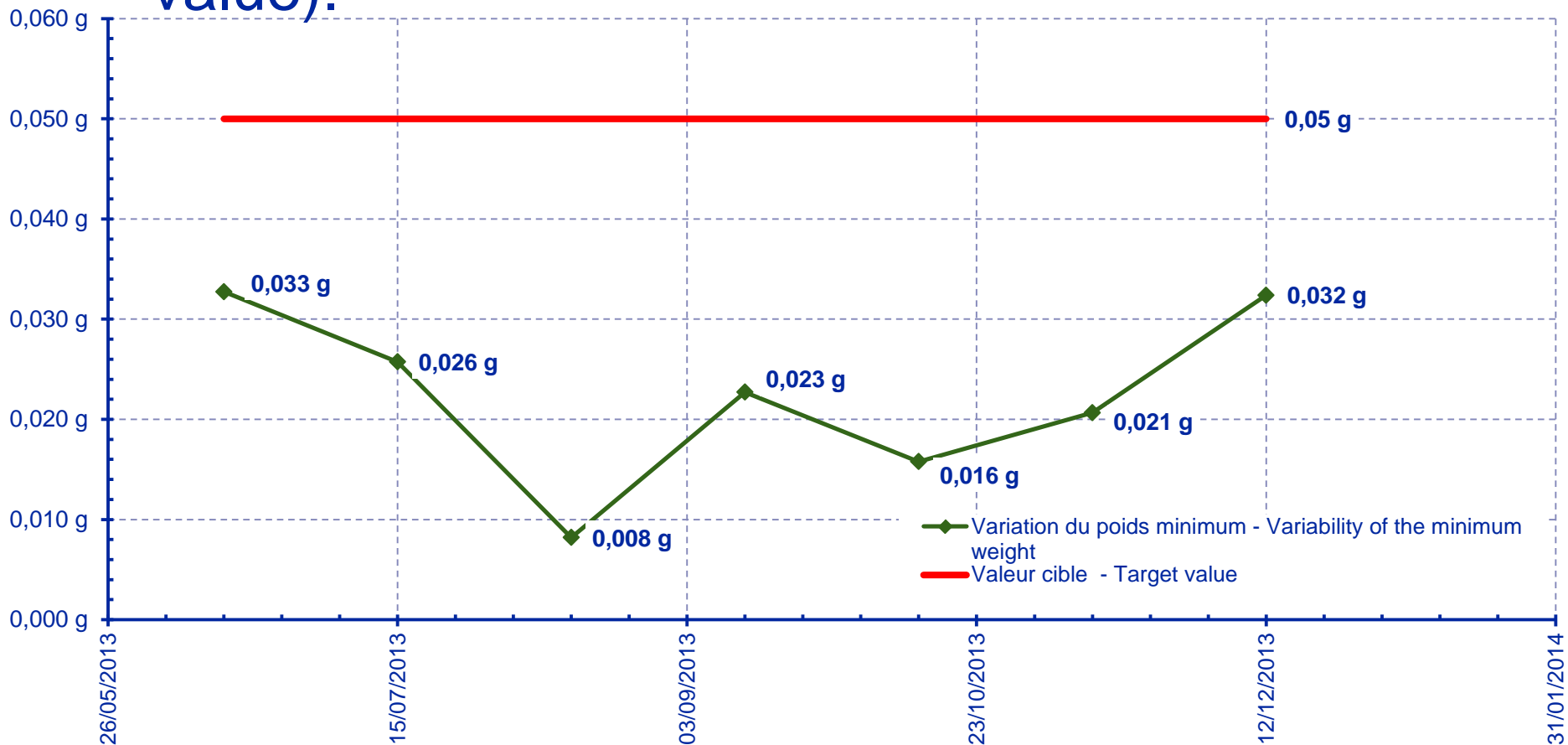
Standard deviation variability (5)

- A monthly control for the repeatability helps to monitor/define the minimum weight.

Balance readability, d	0.00001 g						
Load test	10 g						
Tare value	50 g (100 ml flask)						
Desired smallest net weight, $dsnw$	0,05 g						
Test date	15/06/2013	13/09/2013	13/10/2013	12/11/2013	12/12/2013	13/09/2013	13/10/2013
Weighing result n°1	10.00003 g	10.00002 g	10.00001 g	10.00001 g	10.00003 g	10.00002 g	10.00001 g
Weighing result n°2	9.99997 g	9.99999 g	9.99999 g	9.99998 g	9.99998 g	9.99999 g	9.99999 g
Weighing result n°3	10.00002 g	10.00001 g	10.00001 g	10.00001 g	10.00001 g	10.00001 g	10.00001 g
Weighing result n°4	10.00000 g	10.00000 g	10.00000 g	10.00000 g	10.00000 g	10.00000 g	10.00000 g
Weighing result n°5	9.99999 g	9.99998 g	9.99999 g	9.99999 g	9.99998 g	9.99998 g	9.99999 g
Weighing result n°6	10.00000 g	10.00000 g	10.00000 g	10.00000 g	10.00000 g	10.00000 g	10.00000 g
Weighing result n°7	10.00001 g	10.00001 g	10.00001 g	9.99999 g	9.99998 g	10.00001 g	10.00001 g
Weighing result n°8	10.00001 g	10.00001 g	10.00001 g	10.00001 g	10.00001 g	10.00001 g	10.00001 g
Weighing result n°9	10.00000 g	10.00000 g	10.00000 g	9.99999 g	9.99999 g	10.00000 g	10.00000 g
Weighing result n°10	10.00000 g	10.00000 g	10.00000 g	10.00000 g	10.00000 g	10.00000 g	10.00000 g
$0.41 d =$	0.0000041 g	0.0000041 g	0.0000041 g	0.0000041 g	0.0000041 g	0.0000041 g	0.0000041 g
Standard deviation, s	0.0000164 g	0.0000114 g	0.0000079 g	0.0000103 g	0.0000162 g	0.0000114 g	0.0000079 g
$s > 0.41 d$	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calculated MW	0,033 g	0.023 g	0.016 g	0.021 g	0.032 g	0.023 g	0.016 g
$2s / dsnw$	0.065%	0.045%	0.032%	0.041%	0.065%	0.045%	0.032%

