No. 70

Measurement Good Practice Guide

Weighing in the Pharmaceutical Industry

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NPL National Physical Laboratory

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Weighing in the Pharmaceutical Industry

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Abstract: This document is intended as a guide to the best practice to be adopted when carrying out weighings in the pharmaceutical industry. It includes a discussion of the current regulations applicable to pharmaceutical weighing, descriptions of the types, performance and validation of balances typically used, and introductions to the different weighing styles that may be used. In conclusion there is a description of several methods of data analysis and uncertainty calculation.

ISSN 1368-6550

June 2004

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Acknowledgements

The authors acknowledge the financial support of the National Measurement System Directorate of the UK Department of Trade and Industry.

Weighing in the Pharmaceutical Industry

Contents

1 Introduction

The pharmaceutical industry has been traditionally divided into three sectors, research and development, primary and secondary operations.

1.1 Research and development

The role of research and development is to:

- Discover new pharmaceutically active compounds
- Develop new dosage forms of existing compounds
- Improve existing manufacturing processes.

The development of new compounds will involve biological and / or chemical processes carried out at laboratory scale of operations and will in many cases involve operations at the mg scale. The new compounds will be screened for pharmaceutical activity and in major facilities this will involve thousands of compounds per year. Any compounds that pass the original screening are then subject to further production in a laboratory or small-scale pilot plant for further testing. The small number of compounds that pass this stage will enter the stages of clinical trials.

For those compounds that pass clinical trials and are approved for use the clinical trials will determine the most appropriate dosage form and dosage level of the compound that is effective for the treatment.

1.2 Primary operations

Primary operations are responsible for the production of the pharmaceutically active compounds. This may involve biological, chemical and in some instances sterilisation processes. Processes may be operated as a continuous or batch size operation. Dependent on the compound being manufactured batch sizes may be over a tonne and involve vessels with a capacity of over 100 000 litres.

1.3 Secondary operations

Secondary operations involve preparation of dosage forms suitable for use by a patient. A dosage form will contain one or more pharmaceutically active compounds together with a number of other ingredients. The most common dosage forms are:

- Tablets
- Capsules
- Injections
- Creams
- Ointments
- Aerosols
- Aqueous nasal sprays
- Syrups.

The dosage form selected for a product will depend on its purpose and the most appropriate means of delivery. Some compounds may be produced in a variety of dosage forms. For asthma treatment the same compound may be supplied to a patient as an aerosol for use in the immediate treatment of an attack and as a tablet to attempt to prevent attacks. Secondary operations are typically physical processes and will normally be carried out as batch processes. The scale of operations will be determined by the forecast sales levels. For tablet manufacture batch sizes of over a million tablets are common and for aerosols and injectable preparations batch sizes may be in excess of 100,000 units.

In the formulation of a dosage form a number of ingredients may be required. These can include:

- One or more pharmaceutically active compounds
- A diluent
- A propellant
- Stabilising agents
- Drying agents
- Binding agents
- Bulking agents.

Examples of how a tablet may be formulated are two common products, Paracetamol and Warfarin.

Paracetamol is a commonly used pain killer and is typically sold as a 500 mg tablet. The 500 mg refers to the nominal weight of active compound that will be present in the tablet. The weight of a Paracetamol tablet will be approximately 525 mg with the additional material being compounds added to assist in the binding of the tablet during the manufacturing process.

Warfarin is an anti-coagulant tablet used to stop blood clotting. Patients will be issued with a range of strengths of tablet that include 0.5 mg, 1 mg, 2 mg and 5 mg tablets. The ‘weight’ again refers to the nominal weight of active compound that will be present. As it is not practical to manufacture or handle a tablet of 1 mg these tablets will also include a bulking agent, an inert compound such as starch, in the formulation.

For a small pharmaceutical company the research and development, primary and secondary manufacturing operations may all be co-located. For a larger company the three operations may be performed on separate sites and for multinational companies may be spread over several countries.

During all of these operations a large number of weighings will be performed using a wide range of balances and scales.

2 Regulatory authorities

All pharmaceutical research and development and manufacture are governed by a number of national and international regulatory bodies. In the United Kingdom the Medicines Control Agency (MCA) are the controlling authority and produce the 'Rules and Guidance for Pharmaceutical Manufacturers and Distributors', known as 'The Orange Guide' [1]. To manufacture a pharmaceutical compound for sale in the United Kingdom the product and manufacturing premises must hold a licence issued by the MCA. As part of the issue of a licence the manufacturer will be subject to inspections by inspectors from the MCA. Once a facility has been licensed periodic inspections will continue to be performed by the MCA, typically on an annual basis although for large sites this may be spilt into several visits per year.

In addition to The Orange Guide the British Pharmacopoeia Commission Secretariat produce the British Pharmacopoeia (BP) [2] which contains monographs detailing how specific testing must be performed and containing specifications for a large number of general tests and generic compounds. European Pharmacopoeia monographs are clearly distinguished and cross-referenced, and a full index gives quick access to current legally binding UK standards. When a manufacturer seeks a licence for a new compound or a branded version of a generic compound they must stipulate the tests to be performed and the limits to be applied to the product. Where these tests or limits are specified in the BP the limits set by the manufacturer must be equal to or better than those specified in the BP.

Similar regulatory authorities exist in all European countries and to sell a product in each country either a separate licence, issued by the national authority, may be held for each country or a European wide licence obtained that will meet the requirements of each of the countries.

Manufacturers in the United Kingdom are also subject to general directives issued by the European Union (EU).

For a product to be sold in the United States licences for the product and the manufacturing facilities must be issued by the Food and Drugs Agency (FDA). The FDA produce the 21 Code of Federal Regulations (21 CFR) [3]. In addition the United States Pharmaceutical Convention produce the United States Pharmacopoeia (USP) [4] which contains monographs detailing testing and specifications. The licences issued by the FDA will involve approval inspections by their inspectors that will be carried using 21CFR and the USP.

Many other countries around the world have their own agencies and regulations, some of which detail additional or modified requirements to those of the European and United States authorities.

In order for a manufacturer to market a product widely around the world they must meet the requirements of all the authorities. In some cases operating to the highest standard of any of the authorities can do this. For some countries it is only possible to meet their requirements by manufacturing batches of a product specifically to their requirements.

3 Regulations

Regulations that govern the use of balances in the pharmaceutical industry include:

- The Non-Automatic Weighing Instruments Directive [5]
- United States Pharmacopoeia Monograph 41
- The Rules and Guidance for Pharmaceutical Manufacturers and Distributors.
- 21 Code of Federal Regulations

3.1 The Non-Automatic Weighing Instruments Directive

In the United Kingdom Weights and Measures Legislation traditionally governed point of sale operations where the goods were sold by weight, e.g. a pound of apples, a hundredweight of coal etc. Within the European Union to facilitate free trade within the member countries a number of directives were issued. Directive 90/384/EEC was issued to harmonise the Weights and Measures Legislation.

Article 1(2)(a) of directive 90/384/EEC defined the applications to be covered by the regulations as:

- Determination of mass for commercial transactions.
- Determination of mass for the calculation of a toll, tariff, tax, bonus, penalty, remuneration, indemnity or similar type of payment.
- Determination of mass for the application of laws or regulations including expert opinions given in court proceedings.
- Determination of mass in the practice of medicine for weighing patients for the purpose of monitoring, diagnosis and medical treatment.
- Determination of mass for making up medicines on prescription in a pharmacy and determination of mass in analyses carried out in medical and pharmaceutical laboratories.
- Determination of price on the basis of mass for the purpose of direct sales to the public and the making up of pre-packages.

The Non-Automatic Weighing Instruments (NAWI) directive was incorporated into United Kingdom legislation as a statutory instrument No. 1907, The Non-automatic Weighing Instruments (EEC Requirements) Regulations 1995. This regulation came into force on the 1St September 1995 but a 10 year derogation order was imposed, to allow industry time to adapt to the changes, so that the regulations would not be enforced until January 2003.

Application 5 of the regulation '*determination of mass in analyses carried out in medical and pharmaceutical laboratories*' had extended Weights and Measures legislation into the pharmaceutical industry. Members of the Western European Legal Metrology Convention (WELMEC) drafted the original NAWI directive. WELMEC issued additional documentation to enhance this directive and defined '*pharmaceutical laboratories are quality control laboratories of manufacturers of medicinal products for human use. Pharmaceutical laboratories do not include the research and development laboratories of manufacturers of these medicinal products*'.

Any electrical equipment sold within the European Union must be Stamped as 'Conformance European' (CE) to indicate that they conform with all the applicable regulations, e.g. low voltage, electro-magnetic and radio frequency interference etc. Balances that were in use in the pharmaceutical industry prior to 1st January 2003 can continue to be used indefinitely. Any balances purchased for use after January 1st 2003 that are for use for any application covered by the regulation must be stamped as metrologically approved (M stamped) in addition to the CE stamp.

