Good Weighing Practice
In Pharmaceutical Industry

Pharmacy Risk Assessment
For Mass Measurement Processes

Content

Introduction

Functional abilities and automatics of contemporary electronic balances create a wrong impression that they offer guaranteed measurement precision. Such attitude does not take into account incorrect measurement risk, if interfering factors occur during weighing process. The volume of unintentional changes can be noticed only in case of analytical and semi-microbalances, microbalances and ultra- microbalance. A practical hint results from it: even if such changes take place, they are not registered by precision balances – too low sensitivity of an instrument. It means that operating conditions of such balances do not have to be as strict as, for example, in case of microbalances.

It can be stated that there are no two homogenous weighing processes, there are various models of balances in use, dynamics of ambient conditions changes is different, and different samples are weighed. As for balances, they have different levels of stability of their parameters. Therefore, balance parameters should be controlled in order to assure high quality and at the same time low risk level of the analysis.

2. Measurement errors

In practice, there are no ideal measurements, each measurement is afflicted by an error. Irrespective of chosen method, measured volume real value can never be defined absolutely precisely- because of instruments and methods imperfection. The difference between a measurement result and measured volume real value is commonly called **a measurement error**. Errors are divided into:

- gross (mistakes),
- systematic,
- random

2.1. Gross error

Gross error in most cases occurs because operator's inattention or in result of sudden change of measuring conditions (e.g. shocks, breeze of air). An instance of a gross error is presented on below collection of data:

1. 45,5010
2. 45,5009
3. 45,5012
4. 45,5080 ← gross error / noticeable change of + 70 units /
5. 45,5012

Gross error should not be taken into account in a series of measurements. In most cases it is removed, and the selected measurement is recognized as incorrect. The gross error occurrence cause and corrective activities should be analyzed, to eliminate this error in future measuring processes.

2.2. Systematic error

Measurement error component, that remains stable or changes in predictable way during measurement repetition

International Vocabulary of Terms in Legal Metrology – 2.17 (3.14)

and result of devices and measuring methods imperfection. Systematic errors should be considered if corrections (adjustments) are introduced to measuring result. A correction is a compensation of estimated systematic result. It can have a form of correction, multiplier or a value from a table.

International Vocabulary of Terms in Legal Metrology – 2.53 (3.15)

With reference to balances, a correction can have a form of constant movement of zero, for instance, if a balance does not display exact zero after removing a load from its weighing pan, but it ALWAYS stops on e.g. 0,0012g. In such case, measuring result should be corrected according to below instance:

–reference mass:100g

–reference mass error: + 0,2mg

–measuring result: 99,9996g

–actual value: 99,9996g – 0,2mg = 99,9994g

–actual value corrected by systematic error: 99,9994g – 0,0012g = 99,9982g

In practice, balances that are not characterized by ideal return to zero, can be used successfully. However, such balance should have stable and repeatable characteristics with regard to corrective parameter

2.3. Random error

Random error is a measurement error component, which changes in unpredictable way during repeatable measurements. Random measurement error is equal to: measurement error minus systematic measurement error.

International Vocabulary of Terms in Legal Metrology -2.19 (3.13)

Random error results from various incidental factors (like for instance: temperature oscillations, air movements in close distance from the measuring instrument). If measuring results of the same quantity are not repeatable, than it is caused by random error occurrence.

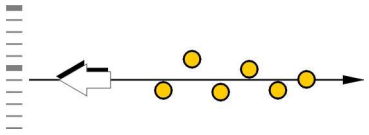


Fig 1. An instance of balance indications dispersion

2.4. Balance accuracy and precision

Evaluation of balances refers to terms and definitions like accuracy, precision and trueness. Proper utilization of these terms is required for proper control of balances.

Definition: accuracy

- closeness of agreement between a measured quantity value and a true quantity value of a measurand. VIM *
- difference between measurements average value and the real value according to USP**

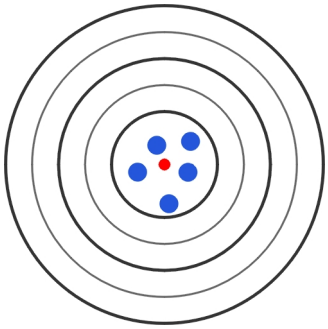
Definition: precision

- closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions. VIM

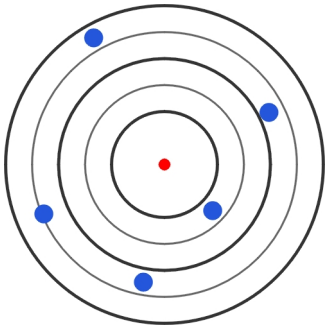
Definition: trueness

- closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value according to VIM 2010

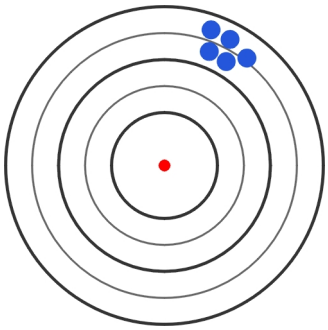
Below figures represent graphic interpretation of above definitions.



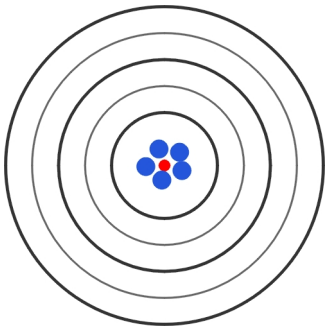
imprecisely, accurately
(values are wide-spread)



imprecisely, inaccurately
(values are wide-spread)



precise, inaccurately
(good balance repeatability)



precise, accurately
(good balance repeatability)

Fig 4 Balance accuracy and precision

***(*) VIM** – International Vocabulary of Terms in Legal Metrology*

***(**) USP** – United States Pharmacopeia*

3. Mass measurement in pharmaceutical industry

Manufacturing process of medicines has been and still is connected with smaller or bigger risk of error occurrence. In this case, the risk refers to introducing to market a medicine that is harmful for a patient. In order to avoid such situation, special attention has been paid for years to quality control process and its extension. However, it did not caused error elimination. Recently, the manufacturers opt for a concept of high quality medicines obtained through its design "**Quality by Design**", and not control process of ready product. When describing **Quality**, it should not be evaluated by product test, but is should be "**implemented into the product**" or guaranteed by project design.

During most processes intended for formula elaborating, mass measurement should be performed. The weighing quality significantly influences the quality of final result. Therefore acceptance criteria are defined by pharmaceutical companies and recommendations for weighing process are presented by American Pharmacopoeia*. Such recommendations are not contained in European Pharmacopoeia and that is why the companies that are not subordinate to American requirements, use their own balance estimation criteria.

(*) Pharmacopoeia, pharmacy code *– the official list of medicines in a given country or in the market, and fortified by the same regulations inventory of substances for the manual preparation of some of the drugs in the pharmacy (prescription drugs). In Poland, official pharmacopoeia is Polish Pharmacopoeia, issued by Drugs, Medical Products and Bio-killers Register Office. At present, Polish Pharmacopoeia VIII is valid, edited in 2008,which is European Pharmacopoeia 6.0 translated to Polish.*

3.1. Balances used for pharmacy

Pharmacy is a well-developed industrial branch, which utilized broad range of balances. For the purpose of warehouse management, four load cell scales are used. Such scales are also used for distribution of big loads into smaller ones.

Production stage utilizes single load cell scales, precision and analytical balances. Laboratory tests are based on analytical balances, semi-microbalances and microbalances (ultra-microbalances). The names to above mentioned balances are given according to below relations.

Balance name	Resolution	Quantity of decimal digits
Ultra-microbalances	0,1μg	0,0000001
Microbalances	1μg	0,000001
Semi-microbalances	0,01mg	0,00001
Analytical balances	0,1mg	0,0001
Precision balances	1g ÷ 1mg	1g ÷ 1mg

Chart 1.Names of balances with regard to their resolution

3.2. Requirements according to quality, control and balance examination

General rules on control and checking procedures are content of Health Ministry Regulation of 1st October 2000 on requirements for Good Manufacturing Practice. Attachment: detailed requirements of good manufacturing practice.

Section 1, Chapter 3: Weighing rooms and instruments

Point. 3.41. Instruments designed for measuring, weighing, weighing records and control should be calibrated and checked with application of specific methods in specific time intervals. Specific documents on these activities should be stored.

Section 2, Chapter 5: Process instruments

Point. 5.3 Calibration

5.30 Instruments designed for calibration, weighing, monitoring, testing , that are critical for semi-finished products and pharmaceutical active substances, should be calibrated according to written procedures and set schedules.

5.31 Calibration of instruments should be performed with application of standard masses that have reference to certified standard masses, if such exist.

5.32 Keep records from performed calibration processes.

5.33 Current calibration status of critical equipment should be determined and accessible for checking.

5.34 Instrument which are not compatible with valid calibration criteria should not be utilized.

5.35 Any deviation from approved calibration standards, which refers to critical instruments should be evaluated for their influence on semi-finished products and pharmaceutical active substances that have been manufactured with use of these instruments since their last correct calibration process.

Above recommendations make obligations for control over the instruments, but they do not specify any acceptance criteria or cautionary limits. It can be assumed, that a pharmaceutical company should manufacture products according to regulation specified in attachment "Detailed Requirements on Good Manufacturing Practice", which states that:

,, Manufacturer of medical products is required to ensure that medical products manufactured by it ***are suitable for their intended purpose****, meet the requirements of authorization to market and* ***do not expose patients to risks*** *from inadequate application of safety, poor quality or too low efficiency.*

In order ***to reliably achieve the objective of quality****, there has to be carefully designed and properly implemented Quality Management System for Good Manufacturing Practice, Quality Control and* ***Quality Risk Management****."*

Apart from definitions mentioned in the above regulation, there is also regulation EN ISO/IEC 17025 which defines criteria for control of weighing instruments: "General requirements on testing and calibration laboratories" point. 5.6.:

"All equipment used for measuring research . . . . . which has significant effect on accuracy . . . . should be CALIBRATED before putting it into use. The laboratory should have specific PROGRAM and PROCEDURE for calibration of its equipment."

Similar record can be found in EN ISO 9001:2008 ,,Quality management System" point 7.6.:

„... Where it is necessary to ensure reliable results, measuring equipment should be: a) calibrated or checked at specified intervals or prior to use in relation to standard units which are linked to international or national standard units..."

In case of companies which operate according to US Pharmacopeia standards, than applicable documentation is specified in 21 CFR 211 US GMP Guide Drugs § 211.68:

„ Automatic, mechanical and electronic equipment . . Should be routinely calibrated, monitored and reviewed in accordance with stored program to ensure the required action."

And document 21 CFR 211 US GMP Guide Drugs § 211.160:

"Calibration of equipment . . . according to valid and established program that contains detailed instructions, schedules, limits for accuracy and precision. . . Equipment, apparatus and recording equipment with no particular specification may not be used".

According to above documents it is clearly stated that there is a need to monitor and check the measuring devices „measuring instruments" in a clearly described and repeatable way which ensures adequate quality. Due to open characteristics of the documentation, it is an open issue on which criteria should be accepted for checking procedures.

3.3. Verify or calibrate?

At the beginning, it should be stated here, that according to requirements in Directive 90/384/EEC there are two kinds of weighing instruments:

a)

1. Mass in commercial transactions
2. Mass for calculation of toll, tariff, tax, bonus, penalty, remuneration, indemnity or similar type of payment;
3. Mass for the application of laws and regulations, expert opinion given in court proceedings;
4. Mass in medical practice for weighing patients for the purpose of monitoring, diagnosis or treatment;
5. Mass for making up medicines on prescription in pharmacies and determination of mass in analysis **carried out in medical and pharmaceutical laboratories**;

6. Determination of price based on weight for the purposes of direct sales to the public and the prepackaging;

b) All other uses not mentioned in point a

Weighing instruments described in point a) are subject to legal metrological control. For them, process of conformity evaluation with basic requirements of 90/384/EEC directive is carried out. The effect of positive outcome of this process is sticking a "**green M**" label to weighing instrument.

All above requirements oblige all users of weighing instruments in pharmaceutical industry to use weighing instruments with declaration of conformity, i.e. those which were positively assessed for requirements of Directive 90/384/EEC. This is a requirement deriving from legal area, which is a national supervision over instruments used for determination of mass.

From the other point of view, Quality Management Systems and GLP, GMP, FDA guidelines require performance of calibration procedures for determination of actual error of a weighing instrument, see point 3.2.