Standard deviation variability (6)

- Previous results allows plotting the MW variation control after control and then the MW choice (target value).



SOP when *dsnw* is unknown (1)


- Value of the test load
 - 5% of the balance maximal capacity
- Records
 - Only stable displayed values are recorded
- Number of weighing results
 - NLT 10
- Type of vessel to test
 - Weighing boat, flask, crucible

SOP when *dsnw* is unknown (2)

- 1) Place the first vessel on the pan
- 2) Reset to zero the balance display
- 3) Place the test weight on the balance pan.
- 4) Record the displayed value after stabilization.
- 5) Transfer the data to the printer
- 6) Remove the load of the pan
- 7) Repeat 9 times from point 2
- 8) Calculate the standard deviation
- 9) Calculate the minimum weight $m_{min} = 2000 \times s$
- 10) Repeat the test with the next vessel

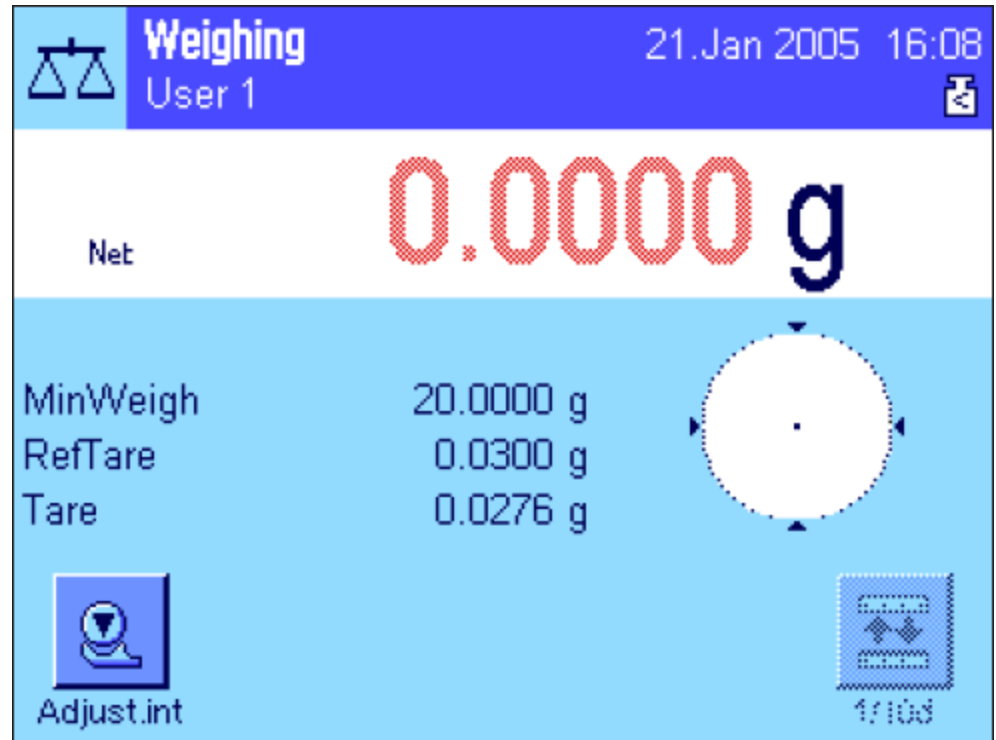
Upload the minimum weight - MW

- With MT balances, you can improve the weighing safety

MinWeigh			
MW-Method		USP	
next Test		14.Jan 2006	
MW-Parameter		3sd, 0.1%	
Min.Weight by Tare			
0.0300 g		20.0000 g	
0.0500 g		200.0000 g	
0.1000 g		500.0000 g	
			<input type="button" value="OK"/>

Work with MW function – Display (1)

- Red color to warn the operator



Work with MW function – Display (2)

- An icon to warn the operator



Work with MW function – Printout

- An asterisk to the left of the net weight to warn the operator

MW-Method		USP
RefTare	0.0300	g
MinWeigh	20.0000	g
*N	18.3386	g
T	0.0276	g
G	18.3662	g

New USP GC <41>

Questions?