For a balance to become metrologically approved it must go through three stages:

- Design approval
- Stage 1 verification
- Stage 2 verification

Design approval involves designing the balance to be within the permitted specifications approved by the regulations and seeking approval from a national authority of the proposed design and manufacturing process.

Stage 1 verification involves ensuring that the balance has been manufactured and tested to the approved design approval.

Stage 2 verification is performed on installation at the premises of the customer. The actions are dependent on the balance model and will be specified by the manufacturer. The minimum action necessary will be to power on the balance and perform a calibration. For some balance models there will be a requirement for the installation and testing to be performed by an engineer trained by the manufacturer.

The NAWI directive incorporates two terms, the actual scale interval (d) and the verification interval (e). The NAWI directive also defines balances into four accuracy classes:

I	Special
II	High
II	Medium
IIII	Ordinary

The specification of these classes are given in Table 1.

Class	Verification scale Interval (e)
I	0.001g <= e
II	0.001g <= e <= 0.05g 0.1g <= e
III	0.1g <= e <= 2g 5g <= e
IIII	5g <= e

Table 1: Specification of balance accuracy classes

For all instruments other than those with auxiliary indicating devices d = e

For instruments with auxiliary indicating devices the following conditions apply:

$e = 1 \times 10^{k}$ g where k is zero or an integer
$d < e <= 10\ d$

except for instruments of class 1 with $d < 10^{-4}$ g where $e = 10^{-3}$ g.

The NAWI directive also specifies the maximum permissible error that is permitted when testing a balance. The maximum permissible error is dependent on the balance accuracy class and the load being applied and is shown in Table 2.

Load				
Class I	Class II	Class III	Class IIII	Maximum permissible error
0<=m<=50,000e 50,000e<m<=200,000e 200,000e<m	0<=m<=5,000e 5,000e<m<=20,000e 20,000e<m<=100,000e	0<=m<=500e 500e<=m<=2,000e 2,000e<m<=10,000e	0<=m<=50e 50e<=m<=200e 200e<m<=1,000e	± 0.5e ± 1.0e ± 1.5e

Table 2: Maximum permissible error for each balance accuracy class

The maximum permissible error shown in the table is that permitted for the original testing during the balance installation. For testing performed after the installation the maximum permitted error is twice that shown in Table 2.

For a balance of Class I, with a resolution of 0.000 1 g and fitted with an auxiliary indicating device that is to be used to accurately weigh a sample of 0.1 g, the maximum permitted error is ±1.0 e i.e. ±0.001 g. For a balance fitted with an auxiliary indicating device the minimum verification interval (e) is 0.001 g so the maximum permissible error remains as ±0.001 g for balances with resolution 0.01 mg, 0.001 mg and 0.000 1 mg. For a M-stamped balance the manufacturer will indicate the verified range on the display by showing the non verified digits with shading, tinting or similar highlights. For results printed from an M-stamped balance the non verified digits will be displayed in brackets of by similar means of highlighting.

If a legal balance is used for point of sale the sale price can only be calculated on the verified digits. e.g. For a balance with a resolution of 0.01 g and verification interval of 0.1 g if a weighing is displayed of 12.34 g the sale must be recorded as 12.3 g. In the pharmaceutical industry weighings are required to a greater accuracy than the minimum permitted verification interval of 0.001 g and so all of the provided scale resolution should be used. For a Class 1 balance fitted with an auxiliary indicating device the user must apply in house limits to the balance that exceed those limits prescribed in Table 2. For balances of Class II, III or IIII the limits applied by the user must equal or exceed those specified in Table 2.

3.2 United States Pharmacopoeia Monograph 41

Monograph 41 of the United States Pharmacopoeia specifies the weight classes that must be used to test balances and also specifies the minimum weight that can be weighed on a balance. This is shown in the following abstract:

'Pharmacopeial tests and assays require balances that vary in capacity, sensitivity, and reproducibility. 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. 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. Unless otherwise specified, for titrimetric limits tests, the weighing shall be performed to provide the number of significant figures in the weight of the analyte that corresponds to the number of significant figures in the concentration of the titrant.'

Table 3 shows 10 replicate weighings for a 10 mg weight performed on a balance with a resolution of 0.01 mg. The variation shown in this table would be typical for most 5 place balances operating at the manufacturer's specification.

Replicate	Result(g)
1	0.01001
2	0.01002
3	0.01003
4	0.01004
5	0.01005
6	0.01001
7	0.01002
8	0.01003
9	0.01004
10	0.01005
Mean	0.01003
sd	1.4907×10^{-5}

Table 3: Results from 10 replicate weighings of a 10 mg weight

For the results in Table 3 the measurement uncertainty (calculated according to Monograph 41) would be calculated as:

$$\frac{3 \times 0.000014907}{0.01000} = 0.00447$$

This value is greater than 0.001 and so this balance would not be suitable for weighing accurately a sample of 10 mg. In table 4 the simulated replicate weighings of a 50 mg weight with the same variance of table 3 is shown:

Replicate	Result(g)
1	0.05001
2	0.05002
3	0.05003
4	0.05004
5	0.05005
6	0.05001
7	0.05002
8	0.05003
9	0.05004
10	0.05005
Mean	0.05003
sd	1.4907×10^{-5}

Table 4: Results from 10 replicate weighings of a 50 mg weight

For the results in Table 4 the measurement uncertainty (calculated according to Monograph 41) would be calculated as:

$$\frac{3 \times 0.000014907}{0.05000} = 0.000894$$

This value is less than 0.001 and so this balance would be suitable for weighing accurately a sample of 50 mg.

3.3 Rules and guidance for pharmaceutical manufacturers and distributors

There are many direct and indirect references to balances and weighing operations in the 2002 Rules and Guidance for Pharmaceutical Manufacturers and Distributors, the 'Orange Guide'.

All of the references come from Part 1 of the Orange Guide, that part governing manufacture. In many of the quoted references the word 'should' is used. In these and the other parts of the guide those organisations wanting to achieve best practice must read the word 'should' as 'must'. In any circumstances, it is difficult to envisage a situation where the decision not to calibrate a balance, not to keep records etc could be defended to an inspector.

Chapter 4 covers EU guidance on manufacture and in sub chapter 3, Premises and Equipment, there are 3 key references:

3.13 Weighing of starting materials usually should be carried out in a separate weighing room designed for that purpose.

In chapter 10.1, the use of balances in a dispensary is discussed.

3.40 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.

3.41 Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

Chapter 10 covers balances used in production and laboratory weighing processes. In an area where there is a requirement to weigh up to 50 g to a resolution of 0.000 1 g and up to 200 g to a resolution of 0.001 g it may be decided that a single balance to weigh 200 g to 0.000 1 g resolution is a more cost-effective solution. In many cases balance manufacturers' offer dual range balances that could also meet the combined requirement with a single balance.

Sub chapter 6, Quality Control, has two generic sections that are very applicable to weighing procedures in the sections on Good Quality Control Laboratory Practice.

6. 15 Analytical methods should be validated. All testing operations described in the marketing authorisation should be carried out according to the approved methods.

6.16 The results obtained should be critically checked to make sure that they are consistent with each other. Any calculations should be critically examined.

Analytical methods may simply involve a weighing operation, e.g. a uniformity of weight test (Chapter 10.2), or the weighing operation may be a step in a multi stage process. An analytical method may be performed in a Quality Control laboratory or may be performed as part of an in-process control check in a production area. Many examples of analytical equipment, including electronic balances, exist in which calculations are being performed. As part of 6.16 it is essential that any calculation algorithm used in the equipment or associated computer software, be understood. If the software or equipment supplier cannot supply adequate validation of the testing of this algorithm then the user must perform this validation as part of the instrument qualification process.

Annex 10, Manufacture of Pressurised Metered Dose Aerosol Preparations for Inhalation, contains the following reference:

8 When a two shot filling process is used, it is necessary to ensure that both shots are of the correct weight in order to achieve the correct composition. For this purpose 100 % weight checking at each stage is often desirable.

Many pressurised metered dose aerosol preparations, e.g. those used for asthma treatment, may include a suspension of a pharmaceutically active ingredient in a propellant mixture. For ease of manufacture it may be decided to use one filling head to add the active ingredient and a second filling head to add the propellant to the aerosol. This situation is described in section 8 of Annex 10 where a 100 % check weighing following each of the filling operations is recommended. If it is not possible to perform 100 % check weighing at the two stages and a statistical sampling strategy is to be used then it is vital that the reliable performance of the two filling heads has been demonstrated by validation.