(*) FDA, Food and Drug Administration *– Agency dealing with Food and Drugs, American governmental agency established in 1906 . It is a part of health and social service department and it is responsible for food control (for people and animals), diet supplements, drugs (for people and veterinary), cosmetics, medical devices and those emitting radiation (including non-medical ones),biological materials and products.*

Summary:

Pharmaceutical industry should use weighing instruments that are accepted by national supervision, i.e. legal area, despite of possible errors of such weighing instruments (errors in use may be two times bigger than errors determined in conformity declaration process). In practice, however, it is known that pharmacy requires precise weighing processes, which require weighing instrument with errors much smaller than those resulting from norm PN-EN 45501. This problem is particularly visible in case of semi-microbalances, microbalances and ultra-microbalances.

3.4. Balance estimation criteria

For estimation of balance parameters while their operation, most metrological supervision departments adopt their own criteria. They result from evaluation of complete manufacturing

process, substance control and consideration of precision with which sample mass is to be determined. It is the first approach that requires good knowledge of production, control process and quality.

Another approach can be focusing on regulations specified in norm **PN-EN 45501**, ”Metrological matters in non-automatic weighing instruments”. The standard defines volume of maximal permissible errors (MPE) that may occur in a balance. It should be mentioned that operating errors are double as big as those specified in the standard. The errors division is presented in the table below.

Maximal Permissible Error (MPE)	Load **m** expressem in verifying units			
	I	II	III	IIII
± 0,5e	0 ≤ m ≤ 50 000	0 ≤ m ≤ 5 000	0 ≤ m ≤ 5 00	0 ≤ m ≤ 50
± 1e	50 000 < m ≤ 200 000	5 000 < m ≤ 20 000	5 00 < m ≤ 2 000	50 < m ≤ 200
± 1,5e	200 000 < m	20 000 < m ≤ 100 000	2 000 < m ≤ 10 000	200 < m ≤ 1000

Chart 2.Maximal permissible errors while conformity evaluation process performed according to basic requirements of directive 90/384/EEC and norm PN-EN 45501

In practice, it is not practical to base only on the standards in balance evaluation – balance can indicate too significant error and it is still treated as well-functioning. It is possible to accept more strict criteria for balance operation in one’s own evaluation system. Such assumption is obligatory during balance control procedure in RADWAG Control Department – it has been assumed that a balance is working correctly if its errors during control are lower than ⅓ of maximal permissible error defined in PN-EN 45501.

$$I_{TEST} \leq \frac{1}{3} Mpe$$

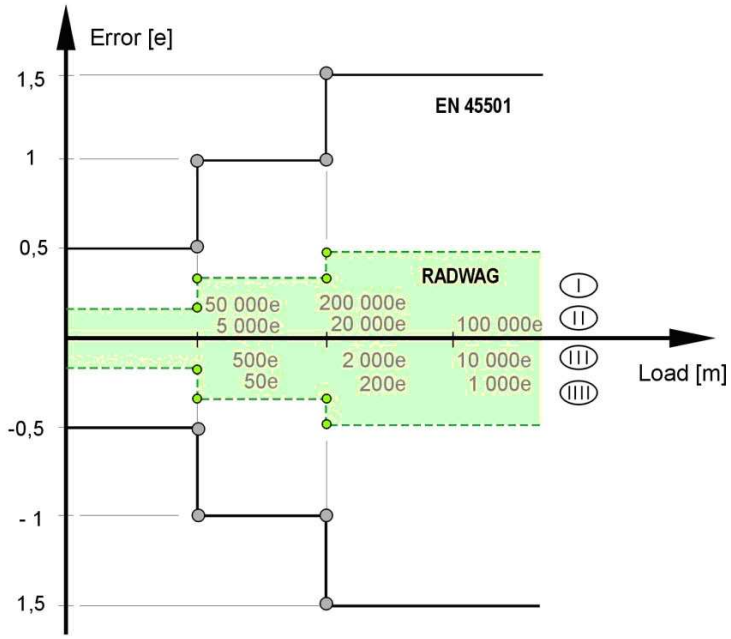


Fig 2. Graphic interpretation of MPE according to PN-EN 45501

Instances of balance estimation process according to standard requirements are presented in tables below. The first one contains MPE for balance PS 510/C/2.

Basic balance characteristics:

- Precision class II
- Max 510 g
- Min 20mg
- d 1 mg
- e 10 mg

Load m	Capacity	MPE	MPE	Real indication error
[verifying unit]	[g]	[verifying unit]	[reading unit]	[reading unit]
0e ≤ m ≤ 5 000e	0 – 50 g	± 0,5 e	± 5 mg	± 10 mg
5 000 e < m ≤ 20 000e	50 – 200 g	± 1 e	± 10 mg	± 20 mg
20 000e < m ≤ 51 000e	200 – 510 g	± 1,5 e	± 15 mg	± 30 mg

Chart 3. MPE according to norm PN-EN 45501 for balance model PS 510/C/2

The second table contains balance-sheet for microbalance MYA 5. Basic balance characteristics:

- precision class I
- Max 5 g
- Min 1mg
- d 1 μg
- e 1 mg

Load m	Capacity	MPE	MPE	Real indication error
[verifying unit]	[g]	[verifying unit]	[reading unit]	[reading unit]
0e ≤ m ≤ 5 000e	0 – 5 g	± 0,5 e	± 500 mg	± 3 μg

Chart 4. MPE according to norm PN-EN 45501 for microbalance MYA 5

If one's criteria are based on acceptance criteria according to standard PN-EN 45501 it should be taken into account that M are twice increased in balance operation. In case of microbalances and ultra-microbalances, so-called verification is quite problematic because of drastic difference between permissible errors accepted by the standard and real errors of balances.

Obviously, as for the range of examination methodology, the standard provides clear instructions that can be commonly used or corrected up to individual needs.

The third attitude for evaluation of balances is connected with requirements of American Pharmacopoeia. This approach defines what precision a balance should have in order to be put into operation:

> *If it is not specified . . ., a substance is correctly weighed (taking random and systematic error into account), if device measurement uncertainty does not exceed 0,1% of readout.*
>
> *USP, General Chapter 41 „Weights and Balances"*
>
> *Measurement uncertainty is satisfactory if 3-times standard deviation from series of at least10 repetitions divided by series average value does not exceed 0,001.*
>
> *USP, General Chapter 41 „Weights and Balances"*

Such approach is used by American market product manufacturers, that are a part of global concerns which are subordinated to periodical controls by FDA.

The fourth approach is directed to Risk Analysis in accordance to document EMEA* ICH Q9** "Quality Risk Management". The document is of general nature and shows how to manage risk. Obviously, it is necessary to adapt the assumptions to balances. How should risk be defined?, How to reduce it? How to manage it? It requires defining. Risk area will depend on the weighing procedures that are performed.

**EMEA – European Drugs Agency, EU agency for medical products estimation and supervision coordination.*

***ICH Q9 – Guide elaborated by a group of experts for pharmaceutical industry*

Irrespective of adapted balance estimation criteria, following 4 parameters should be subject to examination:

- repeatability
- linearity error
- centricity
- sensitivity change

4. Quality Risk Managing in reference to mass measurements

Risk management procedures are used in various areas from finance and insurance to health protection. The idea is so universal that it can be introduced to various fields. Generally, risk is described as probability of damage and its results occurring.

At pharmacy, risk is connected with medicine manufacturing and the medical product use. In case of balances, it is the risk of incorrect weighing performing , which significantly influences the quality of manufactured medicine. In order to avoid it, knowledge of used weighing devices measurement possibilities should be obtained, controlled and used in practice.

Basic mistake made by most users is the belief that they can buy a balance with elementary unit 0,1mg for process that should be performed with precision 0,1mg. Balance elementary unit [d] is something completely different from balance precision*.

(*) measuring instrument precision – measuring instrument ability to give indications close to true value.

International Dictionary of Basic and General Metrological Terms
point 5.18

In order to estimate balance precision, its repeatability ,eccentricity, non-linearity and sensitivity change should be estimated. After taking these factors into account, measured value is close to the real value.

Using the attitude connected with risk analysis aims to:

- obtaining a high quality product
- money saving and expenses cut
- obtaining conformity with legal requirements that are currently valid.

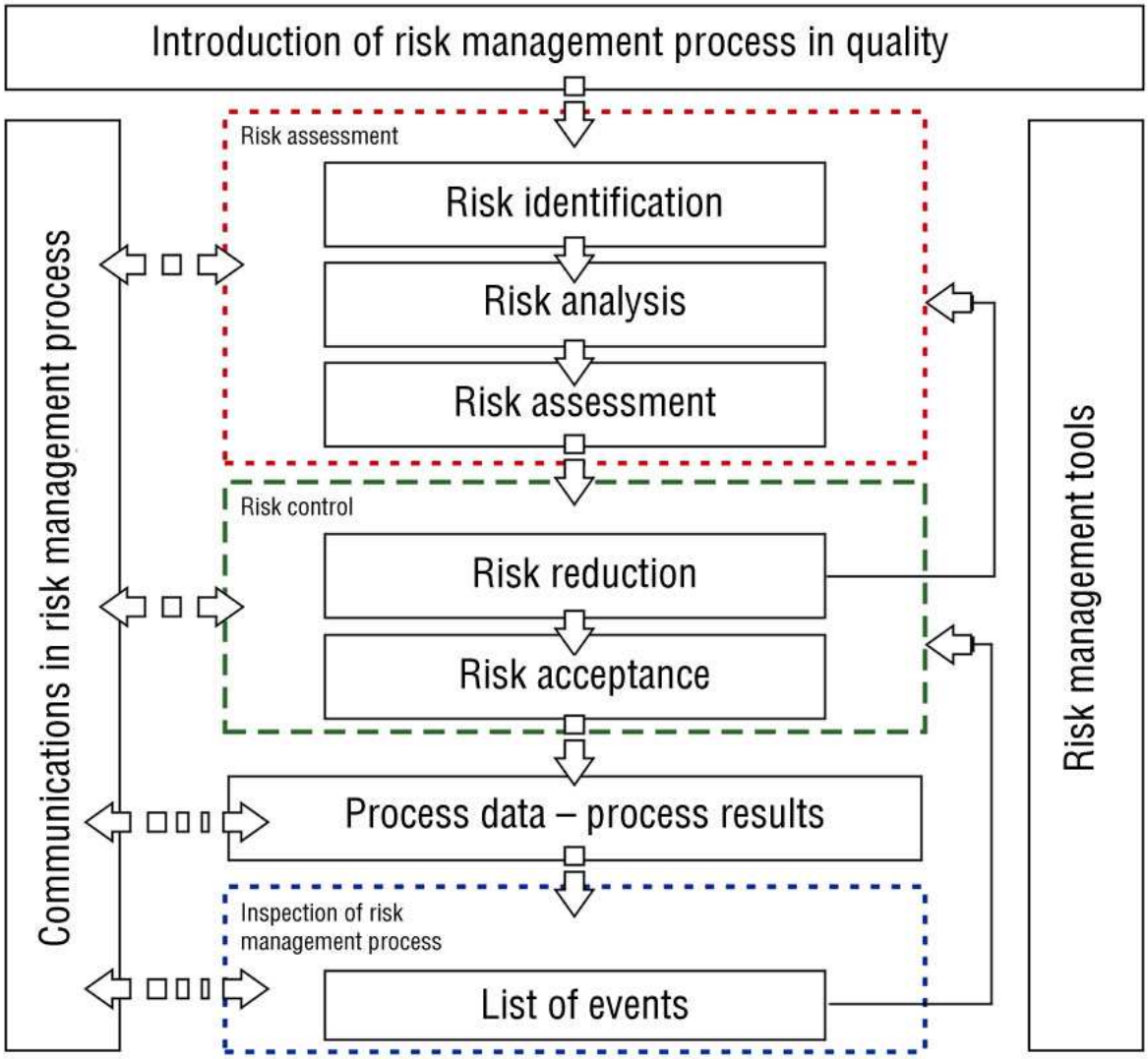
Main problem that some users face is the problem of transmitting risk analysis and manage matters to their own balance analysis. In such case, three questions connected with risk analysis are helpful:

ICH Q9

1. What can go wrong?
2. What is probability of failure?
3. What can be the consequences?

Balance

1. Which balance parameters is decisive?
2. Is the parameter constantly stable or it shows drifters?
3. What does it mean for my balance analysis?



Typical process of Quality Risk Management

Using the above operating scheme for a balance, requires performing of RISK ESTIMATION as the first step. The process consists of:

– **Risk Identification** → Define your own balance analysis

- What are you weighing?
- What is the expected analysis precision?

- How big is the sample?
- What weighing containers do you use?
- What are the external conditions of analysis realization?

– **Risk Analysis**

- Should catalogue data be estimated?
- Should measurement data be estimated?

– **Risk Estimation**

- Estimate mass measurement error influence on product quality

Then the most important stage of risk management should be performed, which helps in decrease it. Balances risk reduction is finding an answer to the question: how to reduce measurement error:

– **Risk Reduction** → how to reduce weighing errors?