Annex 15 describes the principles of Qualification and Validation.

Annex 18, Good Manufacturing Practice for Active Pharmaceutical Ingredients contains the following references:

Under Process Equipment, Calibration:

5.30 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or API's should be calibrated according to written procedures and an established schedule.

5.31 Equipment calibrations should be performed using standards traceable to certified standards, if existing.

5.34 Instruments that do not meet calibration criteria should not be used.

5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API's manufactured using this equipment since the last successful calibration.

Chapter 9 describes the calibration and testing of a balance and discusses the weights that should be used for the calibration and performance testing. Chapter 9 also describes the minimum frequency at which performance testing of a balance must be performed. Section 5.35 states that if a balance fails a performance check then all measurements performed since the last successful calibration check must be assessed. This is a critical factor and is discussed in the following example.

A decision was made on commercial grounds to perform a repeatability test consistent with good practice at the maximum frequency of one week. This would have to be judged against the cost to the organisation if the following performance check showed the balance was out of calibration. There would then be a cost of assessing all the results performed on that balance during the week that the balance was potentially out of specification and the cost of repeating any testing that was considered to be invalid.

Under Process Equipment, Computerised Systems:

5.40 GMP related computerised systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerised application.

A modern electronic balance operating stand alone or with an associated printer may be considered to be a computerised system and appropriate validation of the system must be performed. At the minimum this must include calibration and performance checks and validation of features, including calculation algorithms, that are used.

Under Documentation and Records, Laboratory Control Records:

6.61 Complete records should also be maintained for:

- *any modifications to an existing analytical method.*

- *periodic calibration of laboratory instruments, apparatus, gauges and recording devices.*
- *all stability testing performed on API's and*
- *out-of-specification (OOS) investigations.*

Records of calibrations must be maintained. For balances that contain an automatic internal calibration facility, wherever possible a printer should be connected to the balance to record the automatic calibrations.

Under Validation, Validation Policy

12.10 The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerised systems, and persons responsible for design, review, approval and documentation of each validation phase, should be documented.

Under Validation, Validation of Analytical Methods

12.80 Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognised standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.

12.82 Appropriate qualification of analytical equipment should be considered before validation of analytical methods.

An analytical method involving a weighing operation cannot be validated unless the balance to be used has previously undergone a successful validation and the balance performance checks have all been successfully completed within their specified intervals.

In the Glossary of terms a computer system is defined as:

A group of hardware components and associated software designed and assembled to perform a specific function or group of functions.

A computerised system is defined as:

A system including the input of data, electronic processing and the output of information to be used for reporting or automatic control.

A process or operation integrated with a computer system.

3.4 21 Code of Federal Regulations

Electronic Records and Electronic Signatures

Part 11 of 21 Code of Federal Regulations (21 CFR part 11) details the regulations governing the use of Electronic Records and Electronic Signatures.

21 CFR part 11 defines an electronic record as any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

Section 10 of 21 CFR part 11 specifies that 'Procedures and controls must be designed to ensure the authenticity, integrity, and when appropriate, the confidentiality of electronic records'. Section 10 also requires the 'Use of secure, computer-generated, time stamped audit trails to independently record the date and time of operator entries and actions that create, modify or delete electronic records. Record changes shall not obscure previously recorded information'.

If a balance is used as part of a computer system in which the weighing data is stored and is available for reprocessing then for products manufactured for the United States 21 CFR part 11 must be followed to control the software and the electronic records. These regulations should also be followed when weighing data are stored in spreadsheet programs, e.g. Microsoft Excel©, and several companies provide software packages to allow the 21 CFR part 11 requirements to be met when using Excel©.

21CFR part 11 is not part of the Guide to Pharmaceutical manufacturing in the United Kingdom. However it is necessary to meet the general European Directives on record keeping which includes electronic records. Any weighing data stored by computer programs or spreadsheet applications should meet the requirements of 21CFR part 11.

Many electronic balances and scales contain extensive configurable parameters to allow the balance to be optimised for its task and operating environment. This configuration is not an electronic record but should be treated as electronic raw data. The configuration used during the installation validation of the balance must be recorded and any changes to this configuration and the reason for these changes should be documented. Whenever the balance manufacturer provides features to secure the configurable parameters these must be used to prevent accidental changes to the configuration. This may involve a mechanical feature such as a jumper switch, that can be covered with a tamper evident label, or a software lock requiring the use of a password.

3.5 Measurement Instruments Directive

As part of the continuing directives of the European Union aimed at the harmonisation of regulations, the Measurement Instruments Directive (MID) is about to be approved at the time of writing this section. The MID will cover a wide range of measurement instruments including automatic weighing instruments.

When published the MID will include sections on the manufacture use and testing of these instruments.

The UK regulations to incorporate the MID will then be issued and it is anticipated that the MID will subsequently be incorporated into UK law. When previous directives have been incorporated into UK law existing installations have been

exempted from the new requirements. Any installation of automated weighing instruments effective after the date stated within the UK regulations will however be required to meet the new regulations.

4 Weighing cells

Weighing cells used in the Pharmaceutical industry can be categorised as:

- Load cells
- Electro motive force (EMF) cells
- Others

4.1 Load cells

A load cell operates by adding the sample to be measured to the end of an arm. The bending force is measured by the use of a strain gauge that is then converted into a weight. Load cells have very high capacities, have a very high operating speed but relatively low resolutions.

4.2 Electro motive force (EMF) cells

These are the most common cells used in weighing instruments in the pharmaceutical industry. The sample to be weighed is placed on a platform and a series of levers causes a displacement of a reference point in the weighing cell, which is mounted within an electromagnet. Current is applied to the electromagnet to return the reference point to its initial null position. The current applied is converted into the weight. EMF cells have a relatively low capacity, relatively slow operating speeds but a very high resolution. Modern EMF cells may have a resolution of over 3,000,000 parts which would allow a 0.000 1 g resolution over a 300 g range.

4.3 Others

Some manufacturers have produced a number of other weighing cells, e.g. the vibrating wire. These cells have similar properties to a load cell and are not widely used within the pharmaceutical industry.

5 Types of balance

The pharmaceutical industry use a wide range of weighing instruments. These can be categorised as:

- Load cells
- Platform scales
- Precision balances
- Analytical balances
- Semi-micro balances
- Micro balances.

All of these categories other than the load cells will normally use an Electro motive force weighing cell.

5.1 Load cells

A load cell will have a capacity of 10 kg to several tonnes and will normally have a resolution of 0.1 kg or greater. In manufacturing operations production vessels may be mounted on load cells to control the quantity of materials added during the creation of a batch.

5.2 Platform scales

Platform scales could have a capacity of up to 1 000 kg or more, and will have a resolution of 0.1 g or greater. These are widely used in the pharmaceutical industry to measure the quantity of material to be added to a batch or to weigh the quantity of product manufactured. Some platform scales will be operated with software functions, e.g. piece counting, where the weight of product can be displayed as the number of units, e.g. tablets produced.

5.3 Precision balances

Precision, or top pan, balances will have a capacity up to 20 kg and a resolution of 0.001 g or greater. They are very widely used in the pharmaceutical industry throughout laboratory and production operations. They will be used in the laboratory for general weighing operations, e.g. to weigh materials during the preparation of reagents. In production areas they can be used to weigh small quantities of material for addition to a batch or for checkweighing operations as part of the quality control of the process.

5.4 Analytical balances

Analytical balances will have a capacity up to 500 g and a resolution of 0.1 mg or 0.01 mg. These balances will have an enclosed draft shield to create a weighing chamber. Analytical balances are used mainly in laboratory areas for the weighing of samples during the performance of an assay although they may also be used as an alternative to a precision balance in production areas where small quantities are to be weighed.

5.5 Semi-micro balances

Semi-micro balances will have a capacity up to 30 g and a resolution of 0.001 mg or 0.002 mg. These balances will normally be an extension of a manufacturer’s range of analytical balances and will be used for laboratory weighings where a more accurate weighing is required than is possible on the analytical balance but where a full microbalance is not justified.

5.6 Microbalances

Microbalances will normally have a capacity of less than 1 g and a resolution of at least 0.000 1 mg. They will be used in laboratory areas where very accurate weighings are required.

Before any balance is used for a manufacturing or testing stage the balance must be validated.

6 Location of a balance

The weighing bench on which the balance is to be mounted must be designed so that it will minimise the transmission of vibrations and that sagging cannot occur when weighing operations are being performed. The bench should be earthed, to prevent any build up of an electrostatic charge, and must be made of a non magnetic material. The optimum is a polished granite bench that is floor mounted, independent of the surrounding working area. Wooden or stainless steel benching may be used, although stainless steel is not an ideal surface for weighing benches due to the slight magnetic properties exhibited by all but the highest grades.

The room in which the balance is installed must be temperature and humidity controlled. For a balance with a resolution of 0.1 mg a change of 1 °C in the environment temperature will result in a 0.1 mg change in the reading of a 100 g weight.

The balance should be sited so that it is clear of air conditioning units and fans, including cooling fans from electrical equipment, e.g. a computer. It should also be sited so that direct sunlight cannot fall on the balance as this could generate localised temperature fluctuation in the weighing chamber.

In some installations, particularly in a production environment, it is not possible to site the balance in an ideal location, e.g. the balance may need to be sited near equipment that generates vibration or may be mounted in an extraction cabinet where drafts will affect the balance, although it may be possible for the manufacturer to set balance filter levels to minimize these effects.

In all situations the balance performance must be assessed to demonstrate that it will be adequate for the task that the balance is performing.

7 Calibration weights

Calibration and performance checks of a balance may be performed using internal or external calibration weights. Note: for a metrologically approved balance the calibration adjustment may only be performed by use of the internal weights.

7.1 Internal weights

In many electronic balances the manufacturers will install one or more internal calibration weights. These weights will be designed by the manufacturer to enable

automatic loading and unloading of the weights and will typically be of a dumbbell shape. The manufacturer will accurately know the mass of the weight(s) and these values will be stored within the balance memory. The design and tolerances of these weights are not to any of the Organisation of International Legal Metrology (OIML) specifications [6]. These weights can be used to perform the calibration adjustment when:

- Selected by the user.
- A temperature change specified by the manufacturer, e.g. 1 °C occurs.
- A time period specified by the manufacturer, e.g. 4 hours has elapsed.

The internal calibration will:

- Adjust the zero point of the balance.
- Adjust the maximum load of the balance
- If two weights are used adjust the mid point of the balance linearity.

Performance checks can also be performed using the internal calibration weights. The user can select to add the internal calibration weight(s). The balance display will vary between manufacturers and between models of the same manufacturer. The display will show either:

- The true mass of the calibration weight(s).
- A corrected value of the calibration weight(s) based on their nominal value.
- The difference between the measured and recorded mass of the calibration weight(s).

Some balance models will allow the reproducibility test to be performed by repeated addition of the internal calibration weight(s). For some of these balances the manufacturer may provide an algorithm to allow the minimum weight calculation of United States Pharmacopoeia monograph 41 (USP41) to be performed.

For balances that are calibrated using the internal calibration weights if any performance checks are performed using the internal calibration weights then these tests must be supplemented by testing using external weights of an appropriate OIML specification.

For balances that contain an algorithm to calculate the minimum weight requirement the standard deviation will be calculated by repeated addition of a weight typically of 100% of the nominal capacity of the balance. This testing must be repeated manually at least during the initial installation of the balance using a weight appropriate to the minimum weight of the balance, e.g. 50 mg for a 0.01 mg resolution balance.

7.2 External weights

The OIML specify a number of classes of weights to be used for the calibration adjustment / performance checking of balances. The specifications define the material of construction, the shape and the permitted tolerances for each class. Several of the weight classes are provided with means of adjusting the weights during re-certification.

For weight sets such as F1, where the weights are manufactured from austentitic (non magnetic) stainless steel, the weights are manufactured with a hollow centre which can be accessed via a screw cap. Small stainless steel ball bearings can be added or removed from the hollow to return the weight to tolerance.

Iron weight sets of 100 g and above will typically have a hollow drilled into the base of the weight and lead can be added or removed from this to return the weight to tolerance.

7.3 Calibration of external weights

All weight sets must be re-calibrated regularly: every two years for class E2 weights and annually for class F1 and lower weights. The end user should monitor the drift between calibrations and set a process specification for each weight (which may vary for weights of the same class and size depending on the use, drift rate etc.). The re-calibration must be performed by a laboratory with accreditation to the United Kingdom Accreditation Service (UKAS) and working to the standards of ISO 17025.

7.4 Check weights

Some areas of production may require the use of weights to check the performance of balances but which would preclude the use of calibrated weight sets, e.g. the balance may be used for check weighing in the clean room of a sterile manufacturing facility. In a clean room facility all materials have to be sterilised prior to entry and the sterilisation process would invalidate a calibration certificate. In these circumstances a lower standard of check weights may be used to perform the balance tests and appropriate procedures for assigning values and tolerances for these weights must be developed. When they need to be sterilised solid one piece weights are recommended as they will not be significantly affected by the sterilisation process. If possible they should have an identification number marked on each weight so they can be easily identified in use (and not mixed up).

7.5 Storage and handling of weights

All weights must be stored in a lined container, which must be kept very clean, to prevent contamination of the weights. They may also be stored under glass.

All weights must be handled using a lint free cloth or pair of gloves (one of the better types being washed chamois leather wicket keeper's inner gloves) or by tweezers with a non metallic end. Most weight manufacturers also provide weight forks, better for lifting larger weights.

For further information refer to the Good Practice Guide, "Cleaning, Handling and Storage of Weights" [7].

8 Validation of a balance

8.1 User requirements specification

The initial step of the validation is to create a User Requirements Specification (URS) for the balance. This must always be recorded, either as a proforma or as a written document, as it will form the basis of the testing to be performed for the remainder of the validation exercise. Note: If the new balance is an additional unit of an existing balance to be used for the same purpose then the URS for the existing balance may be used.

The URS must specify the minimum and maximum weighing capacity, the resolution of the balance and if a metrologically approved model of the balance is required. If a dual range balance is to be purchased then capacities and resolution of both ranges must be specified.

The URS may also contain details specific to the use of the balance. This could include:

- any special features required by the balance, e.g. is the balance to be used for piece counting or animal weighing.
- the shape and area of the weighing pan.
- the area and height of the weighing chamber, e.g. are containers to be weighed on the balance.
- the power supply required, e.g. 115v, 240v or battery powered.

When the URS has been completed the requirement may be discussed with a representative of a balance supplier or a review made of manufacturer's literature or websites.

8.2 Design qualification

The Design Qualification (DQ) should be performed before an order for the balance is placed. The DQ exercise will compare the features specified in the URS against the actual values for the balance that it is proposed to purchase. At this point the actual values may be better than the required values, e.g. the balance may have a maximum capacity of 250 g against a requirement of 150 g, or may fail to meet the requirements, e.g. an actual capacity of 250 g against a requirement of 300 g.

If the DQ exercise shows that one or more of the requirements will not be met by the proposed balance then an alternative balance should be selected or a review of the URS performed to see if procedures can be revised to allow the selected balance to be used.

If the DQ exercise has required a change to the URS then this must be documented either in the DQ report or by revising the URS.

8.3 Configuration

Many electronic balances contain a number of user selectable values to allow the user to configure the balance to its operating environment and its required tasks. These may include:

- calibration type
- vibration adapters
- stability detectors
- weight units
- scale resolution
- draft shield control
- interface configuration
- special functions, e.g. piece counting

Before the commencement of the Installation Qualification the balance must be configured to its required settings and these must either be printed or manually recorded, as appropriate to the balance capability, and stored. If a manual or electronic facility is provided to lock the balance configuration this must be applied at this point to prevent any accidental configuration change from occurring.

If there is a requirement to change the balance configuration, e.g. as a result of a change in the operating environment, following the performance of the installation / operational / performance qualifications then the change to the configuration and the reason for the change must be documented and stored. In addition a review of the installation / operational / performance qualifications must be performed and an assessment made and the outcome documented for the need to repeat any of the validation testing. Care must be taken to ensure the settings of the balance are not changed by external service engineers without the knowledge of the end user.

8.4 Installation qualification

The Installation Qualification (IQ) will be performed shortly after the delivery of the balance to the customer and must be performed in the balance's normal operating environment. The IQ exercise must include a check:

- that the correct model of balance has been delivered
- any ancillary equipment has been delivered
- on powering up the balance that no errors are reported
- that the balance calibration has been performed
- that the balance performance checks have been successfully performed

A metrologically approved balance requires Stage 2 verification to be performed on delivery of the balance. The balance manufacturer will specify the Stage 2 verification requirements and these must be performed as part of the IQ exercise. Depending on the balance model the stage 2 verification may simply require the customer to perform the internal calibration of the balance or may require a visit by an engineer to perform the installation.

Dependent on the procedures of the user the balance calibration and performance checks may be carried out by appropriately trained staff of the user, the manufacturer or from a service provider.

8.5 Operational qualification

The operational qualification (OQ) must contain tests so that each of the specified elements in the URS that have not been performed as part of the IQ exercise has been tested. Depending on the URS and the balance model these tests may include testing of the:

- tare facility
- maximum capacity of the balance
- autocalibration feature
- operation of ancillary equipment, e.g. printer
- specialist functions such as piece counting.