- suitable balance choice
- using balance self-adjustment
- weighing techniques internal training
- using standard operational procedures „SOP”?
- using authorized service – service reviews

– **Risk Acceptance** → is balance precision sufficient?

- Estimate weighing errors influence on the whole process risk

Next stage of risk management process is performed process data monitoring. At this stage balance precision is estimated with regard to requirements and effectiveness of carried out operations. Risk Management Process Review is a system procedure. It aims at receiving new ideas and using them in order to reduce risk.

When using risk management in reference to balances, it should be remembered that legal requirements have to be observed. Risk management is designed as a process that supports making decisions based on scientific knowledge and practice.

5. Balances Risk Analysis – practical matters

Balances risk is not only searching for incorrect measurements cause but also ignoring the fact that measurement is afflicted by an error. Such analysis result can show that used balance is properly operating or it shows some deviations. Whether the deviations are significant or not, depends on at what range the balance is used. Therefore following balance parameters should be controlled:

- sensitivity
- non-linearity
- eccentricity
- repeatability

An ideal solution is a balance having a real dependence describing indication in loading function.

Load = Indication

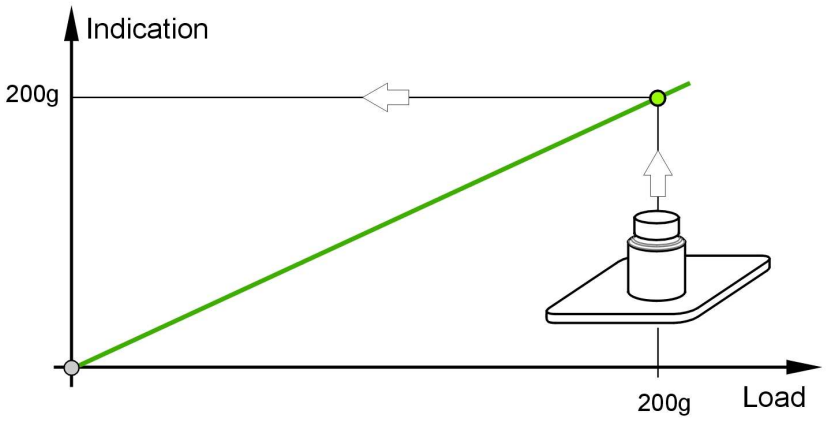
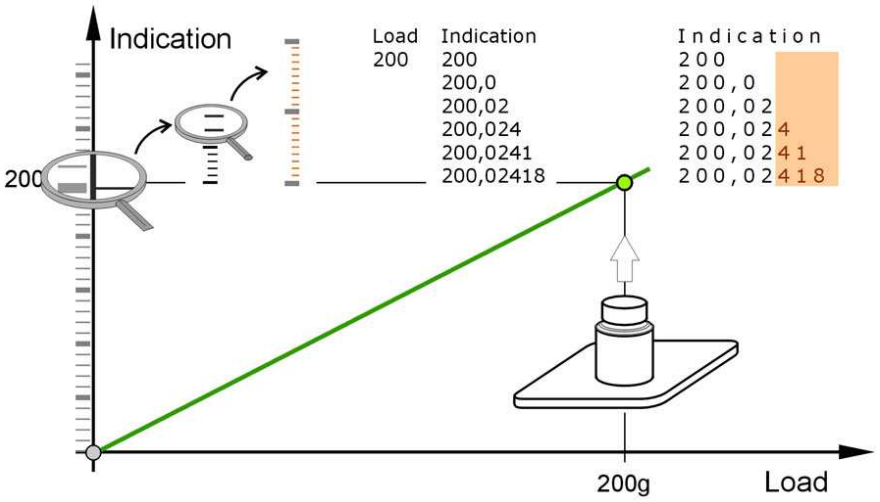


Fig. 3. Relationship:indication → load for ideal balance

Obviously it is only a theoretical solution, because there are no ideal measurements or devices.

5.1. Resolution and precision

Balance resolution derives from its electronic abilities. Practically, it is possible to design a balance with many decimal places, but its precision is still not unequivocal. Therefore, balance precision cannot be estimated only on basis of its resolution. Other characteristic parameters must be estimated.



Electronic balance resolving power

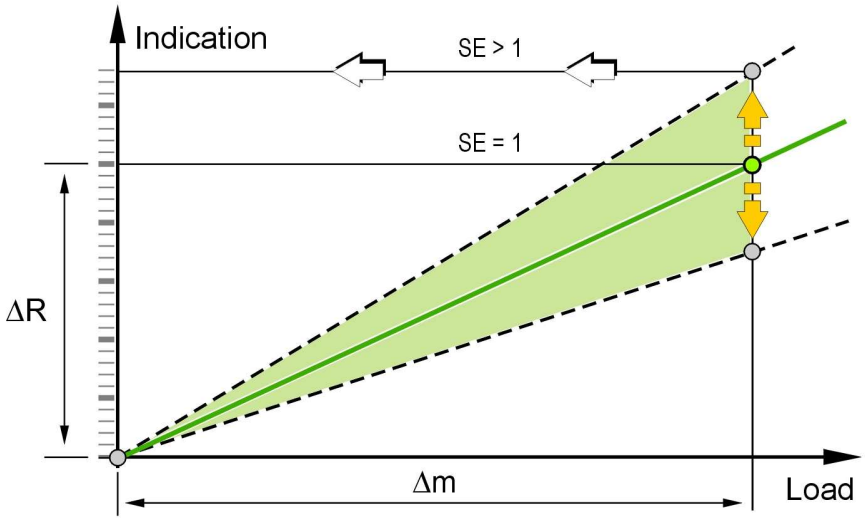
5.2. Electronic balances sensitivity change

Definition

It is a quotient of measuring device increment response (ΔR) and increase of input signal increment relating to it signal (Δm).

$$SE = \frac{\Delta R}{\Delta m}$$

International Dictionary of Basic and General Metrological Terms point 5.10



Balance sensitivity change

The scheme estimation shows that sensitivity changes test is justified only for heavy loads and the error is proportional to sample mass. A practical aspect results from it:

„sensitivity changes do not influence small samples weighing”

Example of sensitivity change calculation for balance of 200g Max capacity

a) $\Delta m = 200$; $\Delta R_{IND} = 205$; $SE = \frac{\Delta R}{\Delta m} = \frac{205}{200} = 1{,}025$

---

b) $\Delta m = 200$; $\Delta R_{IND} = 200$;

$$SE = \frac{\Delta R}{\Delta m} = \frac{200}{200} = 1$$

Example a) shows sensitivity change, example b) is an ideal weight.

The easiest method to introduce the test is Standard Operational Procedure, which describes what should be done and how to do it. As each procedure, it should be short and unequivocal. Such procedure example:

5.2.1. Standard procedure of sensitivity changes test

1. Balance should be thermally stabiliyed
2. Note down standard nominal mass: m_{NOM} – the mass should be close to Max
3. Zero balance indication and note down the result as: m_Z
4. Place standard of nominal mass centrally on the pan and note down the indication as: m_{IND}

Calculation:

1. Indication correction by zero change: that is $A = m_{IND} - m_{ZL}$
2. Sensitivity change calculation:
   substract nominal mass value, that is $SE = A - m_{NOM}$ from obtained result
3. Check if obtained value is contained in your acceptance field.

Procedure note:

1. *Procedure should contain all information needed by personnel , for its proper application*
2. *Warning limits for registered sensitivity changes should be fixed, that is, it should be defined what is permissible and what is not*
3. *Decision track should be defined clearly if limits are exceeded.*

5.3. Balance non-linearity test

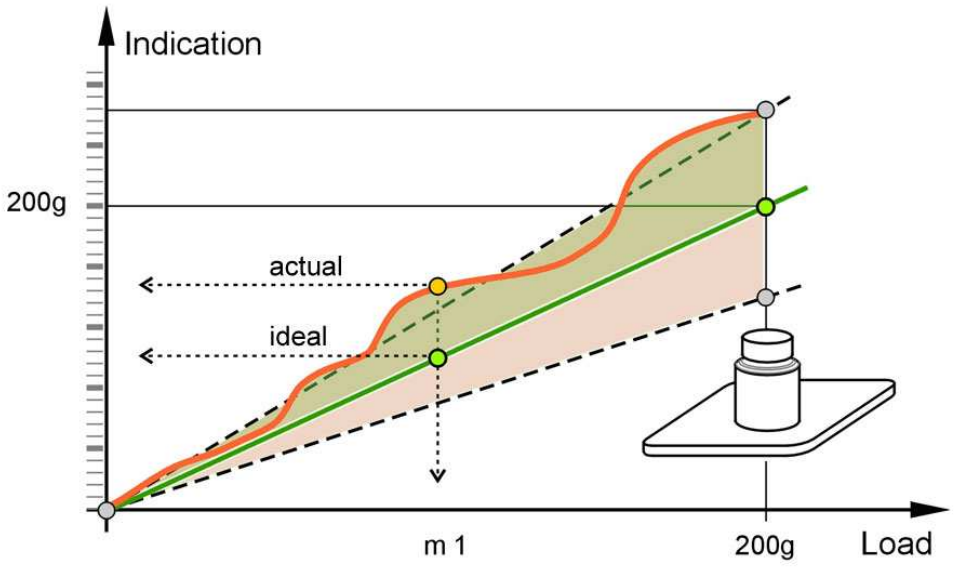
Definition

It is a deviation of balance real curve from straight line joining two points A:B – ideal weight. Non-linearity parameter is not defined by publication concerning weighing matters, therefore, various definitions can be used.

In practice, there are no ideal balances, so balance characteristics is never a straight line. Non-linearity can be tested with use of one of the two methods:

5.3.1. Differential non-linearity test

It should be checked, what deviation from ideal curve of the tested point is. Ideal weight straight line equation ought to be defined, and then, the equation of the real course. Maximal difference between the values is at the same time balance maximal non-linearity.



Balance non-linearity characteristics

Equation of ideal balance characteristics – straight line equation

$$R_L = \frac{R_I - R_Z}{m_I - m_Z} \cdot (m - m_Z) + R_Z$$

where: R_L *– balance ideal characteristics equation*

R_I *– Max loading indication*

R_Z – *zero indication*

m_I – *Max nominal loading*

m_Z – *zero loading*

m – *indirect nominal loading*

$$R_{POINT} = R - R_L = R - \left[\frac{(m - m_Z)}{m_I - m_Z} \cdot (R_I - R_Z) + R_Z \right]$$

where: R_{POINT} – *examined point non-linearity deviation*

Calculation example

Balance non-linearity for loading 70g is tested, when Max loading is equal to 220g

Input data:

- nominal load $m_Z = 0$
- Max nominal loading $m_I = 220{,}0002$g
- Indirect nominal loading $m = 70{,}0005$g

- Zero indication $R_Z = 0{,}0000$g
- Max loading indication $R_I = 220{,}0012$g
- Indirect loading indication $R = 70{,}0008$g

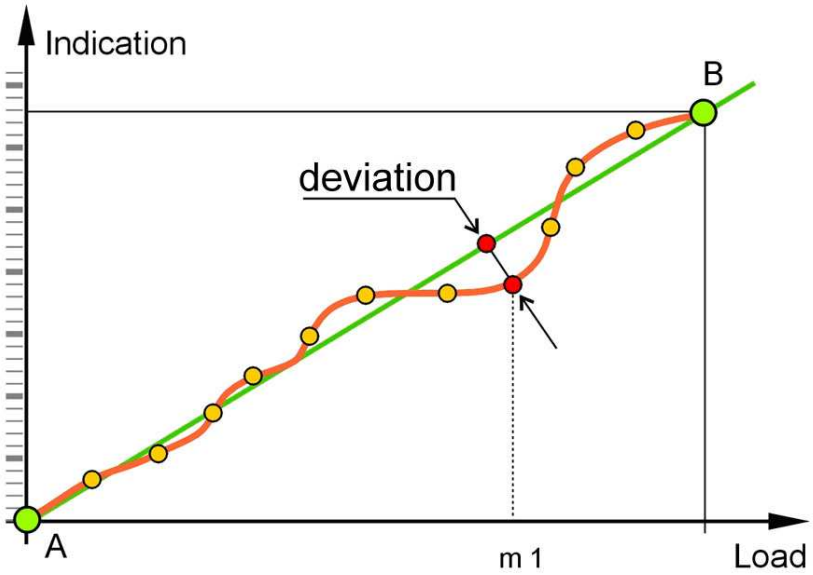


Fig. 4. Non-linearity deviation in a point

$$R_{70} = R - R_L = 70{,}0008 - \left[\frac{(70{,}0005 - 0)}{220{,}0002 - 0} \cdot (220{,}0012 - 0) + 0 \right]$$

$$R_{70} = 1{,}81838016 \cdot 10^{-5} = 0{,}000018 \approx 0{,}00002$$

Non-linearity of point 70g is equal to ± 0,00002g. Practically, mass result in point 70 can be contained in range 70,0006 ÷ 70,0010

Advantage of this testing method is possibility to define non-linearity at any point. Disadvantage of this method is necessity to have several standards and complicated mathematical calculations.