During the operational qualification stage the following steps must also be performed:

- preparation of standard operating procedures for the balance
- training of staff in the use of the balance
- preparation of maintenance routines for the balance

8.6 Performance qualification

Senior members of staff or staff who have specialist skills in validation may perform the installation and Operational Qualification testing. Staff who will use the balance in routine use must perform the Performance Qualification (PQ). This is to demonstrate that the operating procedures developed for the balance and the training of the staff has been satisfactory.

If a balance is being installed as a direct replacement of a previous balance that is still operational then the PQ must include tests showing comparability in the results from the two balances.

The PQ must also include a review of the performance of the balance by the line management after a specified time period, e.g. a month, to show that the balance has fully met its user requirements when operating under normal conditions.

9 Performance checks

Performance or calibration checks are performed to ensure that the balance continues to operate within acceptable limits. Performance checks must be performed with appropriate weights of known value that are traceable to national and thus international standards. In the United Kingdom traceability is normally provided through the national standard, K18, held at the National Physical Laboratory in Teddington and thence to the International Kilogram held at the Bureau International des Poids et Mesures in Sevres, Paris.

The routine performance checks that must be carried out periodically on all balances and scales are:

- reproducibility
- linearity
- hysteresis
- eccentricity

9.1 Exercising a weighing cell

Before commencing any performance checks of a balance the weighing cell must be 'exercised' to allow the temperature of the weighing cell to reach equilibrium.

A balance brush must be used to gently apply pressure to the balance pan until a load of approximately 50% of the maximum capacity of the balance has been applied. The applied load must then be removed from the balance and the test immediately performed.

9.2 Reproducibility

The reproducibility test is performed as follows:

1. Tare the balance.
2. Add a check mass to the balance and record the weight.
3. Remove the weight from the balance
4. Repeat steps 1 to 3 until at least 10 weighings of the same check mass have been performed.
5. Using an appropriate statistical package calculate the mean and standard deviations of the replicate weighings.
6. Repeat steps 1 to 5 until all the specified check masses have been weighed.

The reproducibility test should be performed at the normal capacity of the balance/range as well as at a test point which represents the bulk of the weighings being undertaken with the balance. Additionally, for a dual or poly range balance the reproducibility test must be performed at both fine and coarse scale resolutions.

Reproducibility tests must be performed at a minimum of weekly intervals.

9.3 Linearity

Linearity tests should ideally be of at least ten points spread over the operating weighing range (e.g. at 20 g intervals on a 200 g balance) although a minimum of three points can be used. For an electro motive force balance with two internal calibration weights at 50% and 100% of full capacity, the linearity is known to show the maximum deviation from the theoretical line at approximately 25% and 75% of load as illustrated in Figure 1.

Where there is one internal calibration weight, at 100% of full capacity, the maximum deviation from the theoretical line will occur at approximately 50% of full capacity, as shown in Figure 2.

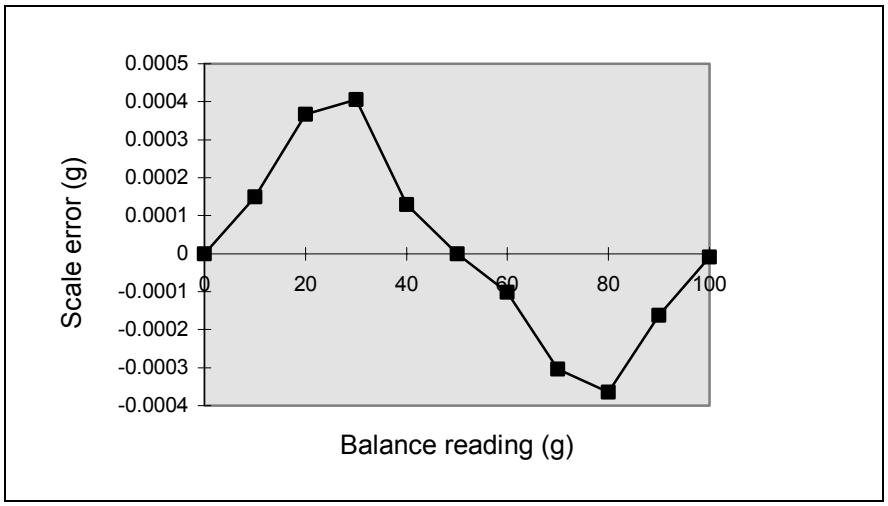


Figure 1 *Linearity of an electro motive force weighing cell with two-point calibration*

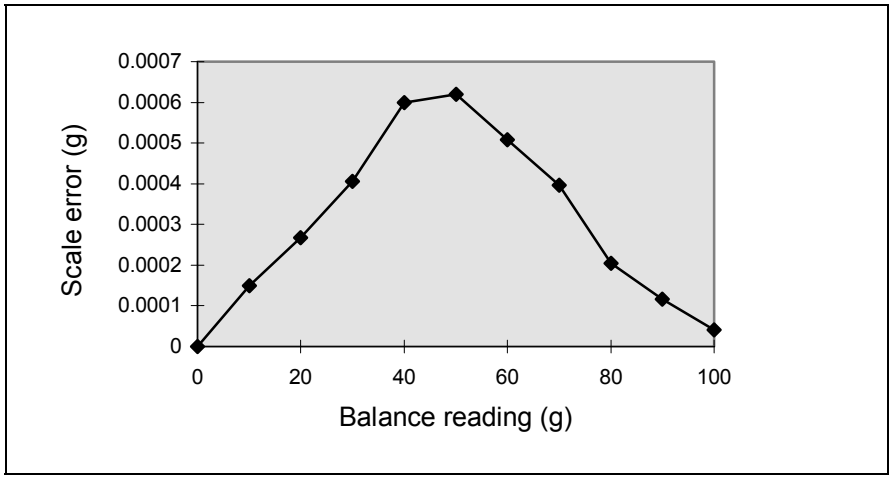


Figure 2 *Linearity of an electro motive force weighing cell with one-point calibration*

Thus, on a balance with two internal calibration weights, three suitable points for performing the linearity check are 0, 25 and 75% of full load. Many balances allow a capacity slightly greater than the nominal maximum load, e.g. a balance that has a nominal capacity of 200 g may have a true capacity of 205 g. When selecting the test points for a linearity test the values chosen should minimise the number of masses to be used. In the example quoted test points of 50 g and 150 g should be selected to allow a 50 g mass and a combination of a 50 g and 100 g mass to be used.

Linearity tests must be performed at a maximum interval of 1 week.

For a balance that contains two or more internal calibration weights that are used during the automatic calibration to adjust the linearity this can be reduced to six monthly intervals.

If a balance is only to be used over a limited range (e.g. up to 100 g on a 200 g balance) it is only necessary to test its linearity over the range used. A label affixed to the balance permanently and visibly should indicate the restricted tested range.

For a dual or poly range balance the reproducibility test must be performed on fine scale resolutions and may be performed on the coarse scale.

9.4 Hysteresis

Hysteresis is the error caused by approaching the same weight from above and below the value. Hysteresis should be tested at a minimum of three points covering the range of the balance, e.g. 0, 50 and 100% of load. As with linearity test points should be selected to allow the minimum masses to be used. Using the balance example shown in linearity tests points of 0 g, 100 g and 200 g should be chosen.

1. Tare the balance so that it reads zero.
2. Add a 100 g mass and record the weight.
3. Add a second 100 g mass and record the weight.
4. Remove the second 100 g mass and record the weight.
5. Any difference in the weights in steps 2 and 4 is a hysteresis error.
6. Remove the first 100 g mass and record the weight.
7. Any difference from zero is a hysteresis error.

Hysteresis testing must be performed at a maximum interval of 6 months.

9.5 Eccentricity

Eccentricity can be induced if a sample weighing is performed when the sample is measured when it has not been physically centred on the balance pan.

For a dual or poly range balance the eccentricity test must be performed on coarse scale resolution.

The eccentricity test should be performed at approximately 50% of the balance capacity. In the example as used in the linearity section a mass of 100 g would be used for the test. The mass is placed in the centre of the balance pan, C, and the balance tared so that it displays zero weight. The weight is then moved to test points A, B, D and E as shown in Figure 2, in turn and the deviation from zero recorded.

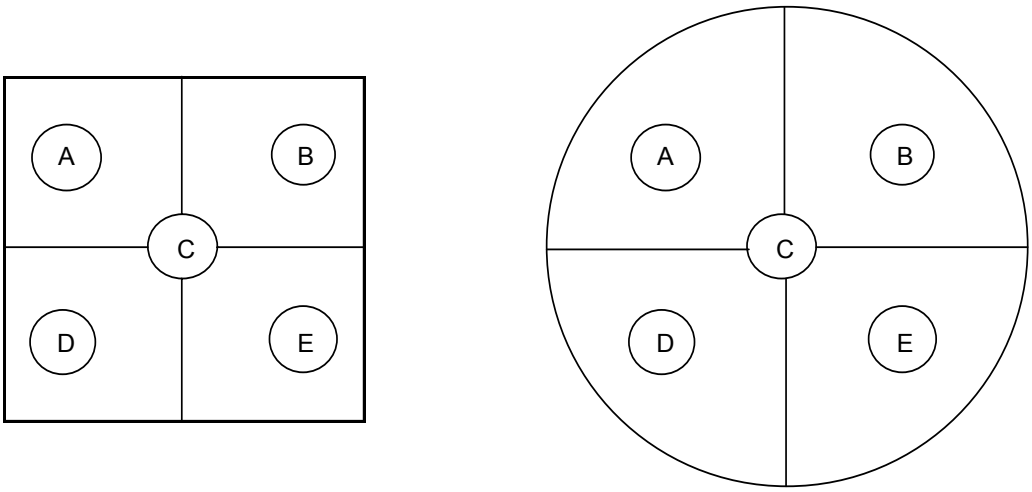


Figure 2: *Eccentricity test positions on square and round balance pan*

10 Production weighing styles

Production Weighing styles can be divided into three categories:

- dispensary operations
- check weighing
- reconciliation

10.1 Dispensary operations

Dispensary operations are performed either directly into a vessel mounted on a load cell where typically the vessel is tared, the required quantity of ingredient 1 is added, the vessel tared, the required quantity of ingredient 2 added and the cycle repeated until all of the ingredients have been added. This technique is appropriate where the accuracy of all the weighings is appropriate to the load cell.

In secondary operations the quantity of the ingredients of a batch can vary largely. In the preparation of a batch of an ointment the requirements may be to weigh:

- 100 kg of the base (typically paraffin wax)
- 1 kg of a stabilising agent
- 0.1 kg of the active ingredient

In this situation a scale capable of weighing 100 kg would not have a scale resolution capable of measuring the active ingredient at the required accuracy. Similarly a balance with the scale resolution to accurately measure the active ingredient would require many repeated weighing operations to weigh the quantity of base required, a time consuming process that would also introduce inaccuracies with the repeated dispensing and transfer operations required. To meet the requirements of this operation a dispensary will have several balances and three are typical, a precision balance with a scale resolution of 0.001 g, a larger precision balance with a resolution of 0.1 g and a platform scale with a capacity in excess of 50 kg. The dispensary should be in a room separate from the main production area to allow different products to be prepared without the risk of cross contamination. When handling quantities of many pharmaceutically active compounds strict precautions must be followed to protect the operators against the compounds. This may involve mounting the weighing instrument in a dust extraction booth or negative pressure glove box. In theses situations the balance will not be operating in a perfect environment and it is essential that performance checks on the balance must be performed with the environment set to that of normal use, i.e. with the extraction system switched on. In these situations test limits for the performance checks must be set appropriate to the tasks being performed and the operating environment.

10.2 Check weighing

Check weighing is a critical part of the secondary manufacturing operation. The specifications of many pharmaceutical compounds will contain a uniformity of weight test. For some injectable products, supplied in vials and ampoules, this will be

specified as a minimum extractable volume but this test will be performed by weight as it is simpler to accurately measure the weight than the volume.

As part of the Quality Control of the product the uniformity of weight test will be performed as a periodic on-line or by-line test within the production area so that any adverse variation in the weights can be immediately corrected minimising the quantity of failed material being produced.

On-line check weighing is typically performed on products filled into bottles by having two in-line load cells. The first load cell measures the weight of the empty container and the second the filled container. The difference in weights will give the fill weight. Dependent on the speed of the filling machine this operation may permit 100% of the containers to be performed or it may be necessary to weigh only a fraction of the filled containers. For this operation to be effective it is essential that the same container is weighed pre and post-filling. To ensure this many commercial on-line check weighing systems will mark the empty container, e.g. using an ultra violet ink, and having an appropriate reader immediately prior to the second weighing station. Due to the limited scale resolution of load cells on-line check weighing systems using load cells are only applicable to products with larger fill weights, typically over 10 g.

Some pharmaceutical manufacturers use automatic by-line check weighing systems comprising two precision balances to weigh products with smaller fill weights. As the precision balances have a stabilisation time too great to be incorporated into many filling lines that operate at speeds of several hundred containers per minute. Robot arms are used to remove and replace the empty and filled containers from the production line and perform the required weighings at a specified frequency. As with the on-line load cells it is essential to ensure that the same container is weighed at the pre and post filling weighing stations.

The majority of check weighing operations performed within the pharmaceutical industry use manual by-line systems performed by the operator. A large number of techniques have been developed for a variety of products. The sample size used will be determined statistically and may be linked to the number of filling ports on the machine. The sampling frequency will be determined to ensure that sufficient samples have been collected during the batch to meet regulatory requirements and to reduce losses caused by instances of process out of specification.

10.3 Tablet weighing

Typically a number of tablets will be weighed at periodic intervals, e.g. 10 tablets every 15 minutes. The sample size and sampling period will be based on the number of ports on the compression machine and the rotation speed of the machine.

The check weighing operation would typically be:

1. Add a container to the balance
2. Tare the balance
3. Add the first tablet to the container
4. Take the weight

5. Tare the balance
6. Add the next tablet to the container
7. Take the weight

The cycle would then be repeated until all the samples were weighed. Note: If the check weighing is being performed on a computerised system removing the second and subsequent tare operations will speed up the process. The tablet weights are then calculated as the difference in initial and final weighings. For computerised systems some manufacturers can supply vibrating tables to automatically feed individual tablets onto the balance pan.

10.4 Capsule weighing

Most pharmaceutical manufacturers will buy the capsule shells from a specialist supplier. The shells will be added to the filling machine that will separate the two parts of the shell, add the micro granules to the shell and then join the two parts of the capsule shell.

For a capsule product the uniformity of weight test is based on the weight of material within the shell. The variation in weight of the capsule shells is relatively small when compared with the fill weight. The typical check weighing process for a capsule product will be to calculate the average weight of the capsule shells and to then perform the weighings as for a tablet product. The filled weight is then calculated as the weight of the capsule less the average shell weight.

Although the variation in capsule shell weight is typically small compared to the fill weight there are situations where a borderline pass or fail may occur, e.g. a low fill weight is coupled with a high capsule shell weight. In these situations the capsule should be weighed, the contents removed and the shell weighed empty to obtain an accurate fill weight. On an electronic balance the technique used is:

1. Add the capsule to the balance.
2. Tare the balance.
3. Remove the capsule from the balance.
4. Remove the contents from the capsule.
5. Add the capsule shell to the balance.

The negative value of the weight displayed is the fill weight of the capsule.

10.5 Fill weight (destructive method)

This technique can be used for a wide variety of packaging types including bottles, vials, ampoules, syringes, tubes, etc. The method is to:

1. Add the full container to the balance.
2. Tare the balance.
3. Remove the container from the balance.
4. Remove the contents from the container.
5. Add the empty container to the balance.

The negative value of the weight displayed is the fill weight of the container. For many products the accuracy of this technique is dependent on the skill of the operator in removing the contents of the container. For a vial or ampoule with a 1ml fill if an operator leaves a drop of liquid in the container this can appear to lower the fill weight by several percent. This technique can also be very costly to the company as the product is destroyed in the performance of the test. For a production line running at 300 samples per minute check weighing could be performed on10 samples every 15 minutes this is a loss of 40 samples or over 1% of production per hour. For a production line running for 12 hours per day this equates to 480 samples and for a 5 day week 2400 samples. For an area with a production of 45 weeks per year the lost samples amounts to 108,000 samples. The value to the company is dependent on the product being filled and may range from a few pence to several pounds per unit. For the more expensive products consideration should be given to the use of a non-destructive technique or by reduction in the number of samples taken or the sampling frequency.

10.6 Fill weight (non-destructive method)

This technique is typically applied to products filled into bottles, ampoules and vials. The technique is to:

1. Tare the balance.
2. Weigh an empty container.
3. Mark the container.
4. Remove the container from the balance
5. Pass the container through the filling machine.
6. Tare the balance.
7. Weigh the filled container.

The fill weight is calculated from the filled weight less the empty weight. For some processes the filling machine may add a top or a unit such as a pump dispenser to the container during the filling process. In this case an average weight of the added part(s) must also be removed from the container weight in the calculation of the fill weight. This can be achieved by adding a representative part to the balance prior to taring the balance in step 6 above. In most instances several bottles will be weighed at the empty and filled stages and so the bottles must be marked in such a way as to ensure that the same bottle is weighed at each stage. This can be achieved by adding a numbered or coloured collar around the neck of the bottle at the empty stage.