5.3.2. Balance non-linearity test with the use of tare

The method is designed for checking whole balance measuring range with the same standard in accordance to fixed interval. It is assumed that at ideal weight, all following measurements should indicate the same value. Such case is presented in the drawing below. The advantage of the method is use of the same standard, that can in fact be of any precision class. In the test, is to define:

- Each measurement deviation from expected value, that is standard nominal mass, (if standard mass is equal to 50,0002 g, the same result should be indicated at the whole test range)

- Whether each following measurement is similar if standard mass is not known. In this case, it cannot be defined, how precise* the balance is. Then a stable, indefinite error δ occurs, which is a standard error. Such case is presented with red measuring points.

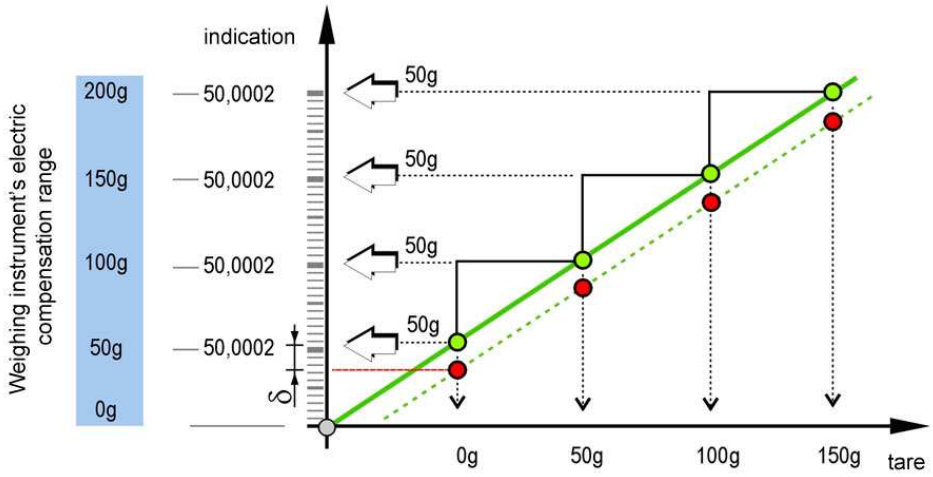


Fig.5 Non-linearity test in whole weighing range of a balance

(*) measuring instrument precision – measuring instrument feature of giving response close to the real value.

International Dictionary of Basic and General Metrological Terms point 5.18

While the test, an interval should be fixed with which the balance will be tested. It is recommended to use compact control mass in form of single mass standard. Obviously, the method can be used for testing the whole balance measurement range or just its sector. In such case, ballast of suitable mass should be used, e.g. 100g. After indication has been tarred, it is possible to test balance linearity with interval, e.g. 20g. The test will then contain the range from 100g to 200g with the assumption that balance is used just at this range. Such solution is presented in drawing number 13

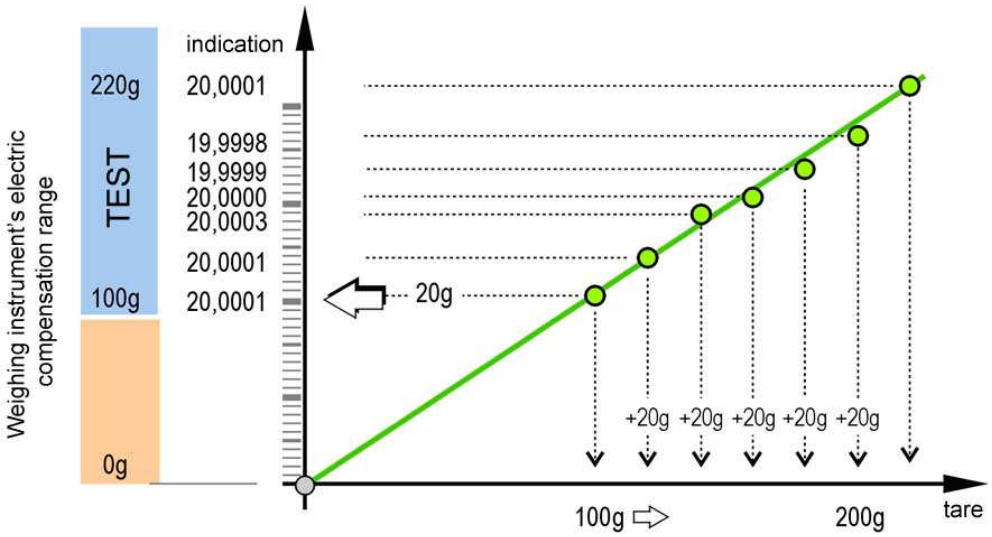


Fig. 6. Non-linearity test in top weighing range of a balance

This way of characteristics examination is used by Quality Control Department in reference to microbalances and ultra-microbalances.

5.3.3. SOP example for balance non-linearity test

1. Balance should be thermally stabilized
2. Prepare ballast weights set. Their quantity depends on measurement points number. Ballast weight value is: Max / measurement points number
3. Note down standard nominal mass [m_{NOM}]
4. Remove load from pan and zero the indication. Note down the result = B_1
5. Place standard and note down the result = I_1
6. Remove standard and place the first ballast weight. Note down the indication as B_2.
7. Add standard to ballast weight and note down indication, note down = I_2 after stabilization
8. Remove standard and add second ballast weight. Note down the indication as B_3.
9. Add standard to ballast weights and note down indication = I_3 after stabilization.
10. Repeat the procedure till obtaining loading close to Max.

11. Calculate balance indication [W_i] corrected by zero drifter for following measurements I_i – B_i
12. Substract standard mass nominal value from obtained indication [W_i]. The obtained result is a linearity deviation for each measurement point

$$NL = W_i - m_{NOM}$$

13. Maximal difference is maximal error of balance linearity.

An instance of checking non+linearitz of a balance model ASY 220/C/2 with set interval every 50g

m_{NOM} = 50g -0,002mg = 49,999996g

T= 0g	B_1 = 0,0000g	I_1=50,0001	W_1 = 50,0001 - 49,999996 = 0,000104
T= 50g	B_2 = 0,0000g	I_2=50,0001	W_2 = 50,0001 - 49,999996 = 0,000104
T= 100g	B_3 = 0,0000g	I_3=50,0000	W_3 = 50,0000 - 49,999996 = 0,000004
T= 150g	B_3 = 0,0000g	I_4=50,0001	W_4 = 50,0001 - 49,999996 = 0,000104

5.3.4. Summary

Evaluation of non-linearity of a balance can be done by means of two methods. As practice shows, method with application of tare is commonly used. Its advantages are speed, direct reading and simplicity. Additionally, it requires only a single mass standard in a specified class for determination of accuracy. Mass for tares do not have to be precise.

5.4. Balance eccentricity test

Definition: eccentricity error

It is an indication deviation in which a load is located in central point of a weighing pan. In practice, a difference is defined between indication when mass standard is put at central point of

weighing pan and indication when the same mass standard is located at another place on the weighing pan.

The location for mass standard on the weighing pan is defined by norm PN-EN 450501 in point 3.6.2 and A.4.7. ,,Eccentric loading tests". Measurement place is presented in drawing below.

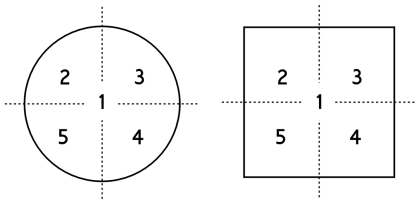


Fig. 7. Balance eccentricity test

Balance eccentricity test is motivated only in case of heavy loads. For low mass, the parameter is non-measurable (repeatability influence is dominant).

Example of centricity error differential calculation:

Formula: $E = R_{(i)} - R_{(1)}$; with: E – centricity differential error

$R_{(i)}$ – following point indication

$R_{(1)}$ –central location indication

$R_{(1)} = 70{,}0003$

$R_{(2)} = 70{,}0002$ $E_{(2)} = 70{,}0002 - 70{,}0003 = -0{,}0001$

$R_{(3)} = 70{,}0006$ $E_{(3)} = 70{,}0006 - 70{,}0003 = 0{,}0003$

$R_{(4)} = 70{,}0007$ $E_{(4)} = 70{,}0007 - 70{,}0003 = 0{,}0004$

$R_{(5)} = 70{,}0002$ $E_{(5)} = 70{,}0002 - 70{,}0003 = -0{,}0001$

In this case, maximal differential eccentricity error is equal to 0,0004g (0,4mg)

5.4.1. SOP example for balance centricity examination

1. Balance should be thermally stabilized
2. Place standard centrally on the pan and note down the result = $R_{(1)}$
3. Place standard at points 2,3,4,5 and note down the results = $R_{(2)}$ . . $R_{(5)}$

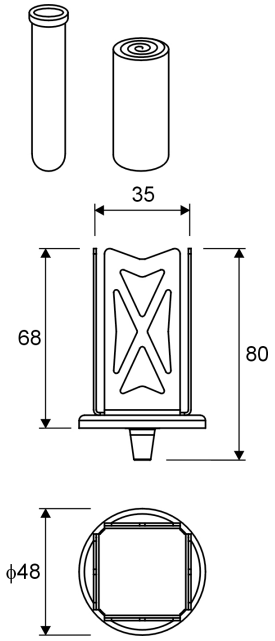
Calculation:

4. Substract value $R_{(1)}$ from following results $R_{(2)}$ . . $R_{(5)}$
5. Maximal deviation of calculated differences is maximal differential centricity error.

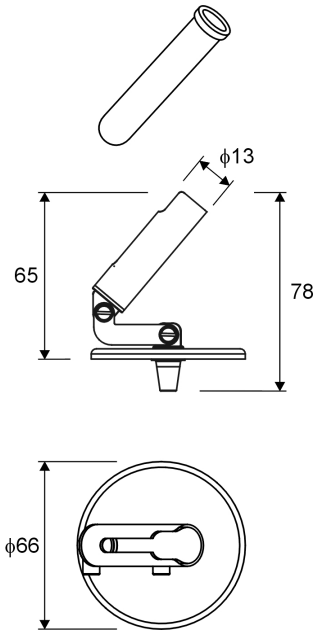
Caution:
Standard mass (1) can be tarred and then deviation from zero state can be defined.

5.4.2. Centricity errors leveling

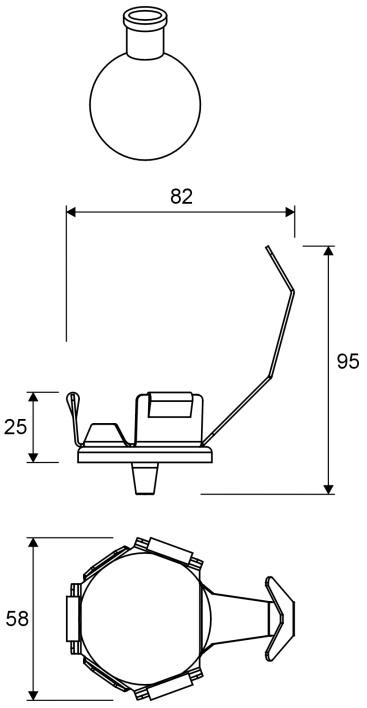
All errors resulting from eccentric load placing on balance weighing pan can be successfully eliminated by special holders intended for certain use.



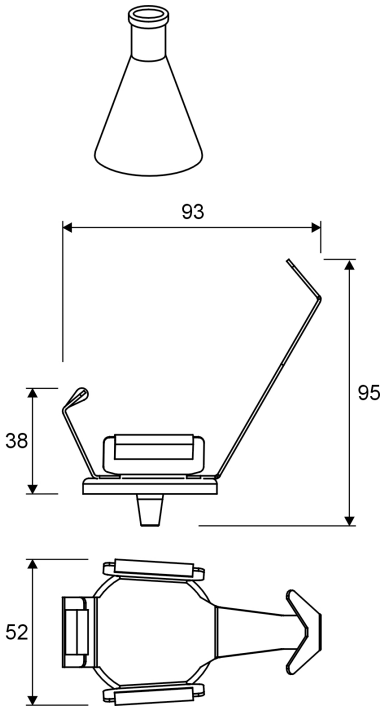
Intended use: Glass and plastic test-tubes, filters, thimbles etc.



Intended use: Glass and plastic test-tubes ø8mm, ø10mm and ø12 mm



Intended use: measuring bulbs with ball-shaped bottom 50ml, 100ml and 250 ml



Intended use: measuring bulbs with flat bottom 50ml, 100 ml

5.5. Balance repeatability test

Definition

Measuring instrument feature according to which its indications are close one to another in case of repeated measurement of the same measured volume in the same conditions

International Dictionary of Basic and General Metrological Terms point 5.27

The conditions contain:

- the same procedure
- the same observer
- the same measuring instrument
- identical ambient conditions
- the same test place
- repeatability in quite short time period

Repeatability can be expressed as maximal deviation between measurements or in terms of quantity as standard deviation from a series. Testing the parameter as maximal deviation between series measurements is compatible with PN-EN 45501 that is:

$$P = I_{MAX} - I_{MIN} \leq Mpe$$

where: I_{MAX} *– maximal indication*
I_{MIN} *– minimal indication*
Mpe – maximal permissible error

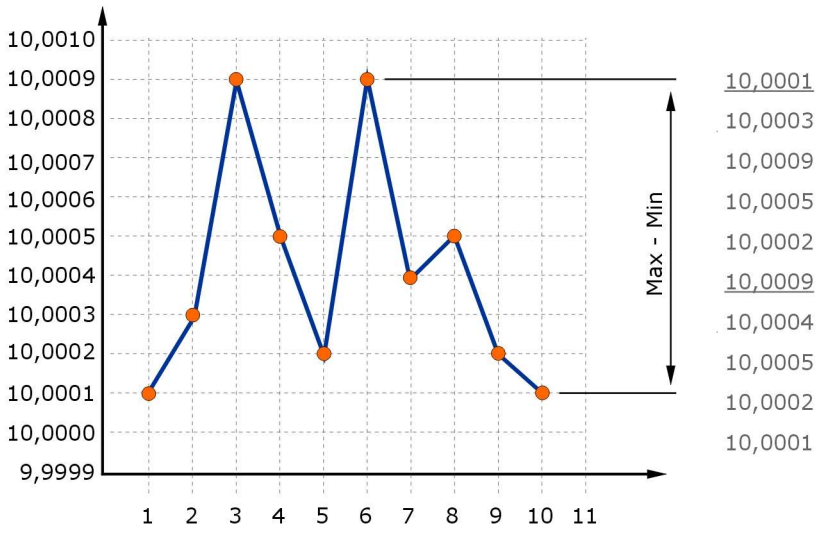


Fig. 8. Balance repeatability

Repeatability for a series of measurement is presented in drawing 16, according to following dependence, is equal to:

$$P = 10{,}0009 - 10{,}0001 = 0{,}0008$$

Repeatability for the same series of measurements can be presented in terms of quantity as standard deviation. It is defined in accordance with following dependence:

$$s = \sqrt{\frac{\sum_{i=1}^{n} (x_i - \overline{x})^2}{n-1}}$$

with: s – *standard deviation*
x_i – *next measurement*
$\overline{x}$ – *measurement series arithmetic average*

Measurement series
1. 10,0001
2. 10,0003
3. 10,0009
4. 10,0005
5. 10,0002
6. 10,0009
7. 10,0004
8. 10,0005
9. 10,0002
10. 10,0001

- Average value determines the middle of data. For this measurement series $\overline{x} = 10{,}0004$
- Standard deviation informs about individual data average distance to average value, s = $0{,}00029 \approx 0{,}0003$
- Subtracting and adding standard deviation to average value, a range is obtained in which measurement value can be contained with some probability.

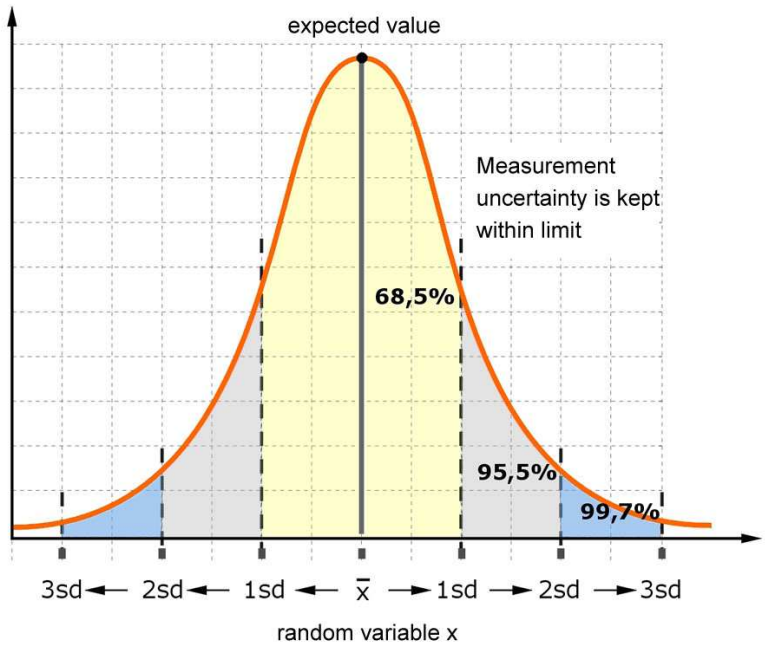


Fig 9. Gauss' random variable scheme

When an x volume is measured (random variable) repeatedly and measurement result indicate **statistic dispersion,** the dispersion is best described by Gauss' function.

If there is no statistic dispersion in measurement series, that is $x = x_1 = x_2 = x_3 \ldots$ then, balance reading unit is the main uncertainty source and following dependence is used:

$$u = \frac{d}{2 \cdot \sqrt{3}}$$

Repeatability in practice

- Individual measurement deviation from average value does not exceed standard deviation, that is ~ 0,0003g with probability **68,5%.**

- Individual measurement deviation does not exceed three standard deviations, that is ~ 0,0009g with probability higher than **99,7%**, so very close to certainty.

5.5.1. Standard procedure for repeatability calculation

The procedure aim is to create repeatable performance methodology during repeatability parameter defining. Procedure example

1. Balance should be thermally stabilized
2. Remove load from weighing pan and zero the indication
3. Note down measurement result of empty pan $\Rightarrow R_{(Z-1)}$
4. Place standard and note down measurement result $\Rightarrow R_{(1)}$
5. Remove standard and note down empty pan result $\Rightarrow R_{(Z-2)}$
6. Place standard and note down measurement result $R_{(2)}$
7. Repeat points 5 – 6 till the series is finished

Calculation:

8. Substract values $R_{(Z-1)} \ldots R_{(Z-5)}$ from following results $R_{(1)} \ldots R_{(5)}$
9. On the basis of obtained results, define maximal difference Max – Min or define standard deviation.

Calculation example:

- Analytical balance XAY 220;
- Max 220g;
- d = 0,1mg

No.	Tare value	Measurement result	Difference
	$R_{(Z-i)}$	$R_{(i)}$	$R_{(i)} - R_{(z-i)}$
1.	0,0000	200,0001	200,0001
2.	0,0001	200,0001	200,0000
3.	0,0001	200,0003	200,0002
4.	0,0000	200,0001	200,0001
5.	-0,0002	199,9999	200,0001
		Max – Min	0,0002
s =			0,00007

Chart 5. Balance repeatability expressed by standard deviation

5.5.2. Repeatability in practice

Defining repeatability with mass standards is a form an approximation, as the parameter depends on:

- balance model
- balance configuration (filters, stability setting)
- applied gross mass
- correct weighing skill
- external factors: breeze of air, temperature change
- weighing methods
- used peripheral equipment: size, material, shape

Taking the above into account, repeatability should be defined at its operating location of a balance, with use of a sample and other objects connected with weighing process.

5.6. How often should balance parameters be tested?

Intervals defining balance testing should take into account: range of jobs performed on a balance, their intensity, balance stability in time and expected weighing process measurement

precision. Assuming that external conditions are stable, following balance parameters control periods can be fixed:

- calibration annually
- repeatability monthly
- centricity monthly
- sensitivity change weekly
- adjustment daily

5.6.1. Low mass measurement

When a balance is used only for weighing samples of mass up to 5% balance maximal capacity, the only justified test is repeatability control. In this case, it is assumed that even if prominent tare is used, e.g. 30% of Max capacity, it is still located at the central pan point.

For low mass measurement, other balance errors influence deriving from linearity, sensitivity change or eccentricity, is negligible.

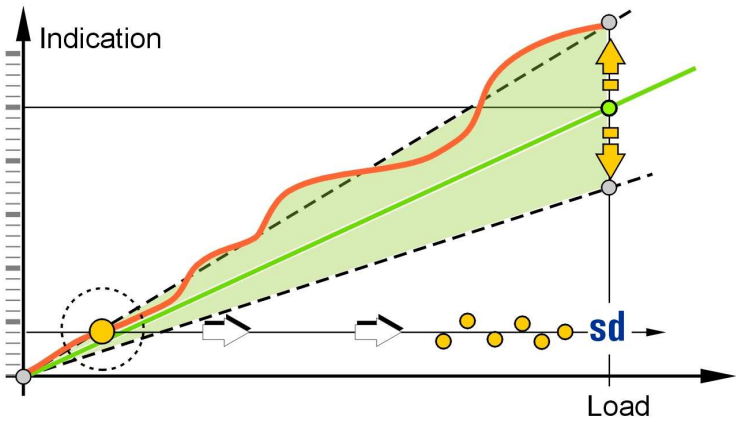


Fig.10 Non-linear balance characteristics

5.6.2. All-purpose balance

Optimal solution for balances is their utilization at 100% which in practice means good measurement ability for light and heavy loads. In case of such balance, sensitivity drift should be checked more often. Practice shows that multiple organizations perform checking procedure on daily basis. An operator places a mass standard which is close to balance Max capacity on the a weighing pan of a balance and registers the indication. The procedure is quite short and it can evaluate balance usability.

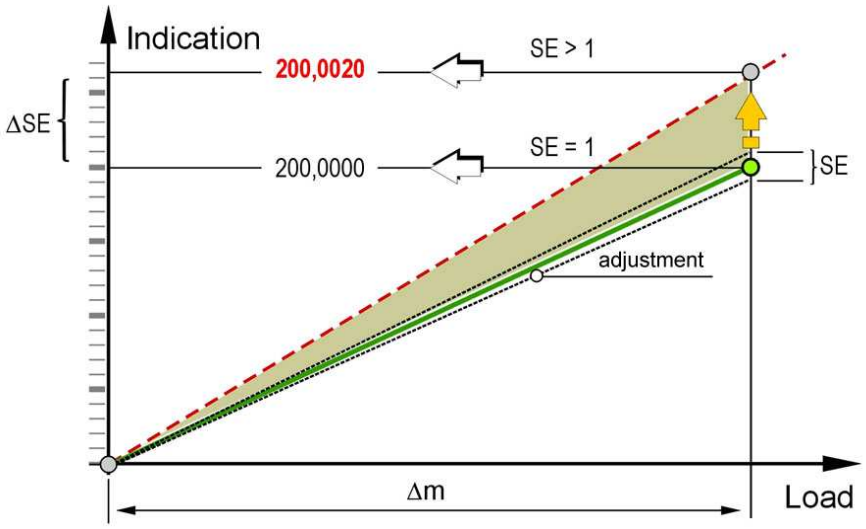


Fig. 11 Sensitivity change test – balance adjustment

Sensitivity drift can occur even though most balances are equipped with self-adjustment system. It can be caused by device drift as a result of ambient conditions change. If it occurs, than situation from above drawing takes place.

According to Good Laboratory Practice, before taking a measurement, an operator is to perform an adjusting procedure. Then all errors connected with sensitivity changes are leveled. After the operation, error-free value should not be expected, because adjustment process relates to mass weighing, and has been already said, there are not ideal measurements. In most organizations, sensitivity changes are not tested. Organizations perform tests on adjustment effectiveness, and balance accuracy is controlled after adjustment with mass standard with precisely specified weight.

6. Measurement uncertainty

Definition: it is a parameter connected with measurement result, characterizing dispersion value, that can be assigned to measured value in justified way.

International Dictionary of Basic and General Metrological Terms – 3.9.

Uncertainty:

- determins, that measurement is actually not ideal
- determins, how precisely a value is measured: how close values are in relation to expected value

A parameter expressed by uncertainty cab be for instance standard deviation or its multiple. Standard deviation from a series of measurements is also uncertainty. There are two basic types of uncertainty which differ in parameters origin: type A and type B.