This weighing technique offers the benefit over the destructive method in that if appropriate controls are in place the samples that have been tested can be returned to the production line. This technique is not applicable to the testing of sterile products where the cleaned and sterilised containers may not be handled immediately prior to the filling machine.

10.7 Fill weight (average tare method)

This technique can only be applied to products filled into containers where the variation in the average weight of the container is small compared to the fill weight. It is typically applied to products filled into plastic bottles. The technique is to:

1. Calculate the average container weight
2. Add an empty container to the balance
3. Tare the balance
4. Remove the empty container
5. Add the filled container to the balance

The fill weight is displayed on the balance.

This is a non-destructive test method and if appropriate controls are in place the samples that have been tested can be returned to the production line.

10.8 Reconciliation

In many processes it is important to reconcile the product obtained from the process with the quantity of ingredients added. This is typically done by weight.

In primary operations the product will be filled into one or more containers for which the tare weight is known and thus the yield of product can be calculated. This can be then compared with the weights of ingredients used for the process. If a discrepancy occurs that is outside the operating limits for the process an investigation must be performed to determine the reason. For operations involving a campaign of several batches of the same product the reconciliation may be performed at the end of the campaign.

In secondary operations reconciliation is a critical process to remove the possibility of cross contamination. In processes where a product is being filled into a container e.g. a vial, it is not practical to weigh the final product. In these situations the average fill weight, obtained from the check weighing process, is multiplied by the total number of containers weighed to give the process yield. The yield is then compared to the input weight. As for primary operations if the discrepancy is outside the permitted range an investigation must be performed to determine the cause. For operations involving a campaign of several batches of the same product the reconciliation may be performed at the end of the campaign.

11 Laboratory weighing styles

Weighings are performed in the laboratories as part of:

- check weighing
- quantitative analysis
- other tests

11.1 Check weighing

Check weighing can be performed in a laboratory as an option on performing check weighing operations in the production area or to supplement results from the production area. As the operation is performed after the batch has been completed the non-destructive test method is not applicable in the laboratory environment. As the

check weighing results are only available at the end of the batch an out of specification result would lead to the rejection of a whole batch.

11.2 Quantitative analysis

Many quantitative analysis tests performed in a laboratory will contain the statement 'accurately weigh xg of sample' where x is the required weight. Typically this will be the first stage in a multi step process and so any errors introduced at this stage will have a detrimental effect on the accuracy of the assay result. To improve the accuracy of the weighing step and the subsequent transfer of the sample to the weighing vessel a number of techniques have been developed.

11.3 Addition weighing

This technique will mainly be used for the dispensing of powders.

1. Add the weighing boat to the balance.
2. Tare the balance.
3. Add the required amount of sample to the weighing boat.

The balance will then display the weight of sample taken. The weighing boat is removed from the balance and quantitatively transferred to the appropriate piece of equipment, e.g. a volumetric flask.

11.4 Dispense weighing

This technique is mainly applicable to the weighing of creams and ointments where the nature of the product makes it unsuitable for addition to a weighing boat and the subsequent accurate transfer to the analytical vessel.

1. Transfer a quantity of the sample greater than required to a syringe.
2. Add the filled syringe to the balance.
3. Tare the balance.
4. Transfer the required quantity of sample to the flask.
5. Return the syringe to the balance.

The negative weight of the display is the weight of sample taken.

11.5 Other tests

Many tests are performed as part of the product development / quality control / quality assurance processes where a weighing operation is the major part of the test. These tests include:

- water vapour permeability test
- accelerated stability trials
- aerosol shot weight test
- aerosol valve leak test
- loss on drying

- ash / sulphated ash
- sieve test
- friability test

11.5.1 Water vapour permeability test.

All pharmaceutical products supplied to a patient will be supplied in a primary packaging material. Examples are tablets supplied in a plastic bottle or an aqueous nasal spray supplied in a glass bottle. Each product will be assigned a shelf life based on stability trials, which will be up to 5 years. Within the shelf life a product may be stored in warehouses or on a shelf in a pharmacy where the temperature and humidity may vary widely. During this period it is essential that water vapour cannot escape from or enter the primary packaging material as this can lead to degradation of the product.

Before the regulatory authorities will give approval to the primary packaging a number of tests, including the water vapour permeability test will be required to be satisfactorily completed. This test ensures the suitability of the packaging material.

To perform the water vapour permeability test a number of containers, typically 10, are filled with a hydroscopic compound, e.g. calcium chloride. Other containers, typically 2, are filled with an equal weight of an inert material, e.g. glass beads, as a control. The containers are sealed and allowed to equilibrate in a room with strictly controlled temperature and humidity, and are then weighed. The containers are then stored for 14 days in a temperature and humidity controlled environment, typically 35 °C / 75 %rh. The containers are then allowed to equilibrate to room temperature and the containers reweighed. The weight change of the test containers is compared to the controls and a test result calculated in mg per day.

11.5.2 Accelerated stability trials

During the development of a new product accelerated stability trials are performed as a means of establishing the shelf life of the product. Samples of the packaged product are stored in environmentally controlled rooms under a range of temperatures, typically 4 to 37 °C, and humidities, typically 25 to 75 %rh. A series of test points will be established which may include 1, 3 and 6 months and 1, 2, 3 and 5 years. Physical and chemical tests appropriate to the product will be performed at the start of the trial and repeated at specified test points. Historical data has shown samples stored at the higher temperature and humidity combinations for short periods of time equate to samples stored at lower temperature and humidity conditions for longer time periods. Using the data from the early time points allows a provisional shelf life to be applied to the product. The data from the later test points allow this to be confirmed or modified if required before product that has been added to the supply chain approaches critical points. As part of the accelerated stability trials each sample may be weighed at the initial time point. A number of samples will be weighed as controls at each time point together with each sample removed for testing. Any weight change of a test sample that is significantly different from the controls must then be investigated to ensure that the container to be tested has not been damaged allowing the ingress / egress of water vapour. If water vapour has leaked from or contaminated

a sample this could lead to degradation of the product. The recorded weight change would be cause for that sample to be excluded from the stability trial.

In secondary production selected packaged batches of each product will be placed on accelerated stability trials each year to ensure the maintenance of the product shelf life.

The weight of a packaged pharmaceutical product can vary from a few grams to several hundred. The balance capacity and scale resolution selected for this work must be appropriate to the samples being weighed. The balance used for the weighings must be recorded. As this test is spread over several years the balance used for the initial weighings may have been replaced when the final weighings are performed. The balance used for subsequent time points must be of similar performance to that used for the initial weighings and the same balance must be used for the weighings of all the control and test samples at each time point.

11.5.3 Aerosol shot weight test

Products filled into aerosols are typically used where a patient is required to inhale the product and is mainly used in the treatment of asthma. In this type of application the aerosol valve is designed to deliver a fixed dose of product at each activation. The basis of the valve is a chamber, typically 23 µl that is contained within the aerosol when the valve is closed and fills with the propellant / product mixture. When the patient activates the valve this chamber is isolated from the body of the aerosol and is exposed to the air. The patient is required to inhale simultaneously with the activation. The inhalation coupled with the vaporisation of the propellant ensures that a fine suspension of product will enter the throat and lung cavities of the patient. Tests are required to ensure that the shot weight, i.e. the weight of propellant discharged at the valve activation, is reproducible.

An aerosol may contain up to 200 doses. The shot weight test will require a number of shots to be performed to activate the valve. The aerosol will then be weighed, shaken so that the propellant / product suspension is evenly maintained, a number of shots, typically 10, discharged and the container reweighed. The average shot weight is then calculated and must be within specified limits. Further shots are discharged and the test repeated with the aerosol approximately half full and almost empty to ensure that the shot weight remains consistent throughout its life. This test will typically be performed on 10 aerosols per batch.

11.5.4 Aerosol valve leak test

When a patient is suffering from asthma they will be given an aerosol, or equivalent, containing a product to be used in relieving the symptoms of an attack. They must carry this aerosol with them at all times and this will normally be in a pocket or a handbag so it is readily available. The carriage of the aerosol will mean that the valve may be in contact with the pressurised propellant, typically a chlorofluorocarbon compound, for long periods of time. It is essential that no leakage occurs during the life of the aerosol and so the aerosol valve leak test is performed on each batch. Typically 100 aerosols will be statistically sampled from the batch, the aerosols weighed and stored inverted for one month. The aerosols are then reweighed and any

weight loss determined. The aerosols are then returned to inverted storage for a further two months and then weighed again.