Type A uncertainty

Method A describes the calculation of standard uncertainty by analyzing the statistic series of observations. In such case the standard uncertainty is actually the standard deviation. This method requires large amount of measurements and their repetitions, and it is successfully implemented in case of random errors. Method A is applied if it is possible to perform a series of equal measurements in equal measuring conditions. Such is the case for checking the repeatability of an electronic balance,

For the uncertainty type A the standard distribution is employed, which is graphically expressed as Gaussian curve.

Type B uncertainty

Uncertainty type B is determined by a scientific analysis based on all accessible information on input volume variability.

Those data can be:

- based on previously performed measurements,
- operator's experience,
- characteristic features of measured materials and measuring devices,
- data from manufacturer's product specification,
- uncertainty reference data, handbook and manual content, all accessible publications and other.

Complex uncertainty

Complex uncertainty – in simple words – is a connection of uncertainty type A and type B. the most common is the complex uncertainty, there are, however, some cases, where complete uncertainty analysis is based on the type B.

Extended uncertainty

Extended uncertainty is a value describing the range of values surrounding the measuring result, which, as expected, can cover a large part of values distribution, which are commonly assigned to measured value.

According to Guide to Expression of Uncertainty in Measurements, letter *u* has been assigned to match uncertainty, and expression of extended uncertainty is realized by capital letter U. An extension ratio *k* is a numerically expressed ratio, used as a multiplier of standard complex uncertainty, determined to set extended uncertainty.

The extended uncertainty is expressed by a below relationship:

$$U = k \cdot u(x)$$

Where:
U – extended uncertainty
k – extension ratio
u(x) – complex uncertainty

6.1. Mass measurement uncertainty

Taking into account, that each measurement is affected by an error, suitable values should be introduced to operator's own mass measurement process. Example of sample weighing procedure is described with following measurement equation:

$$R = m + \delta m_1 + \delta m_2 + \delta m_3 + \delta m_4$$

with: *R – balance readout*
m – loading mass
δm_1 – uncertainty participation connected with readout precision
δm_2 – uncertainty participation connected with balance repeatability
δm_3 – uncertainty participation connected with balance non-linearity
δm_4 – uncertainty participation connected with balance eccentricity

Uncertainty equation is the total of all uncertainties:

$$u^2(R) = u^2(m_1) + u^2(\delta m_2) + u^2(\delta m_3) + u^2(\delta m_4)$$

Individual components participation in uncertainty budget is presented in the table below.

Component	**Symbol**	**Uncertainty type A**	**Uncertainty type B**
Readout precision	δm_1		$u(\delta m_1) = \frac{d}{2 \cdot \sqrt{3}}$
Repeatability	δm_2	$u(\delta m_2) = \frac{s_d}{\sqrt{n}}$	
Non-linearity	δm_3		$u(\delta m_3) = \sqrt{\frac{2}{3} \cdot (NL)^2}$
Eccentricity	δm_4		$u(\delta m_4) = \frac{\lvert \Delta I_{ecc} \rvert_{\max}}{2 \cdot L_{ecc} \cdot \sqrt{3}}$
Sensitivity	c_{SE}		$u_{se} = \frac{c_{SE}}{\sqrt{3}}$

Basic uncertainty components related to weighing procedure include:

- type B uncertainty component connected with readout precision, that is counted with following equation:

$$u(\delta m_1) = \frac{d}{2 \cdot \sqrt{3}}$$

where: d – balance elementary unit value

CAUTION

Uncertainty component related to readout precision is often taken into account in standard deviation and it is not taken into account in calculations.

- Type A uncertainty component connected with repeatability ,which is measured by standard deviation:

$$u(\delta m_2) = \frac{s_d}{\sqrt{n}}$$

where: s_d – standard deviation

- Type B uncertainty component connected with linearity errors, which is calculated with the equation:

$$u(\delta m_3) = \sqrt{\frac{2}{3} \cdot (NL)^2}$$

where: NL – non-linearity factor

- Type B uncertainty component connected with eccentricity errors, which is calculated with the equation:

$$u(\delta m_4) = \frac{\left|\Delta I_{ecc}\right|_{\max}}{2 \cdot L_{ecc} \cdot \sqrt{3}}$$

with: $|\Delta I_{ecc}|_{max}$ *- absolute maximal eccentricity error*

L_{ecc} *– test load*

- B type uncertainty component connected with sensitivity that is calculated with the equation:

$$u(c_{SE}) = \frac{c_{SE}}{\sqrt{3}}$$

with: c_{se} *–sensitivity factor*

Complex uncertainty is defined with following equation:

$$u = \sqrt{u^2(\delta m_1) + u^2(\delta m_2) + u^2(\delta m_3) + u^2(\delta m_4) + u^2(c_{SE})}$$

Extended uncertainty is defined with following equation:

$$U = u \cdot k$$

where: k extension factor: k= 2 for probability ~ 95,5%
k=3 for probability ~ 99,7%

Example of balances technical data for uncertainty calculation

	UYA 2	**MYA 5**	**XA 60/220Y**	**XA 160Y**	**PS 600/Y**
Max capacity	2g	5g	60/220g	160g	600g
Reading unit [d]	0,0001mg	0,001mg	0,01mg	0,1mg	1mg
Reading unit [d2]	x	x	0,1mg	x	x
Repeatability ~ Max	2g: 0,0004mg	5g: 0,003mg	200g: 0,1mg	100g: 0,1mg	500g: 1,5mg
Repeatability ~ 5%Max	x	x	10g 0,025mg	x	x
Linearity	0,001mg	0,005mg	0,15mg		3mg
Eccentricity	1g 5E-07g	2g 5E-07g	50g 0,2mg	50g 0,2mg	200g 5mg
Sensitivity [ppm/^{o}C]	0,000002	0,000002	0,000002	0,000002	0,000002

Chart 7. Parameters for balances series "Y"

Typical values for measurement uncertainty calculation

	UYA 2	**MYA 5**	**XA 60/220Y**	**XA 160Y**	**PS 600/Y**
Repeatability	2g: 0,00018mg	5g: 0,0013mg	200g: 0,04mg	100g: 0,04mg	500g: 0,67mg
Repeatability 5%Max	x	x	10g 0,011mg	x	x
Linearity	6,7E-13g	1,7E-11g	1,5E-08g	2,7E-08g	6,0E-06g
Eccentricity	1,0E-07g	7,0E-07g	1,0E-06g	1,0E-06g	7,0E-06g
Sensitivity	1,0E-06g	1,0E-06g	1,0E-06g	1,0E-06g	1,0E-06g
Minimal sample U=0,1%; k=3	0,54mg	4,0mg	34mg	124mg	2012mg
Minimal sample U=1%; k=2	0,04mg	0,3mg	2mg	9mg	134mg

Chart 8. Uncertainty components for balances series "Y"

7. Low mass measurement

Low mass measurement requires defining whether such measurement is correct.

Here, two approaches are applicable:

1. Operator's can set their own criteria
2. An assumption can be made, that weighing analysis is carried out precisely, if weighing result is contained in tolerance 0,1% of weighed standard nominal value.

USP, General Chapter 41 ,,Weights and Balances

In the next step minimal mass should be defined.

Definition:

It is the smallest sample net mass that can be weighed maintaining precise weighing requirements.

If an organization works in accordance with USP requirements, 0,1% tolerance is valid. Suitable instructions are contained in USP General Chapter 41 ,,Weights and Balances:

If it is not specified . . . a substance is weighed correctly (taking random and systematic errors into account),if device measurement uncertainty does not go beyond 0,1% of readout.

The same document also describes measurement uncertainty requirements as:

Measurement uncertainty is satisfactory if 3-times standard deviation of at least 10 repetitions series, divided by series average value does not exceed 0,001.

Some discussions take place at Pharmaceutical Forum PF 36 (2) 2010 concerning introduction of change of the definition consisting in introducing requirement of 2-times standard deviation

$$k=3 \rightarrow k=2$$

If production is based on European Pharmacopoeia requirements, the tolerance level can be different (individual criteria).

7.1. Minimal Mass rule

Minimal mass can be calculated from:

- balance repeatability or
- required analysis precision

$$m_{\min} = \frac{k}{A_{REQ}} \cdot s$$

where: k *– extension factor (k=3; k=2)*

A_{REQ} *– required weighing precision (0,1% lub 1%)*

s *– repeatability,standard deviation of at least10 repetitions*

In practice, minimal mass depends on:

- sensitivity, non-linearity
- eccentricity

In practice, if the requirements below are taken into account:

- measurement uncertainty . . cannot exceed 0,001 [A]
- three standard deviations . . [k]

then, a rule according to which definition of minimal mass can be simplified to the form:

$$m_{\min} = \frac{k}{A_{REQ}} \cdot s = \frac{3}{0{,}1\%} \cdot s = 3000 \cdot s$$

For factor k=3 or

$$m_{\min} = \frac{k}{A_{REQ}} \cdot s = \frac{2}{0{,}1\%} \cdot s = 2000 \cdot s$$

For factor k=2

That is:

Multiply standard deviation value
by constant factor = 2000 for k=2, or 3000 for k=3

The above statement shows clearly, which balance parameter is the most important while minimal mass defining. The parameter is:

REPEATABILITY

7.1.1. Calculation of minimal mass – instance

Using the above relationship, minimal mass value of any balance can be counted. Its repeatability should be defined of read out from product technical data.

Instance:

Calculation of minimal mass in case of balance series **XA 60/220?**

- analysis required precision 0,1%,
- standard deviation is taken from balance catalogue card.

Balance data:

- Max 220g; d=0,01mg/0,1mg; s = 0,025mg; k = 2; A = 0,1%

$$m_{\min} = \frac{k}{A_{REQ}} \cdot s = \frac{2}{0{,}1\%} \cdot 0{,}025mg = 2000 \cdot 0{,}025mg = 50mg$$

Minimal weighing for the balance is 50mg, if analysis is supposed to be performed with precision 0,1%.

7.1.2. Permissible repeatability of a balance in minimal mass

Operator can also try to find a balance for their own analysis.

Then the question occurs:

What should be balance repeatability if 40mg is weighed, and process precision is maintained 0,1%? .

Basic equation should be transformed to the following form:

$$s = \frac{A_{REQ}}{k} \cdot m_{\min}$$

Calculation:

$$s = \frac{0{,}1\%}{2} \cdot 40mg = 0{,}02mg$$

Answer: a balance should be used, which repeatability is lower than 0,02mg. It can be microbalance MYA 5.

	MYA 2	MYA 5	MYA 11	MYA 21	MYA 31
Max capacity	2 g	5 g	11 g	21 g	31 g
Readability	1 µg	1 µg	1 µg	1 µg	1 µg
Repeatability	0,8 µg	2,1 µg			
Linearity	±2 µg	±5 µg	±6 µg	±7 µg	±7 µg
Pancsize	ø 16 mm	ø 26 mm			
Display	5,7" touch panel				
Interface	2×USB, RS 232, Ethernet, 2in / 2out (digital)				

Chart 9. Parameters of microbalance series „Y”

Summary

Two basic criteria for selection of a balance can be considered:

1. Maximal load capacity has to be higher than the maximal gross mass, that is, total of tare load and net load (sample mass).

2. Uncertainty while the smallest sample weighing has to be lower or equal to required analysis precision [A]

Readout does not determine balance precision. It is determined by its repeatability and minimal mass volume that depends on repeatability.

8. Balance routine examination

Routine tests are a means to guarantee proper accuracy of an instrument which is used for analysis , and for minimization of possible error occurrence. The basic aspect of routine examination refers to its intervals:

How often should routine texts be performed?

Routine tests can be performed according to company accepted intervals. Then, it is assumed, that between the tests, a balance operates properly, i.e. its indications are within set acceptance thresholds. In such case, it is helpful to introduce two limits for controlled parameters. The first one is cautionary limit, which exceeding does not affect balance operation.

The other one is a critical limit, which exceeding causes balance recognition as defected if utilized in this specific range. In case of sensitivity control, it is necessary to consider actual balance error for loads below max capacity, like 50% Max. in such case balance error can occur as acceptable. And so, exceeding of limit no. 2 does not always result is separating a balance and recognizing it as out of order.

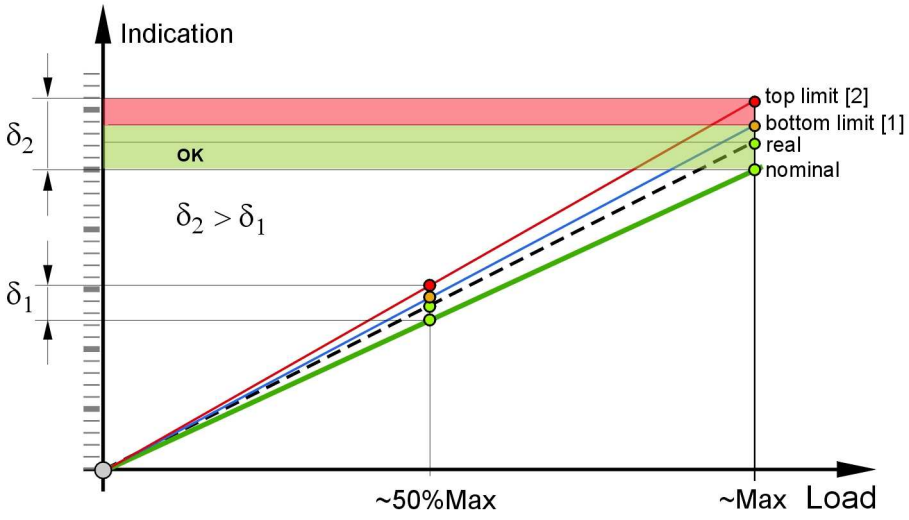


Chart. 13. Sensitivity drift – cautionary limits

Then a question emerges, on the criteria according to which a balance should be checked. Generally, it can be assumed that:

- It depends of expected weighing accuracy
- It depends on parameter which is tested

– It depends on weighing process and its acceptance within specified thresholds

The other approach is testing a balance before each measurement process. It is possible practically only if a balance is not on heavy duty (relatively low quantity of measurements, and a couple of operators). In such case it is necessary to create a specific procedure, according to which a balance will be tested. Test results should be noted down with date , time and operator code. However, application of such procedure may be a problem, as it requires very high exploitation of mass standard, and supervision over this mass standard.

Thus, is it possible to decrease test frequency?

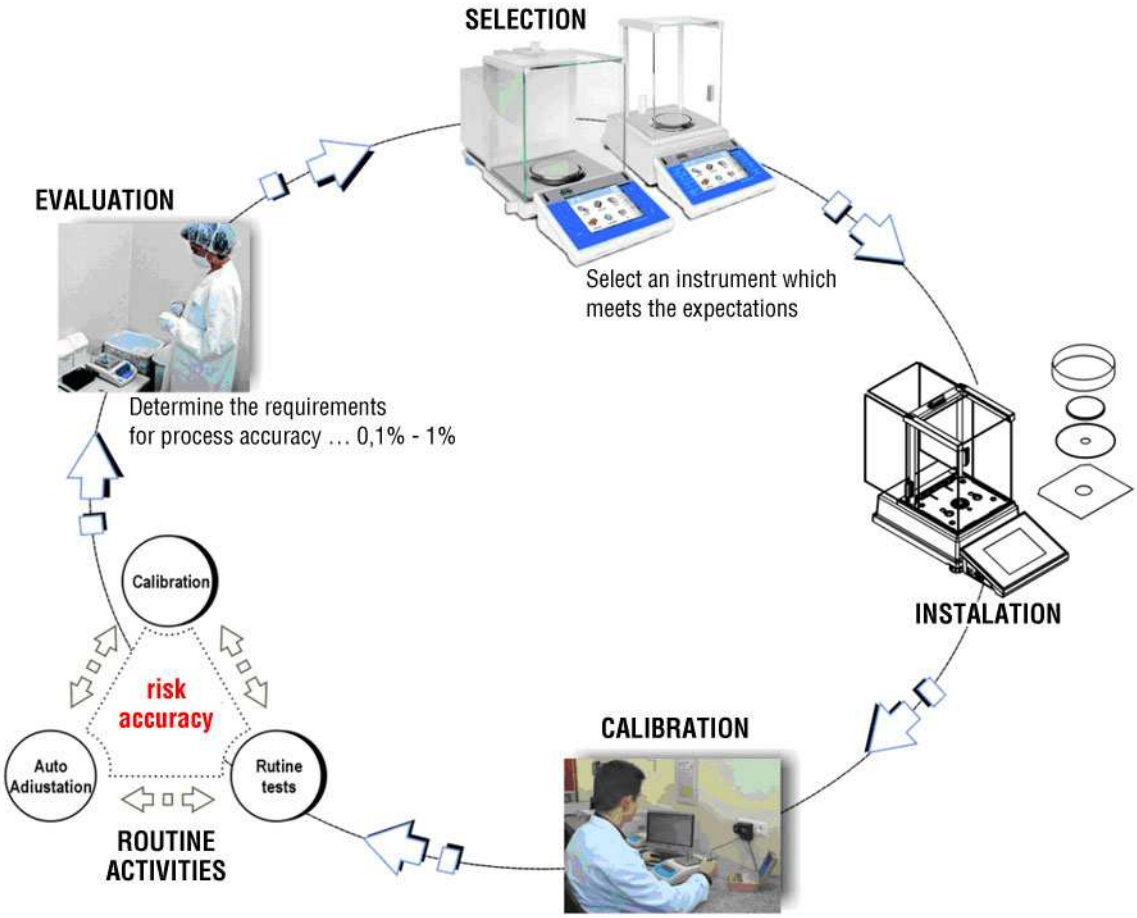
It is recommended to decrease quantity of tests. A balance is a working device, and too frequent tests may disturb its working cycle. It is recommended to observe stability of balance parameters and with regard to their results increase or decrease quantity of tests. Analysis accuracy is the main factor here, and test frequency should be adjusted according to it. Generally, the rule is:

high risk = frequent tests

8.1. Measuring instrument life cycle

Life cycle of a measuring instrument start from evaluation of operator's requirements. At this stage the operator should be familiar with production and control aspects. It is necessary to define one's expectations regarding a balance. Presently, a balance is expected to offer more than just a reliable measuring result, like cooperation with company network, compatibility in sending data to other devices.

The other important aspect is proper selection of a balance, which meets the requirements. Here, the operator should compare balance features with economic aspect, service reaction to defect, adaptation possibilities. Installation of balances with low readabilities is a job for company control department. In case of high precision balances, like microbalances, ultra-microbalances, they should be installed by authorized service of the manufacturer. This way, the parameters of a b lance will be adjusted to company profile and realized processes. This includes filter settings, and stability criteria setting. These activities are also offered and performed by RADWAG personnel as a supervision packet over a balance (technical inspection book).



Calibration of a balance is a inseparable part of life cycle of a measuring instrument. It determines the actual balance errors. Calibration should be connected with determination of minimal mass, if such data is necessary.

Routine activities are all the work that is performed by an operator that aims at decreasing level of risk which occurs in weighing process. Risk decreasing activities also include calibration and adjustment processes.

8.2. Balances and weighing systems qualification process

Qualification process can be described as set of activities which aim at confirmation with rules of Good manufacturing Practice, that procedures, processes, devices, substances, and systems are used in a way which gives expected results. Qualification provides is planned to give a result which:

Provides objective evaluation, that measuring errors do not exceed set criteria. Based on such criteria, a balance is qualified as meeting the requirements. The next step is comparison of requirements with actual measuring possibilities of a balance. On the other hand, qualification

process can give an answer to question whether a balance provides specified functionality, ergonomics, weighing speed and other if valid.

Qualification process is specified in details by Qualification Policy, Documentation and Qualification Process. Basic requirements relating to it are described in Health Ministry Regulation of 1st October 2008 "On requirements of Good Manufacturing Practice" – Dz. U. from 17.10.2008.

One of activities which relates to qualification process is Qualification, which is performed according to below presented schema. Qualifications are usually performed as single or complex and they include:

- **Design Qualification (DQ)**:
  documented testing and approving that design of rooms, devices, installation is suitable for realization of intentional actions.

  In case of balances, it comes to a statement, that a balance in use meets requirements on functionality and measuring reliability.

- **Installation Qualification (IQ)**:
  documented testing and approving that installed or modified devices or installation are compatible with approved design, manufacturer recommendations or user requirements.

  This stage of qualification process is more like formality – the controller is to check whether type of balance that is qualified is the same as stated in documents. Controller is to check documentation, descriptions, parameters, etc.

- **Operational Qualification (OQ)**:
  documented testing and approving that installed or modified devices or installation operate correctly at the whole range of assumed operational conditions.

  At this stage, controlling personnel should check whether balance functional parameters and balance accuracy are within limits specified in **DQ**

- **Process Qualification (activities) (PQ)**:

documented testing and approving that devices and supporting installation, joined into one functional set, can operate effectively and repeatedly, in accordance to approved process performance method and specifications.

This stage is realized for balances that are in cooperation with other devices, and they exchange, collect or process data.

The aim of qualification process is to make sure that obtained product is safe in use, and risk of level in production or control process will not increase.

Common practice in qualification process is to prepare corresponding forms, tests and reports which are confirmed by Quality Control Department. In most cases, such documents are in a company for several years, they were prepared according to Quality Management System and their shape does not change. Such universality may lead to routine tests performance, which results in omitting important aspects of balance control, like processes related to mass control and balance parameters. High importance refers to formal side of the process. Such approach is relatively „strict" and it does not allow to modify the procedures. Thus, there appears new approach, like FDA document "Guidance on General Principles of Process Validation", which provides another approach to qualification process, namely:

It is a process to obtain the quality of a medicine, which should be produced in a way to correspond to a scheduled activity.

This quality is guaranteed by continuous activity in three following cycles: process planning, its qualification and verification based on results, analysis and observations. According to FDA, qualification process is:

Activity taken to demonstrate that systems and equipment are suitable for the intended use and operate properly.

Thus, it is proposed not to perform routine tests, and notes resulting from strict internal procedures, but perform qualification in a form of **confirmative activities**, according to which a balance (device) is proper for its intended use. FDA does not specify qualification procedure, but it requires summary of obtained results. FDA refers to risk management as described in ICH Q9.

Such approach gives relative freedom in performance of qualification process, but is also orders combining of practical knowledge on production process and control with possibilities of balances. This way, personnel knowledge and responsibility should increase.

9. External factors in weighing process

All balance parameters presented in publications are related to typical laboratory conditions, that is the ones which take interfering factors into account. The term includes all factors originating from the ambient area and people who influence measurement result.

It is not possible to define all of them, but the main factors include:

- Oscillations, vibrations
- Breeze of air
- Temperature drifts
- Electrostatics
- Evaporation and absorption phenomena (hygroscopicity)
- Magnetism

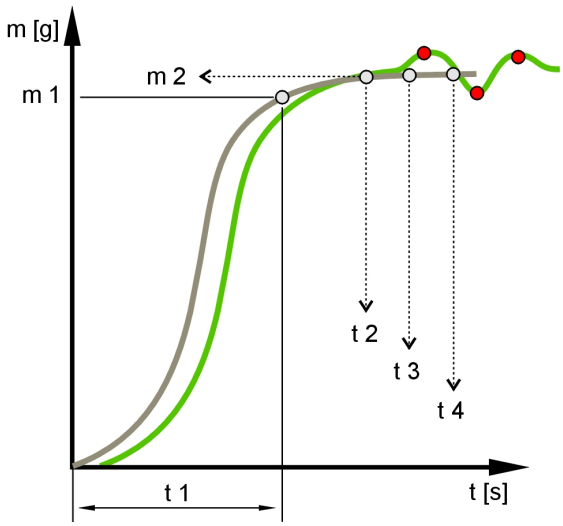
It should be remembered, that the factors influence both balance and the weighed object. When estimating weighing process as a whole, factors should be distinguished and diagnosed, which of them is of decisive significance for analysis correction. The operator should focus on connection:

- Balance – external factor or
- sample – external factor?

9.1. Oscillations - vibrations

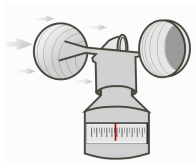
They are transmitted by the ground and walls, and the source that generates them are the devices and objects moving in communication course and the staff. Visible effect is longer measurement time and higher indication dispersion. Vibrations are transmitted to balance mechanical system, so the most successful method of preventing them, is to remove them from weighing process.

Another commonly used way to prevent vibrations is application of anti-vibration table. It is a construction based on a double rubber console, which task is to suppress vibrations. In RADWAG offer, such tables are manufactured in mild steel or stainless construction. Operating desktop is a stone plate.

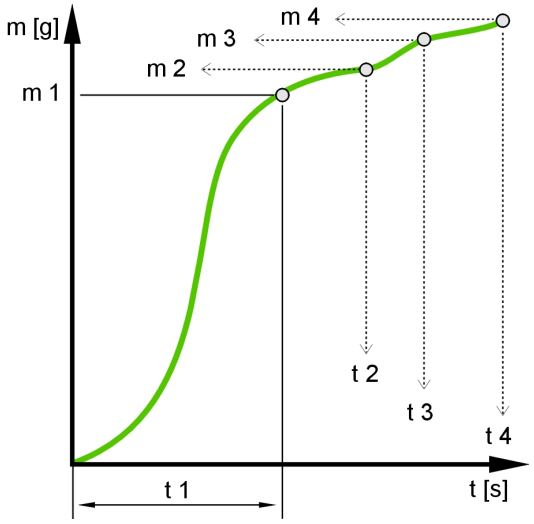


Drawing 15. Balance indication instability - vibrations

9.2. Breeze of air



Visible result of their influence is indication instability and long weighing time. Balance workstation **should not** be located close to doors or windows. Closeness to devices such as air-conditioning, fans, as well as places like communication courses should be avoided.



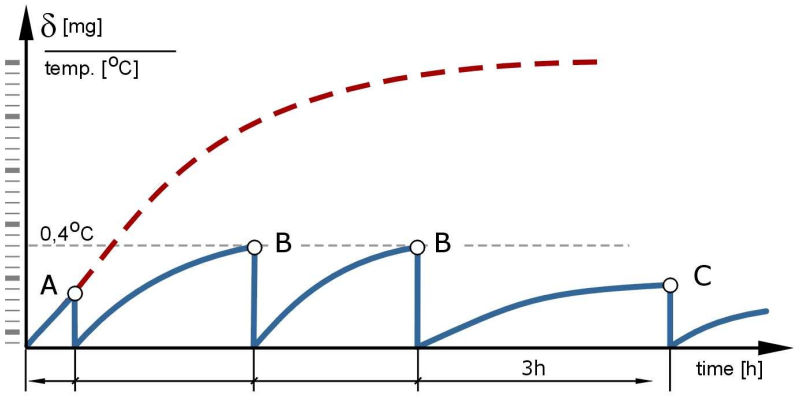
Drawing 16. Balance weighing time –blast air

9.3. Temperature in analysis process

It is one of the most important factors of weighing process. Weighing room temperature should be maintained at constant level. Before analysis start, while performing it and after its finishing, temperature should be stable. The of “Constant level” temperature is a disputable matter. It is defined differently in relation to balances with 1mg elementary unit and still differently for

balances with d=0,01mg. It is accepted that temperature is treated as stable if its changes are not higher than 0,5°C/hour.

For balances equipped with automatic adjustment system, balance precision restoring process is carried out automatically, with consideration of temperature and time changes. Such solution is commonly used in RADWAG balances.



Drawing 17. Self-adjustment system in RADWAG balances

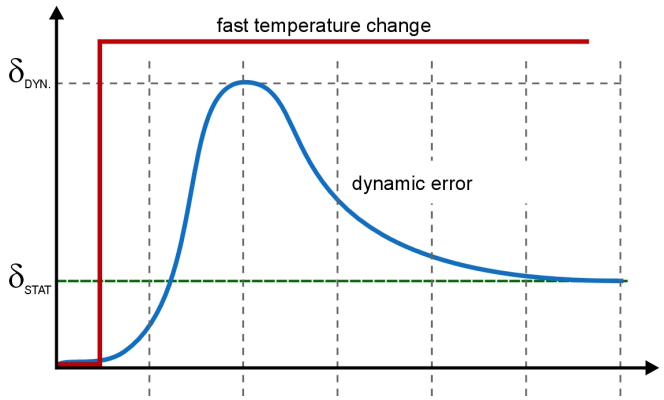
In some cases, even if ambient conditions are fine, a balance does not stabilize, and operator can observe drift of indications. It can be caused by lack of temperature stability of a balance that has been plugged to mains just before the measurement procedure. When assessing influence of temperature on a sample or a weighing vessel, it needs to be stressed, that if a temperature of the sample or weighing vessel is significantly different than ambient temperature, than it may cause air drifts.

The statements above result in practical aspects for weighing process:

- acclimatize the samples before analyzing their mass
- operator should not put their hands into weighing chamber (causes change of weighing chamber temperature)
- pick up the samples with use of tweezers or other holders (if touched with hands, samples change their temperature)

9.3.1. Balance temperature changes

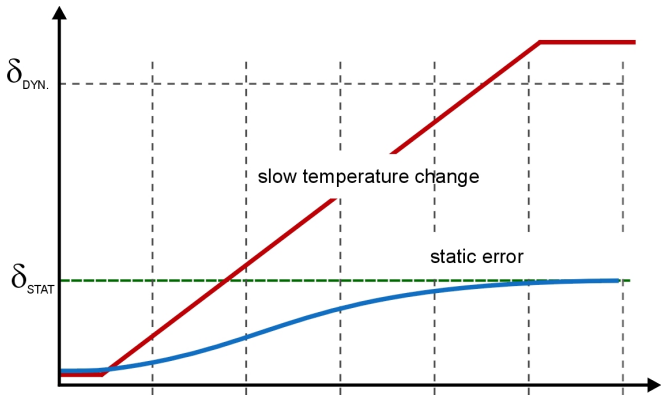
The effect of dynamic temperature changes in a weighing room is dynamic temperature error. In practice, if dynamic temperature error occurs, measuring parameters of a balance, like repeatability and linearity, may get worse.



Drawing 18. Temperature dynamic error

The problem of dynamic temperature error is particularly dangerous for balances equipped with system of external calibration. Such balances are not equipped with system notifying on temperature change.

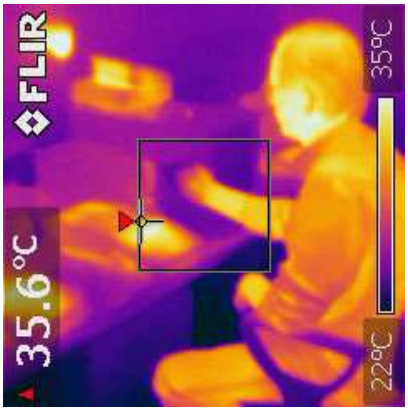
In case of slow temperature changes, a balance will warm together with a weighing room. Such process is not source of errors due to its slow dynamics, and static errors compensating factors.



Drawing 19. Temperature static error

Considering temperature influence on weighing process, balance and ambient area warming up process caused by operator influence should be taken into account. It is assumed, that a man is a source of about 70W power. Bearing in mind this factor, quantity of operators working in the weighing room at the same time cannot be large. Practically, it depends on the room size and air-

conditioning system. Process of balance warming by an operator and temperature distribution in balance area is presented in the picture below



Drawing. 20. Operator temperature influence on balance

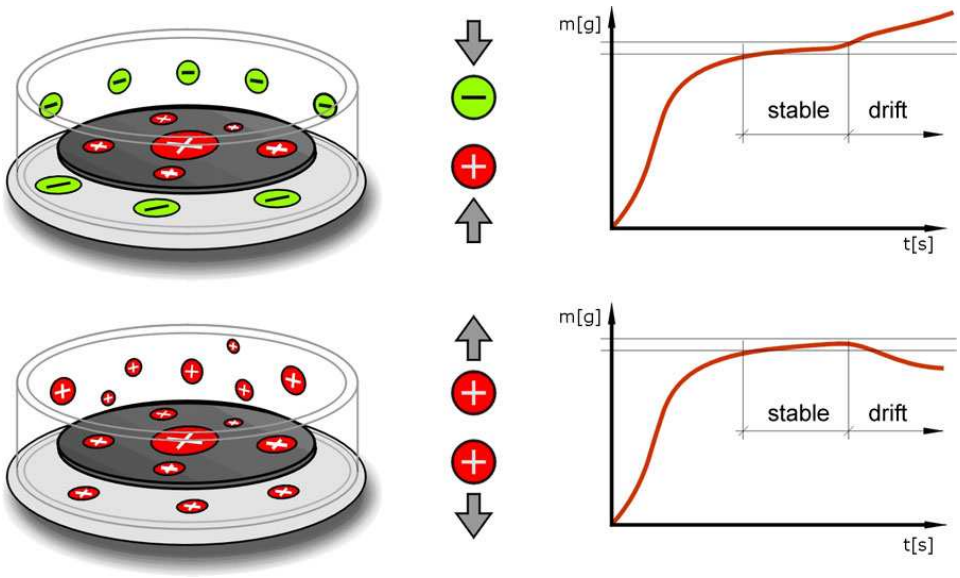
9.4. Electrostatics in weighing process

Evaluation of electrostatics in weighing process is complicated, as an operator has to determine a factor that is not visible. The operator can only observe the effect of electrostatic presence. Electrostatic discharges may occur on:

- compensated ions (positive or negative) are taken over from the air,
- by rubbing two non-conducive substances,
- touching a sample with hand
- low humidity in weighing room

Visible effect of electrostatics presence is:

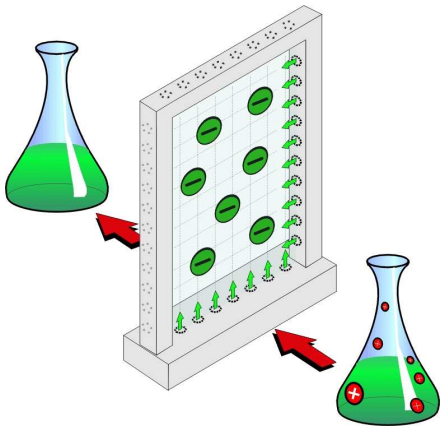
- slow drift of weighing result,
- large dispersion of weighing results in a series of measurements, and
- no return to zero if a load is taken off the weighing pan.



Drawing 21. Balance electrostatics phenomenon

As it is not possible to remove the source of electrostatics, it is common to use factors that eliminate or compensate the influence of undesired electrostatic charges.

One of the methods that partially eliminates the problem is providing proper air humidity in a weighing room. It is recommended to set relative humidity of a weighing room in between 40 % and 60 %. There are, however, cases where setting such humidity is not desired or impossible. If such is the case, than operator should install an ionizer – ionizing frame.



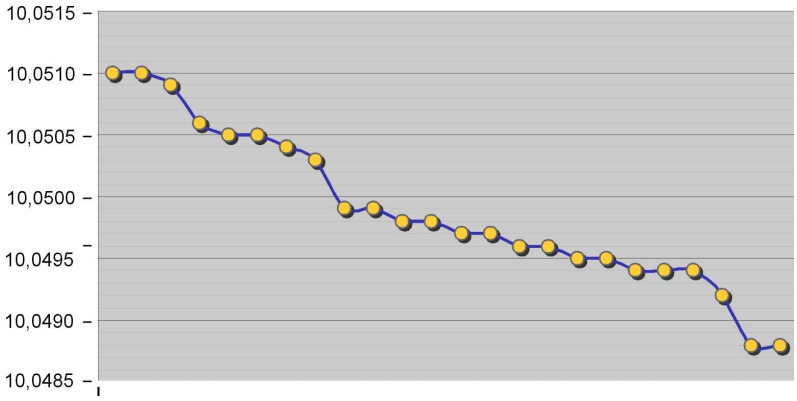
Drawing 22. Ionizing frame operating principle

Ionizing frame is a device that generates ions, so called aero-ions, which charge is opposite to charges that operator wants to eliminate. The means of operation of a ionizing frame is eliminating

charges that are on operator's hand and inside weighing chamber on its opening. If balance conditions, ionizing rate is equal to recombination rate, which maintains constant ionization rate. Additionally, an operator can apply specially designed mats, antistatic foils and selected uniforms.

9.5. Sample structure, hygroscopicity

Weighing result, as obtained during an analysis period is influenced by a series of factors relating to balance and ambient conditions. However, one should also consider sample features during weighing process. Samples that are liquids, can undergo process of evaporation.
In such case, balance indication will be influenced by a drift. Weighing result will continuously decrease. Additionally, it can be concealed by balance filters. In order to prevent such situations, liquid samples should be weighed in weighing vessels, like bulbs with narrow necks or vessels with top cover. If operator is determining evaporation level, not the mass, balance settings should be modified, so that it is possible to perform ordered analysis.



Drawing 23.Mass change- evaporation phenomenon

A factor reverse to evaporation is absorption of moisture from ambient air by a sample. it is very important in case of hygroscopic samples. The effect of moisture absorption is differences in mass determination, each measurement will have higher mass readout than the previous one. For the purpose of proper weighing of such substances, weighing vessel should be clean and dry. The easiest way to eliminate moisture absorption factor is application of hermetic vessels.

9.6. Magnetism as weighing process interfering factor

Most of weighing mechanisms of high resolution balances are constructed on basis of electromagnetic sets which include a force-motor and magnet. In case magnetic loads are measured,

there is a risk, that electromagnetic field of a balance is disturbed or weighed sample is influenced by magnet installed in a balance. The effect is incorrect mass reading of a weighed sample.

A solution for this problem is removal of a weighed sample from electromagnetic field of a balance, i.e. increasing a distance between a sample and balance mechanism. It is possible through so called under-hook weighing with application of special racks or hooks made of aluminum.

RADWAG ELECTRONIC BALANCES
Poland, 26-600 RADOM, 28 Bracka Street
tel.+48 48 38 48 800; tel./fax. +48 48 385 00 10
http://www.radwag.com