This test will typically be performed on a 0.1 mg or 0.01 mg resolution balance as the weight of the aerosol and contents will be greater than the capacity of a balance with a higher scale resolution. A facility with a major aerosol unit may have several batches per day undergoing this test. With initial, intermediate and final weighings being performed this may involve over a thousand weighings per day for this test alone. A laboratory involved in this testing will probably have several balances in use at the same time. The number of weighings performed together with the relatively large time period between the weighings may result in a different balance being used for the different time points. The balances used for the each of the weighing stages must be recorded. Very small weight changes are significant in this test. The laboratory supervisor must ensure that all of the performance checks of the balances used for this test are within specification and that any balance to balance variation in the results of the same check weight be investigated.

11.5.5 Loss on drying

This test is performed on many powders and is to ensure that the product has been correctly dried during its production cycle and is not contaminated with water or solvent residues. Approximately 1 g of compound will be added to a glass container and weighed. The container is then stored in an oven for a specified period of time and is then transferred to a dessicator to allow the container to equilibrate to room temperature. The container is then reweighed and any loss calculated.

To minimise errors in this test the balance used for the initial and final weighings must be recorded and whenever possible the same balance be used for both weighings.

11.5.6 Ash / sulphated ash

Most pharmaceutical compounds produced during primary operations are organic compounds. Primary operations typically involve large scale stainless steel or glass lined vessels and the processing routinely involves high powered stirrers or impellers. It is essential that during this processing that no metallic contamination of the product can occur as a result of abrasion or minor mechanical failure. One test to ensure this is the ash / sulphated ash test.

A crucible will be weighed, approximately 1 g of product added to the crucible which is then reweighed. The crucible will then be ashed initially by the use of a gas flame and then in a thermally controlled furnace at a temperature of several hundred degrees. The actual temperature used will be product dependent with higher temperatures required for compounds that were initially a salt. The crucible will then be transferred to a dessicator to allow the crucible to equilibrate to room temperature. The crucible is then reweighed and any residue calculated. Note: For a sulphated ash the product will initially be treated with concentrated sulphuric acid.

To minimise errors in this test the balance used for the initial and final weighings must be recorded and whenever possible the same balance be used for both weighings.

11.5.7 Sieve test

During the manufacture of a tablet product the ingredients are mixed and formed into granules. For many products the size of the granules are critical. If the particle size is too small the product may not flow efficiently within the compression machine and too large a particle size may result in insufficient product entering the former for compression.

One technique used to measure the particle size distribution is the sieve test. A stated quantity of granule, typically 100 g, will be accurately weighed and added to the top section of a sieve stack, the accurate weight of each sieve having been recorded prior to the test. The stack will typically contain 4 sieves organised with the coarsest sieve at the top with each lower sieve being finer. The base of the sieve stack contains a vibrating table and allows a vacuum supply to be applied to the bottom of the stack.

After the specified time for the test the power is switched off and each sieve is weighed. The increase in weight allows the percentage distribution to be recorded. If the mesh sizes used for 4 sieves were 20, 40, 60 and 80 mesh the results would be in the form a % > 20#, b % 20-40#, c % 40-60#, d % 60-80# and e % <80#. The value for the fines that passed the 80# sieve in this example is calculated by subtracting the weight of material retained on the 20, 40, 60 and 80 mesh sieves from the weight of sample input to the test.

The weighings performed for this test will be performed on a precision balance.

11.5.8 Friability test

During tablet manufacture a batch of cores will be produced from a compression machine. For most products for the cores to be turned into the final product for distribution to the patients the cores will be coated with an appropriate spray mixture. The coating machine consists of a rotating drum that uses a tumbling motion to allow the coating to be evenly sprayed to the product. It is critical that the tablet cores will allow this process to be performed without any significant weight loss or disintegration of the tablet cores. To ensure the tablet cores are of an acceptable quality to undergo the coating process the friability test is performed.

A stated weight of tablets is added to a friabulator. The friabulator consists of a plastic drum that is vertically mounted on a rotating drive shaft. The drum contains a fixed curved plate that lifts the tablets to the vertical and then drops them in free fall. The unit is programmed to run for a stated time period. At the end of the time the tablets are reweighed and the tablets are satisfactory for processing if the weight loss is less than a set limit.

The weighings performed for this test will be performed on a precision balance.

12 Problem samples

When performing weighings in a laboratory or a production environment a number of situations may arise where special procedures need to be applied:

- Static electricity
- Volatile samples
- Deliquescent samples
- Sterile weighing
- Physiologically active compounds
- Animal weighing

Procedures for use with these samples / weighing types are described below:

12.1 Static electricity

Many of the powders that are to be weighed will be charged with static electricity as a result of handling procedures. This may be either a positive or negative charge.

If a powder containing a static charge is added to a weighing container on a balance either an inaccurate weighing result will be obtained as a result of interference by the charge or an unstable reading will be obtained as a result of leakage of the charge to the environment. The most common symptom of attempting to weigh a powder with a static charge is that the weighing display will show a rapid continuous change in the reading. If powders that contain a static charge are to be weighed then procedures must be followed to dissipate this charge.

Some modern analytical balances are fitted with devices that can detect the static charge and automatically generate an opposite charge to neutralise the charge on the powder.

For other balances a static gun must be used to generate an appropriate positive or negative charge.

12.2 Volatile samples

In some situations a weighing must be performed on a liquid which has a low boiling point. In this situation if the weighing was performed in an open vessel part of the sample would continuously vaporise. The symptom would be a continuously decreasing weight.

When weighing a volatile sample the sample must be weighed in an enclosed weighing vessel with the minimum practical cross sectional surface area, e.g. a conical flask.

12.3 Deliquescent samples

Deliquescent samples will readily adsorb water vapour from the air surrounding them. If a deliquescent sample was weighed in an open vessel the symptom would be a

continuously increasing weight. It is not practical to perform these weighings in a totally dry atmosphere as this would adversely increase the effects of any static charge on the sample and is uncomfortable to the operator performing the weighings.

When weighing a deliquescent sample the sample must be weighed in an enclosed weighing vessel

12.4 Sterile weighing

In some biological laboratories it is necessary to perform weighing operations under sterile conditions, e.g. dispensing of a media for an aseptic trial. These operations will be performed in a laminar flow cabinet with an air flow moving from top to bottom and back to front of the cabinet. Operating in these conditions it will normally not be possible to operate the balance with a draft shield as this would provide an area of the cabinet in which the required laminar flow was not being maintained.

To minimise the effect of the airflow on the balance:

- the operating parameters must be selected for an unstable environment
- the working area must be organised so that the balance is located as close to the centre of the cabinet as is practical
- the operator must work as far as possible centrally to the balance

12.5 Physiologically active compounds

Many of the powders weighed within the pharmaceutical industry are physiologically active and many are of a small particle size. These compounds can readily become airborne in a weighing operation and can pose a health threat to the operator as a result of skin or respiratory contact.

To protect the operator in these operations the balance will be mounted in a dust cabinet where there will be a positive flow of air from the front to the back and from the bottom to the top of the cabinet. It will not be possible to operate the balance with a draft shield as this would provide an area of the cabinet in which the air flow was not being maintained and contamination would build up.

To minimise the effect of the airflow on the balance:

- the operating parameters must be selected for an unstable environment
- the working area must be organised so that the balance is located as close to the centre of the cabinet as is practical
- the operator must work as far as possible centrally to the balance

13 Laboratory automation

In recent years the cost of robotic and automation equipment has fallen and the reliability and reproducibility has increased. Many laboratories have introduced or are considering automation options as a means of:

- improving staff utilisation, e.g. a manual weighing of 100 aerosol cans against adding the cans to a robot.
- improving the reproducibility of a test step, e.g. a test requirement to shake an aerosol can 10 times prior to discharging a shot

Many laboratory operations involve a balance and thus much of the automation requirements will also include a balance.

Most modern electronic balances have been designed for use with human operators and not for robots. If a balance is to be incorporated within an automation system then the following points must be considered. Note: in this section the term 'robot' is used to cover cartesian, i.e. XYZ, devices as well as 6 axis motion devices

13.1 Shielding

If a robot arm is capable of moving at a speed greater than 1 metre per second it must be shielded from the operator. If the arm moves at a slower speed but is of such a weight that a contact with an operator could result in an injury then shielding should also be applied.

13.2 Balance draft shields

Most electronic balances with a resolution of 0.000 1 g or less will be supplied fitted with a draft shield. Many modern balances are supplied with a motor driven rotational or linear mechanism that can be activated to open and close the draft shield. Several points must be considered when a robot arm is to be used for pick and place operations with a balance fitted with a draft shield:

- with the draft shield fully open can the proposed robot arm obtain full access to the weighing chamber?
- when the draft shield is motor driven can the proposed robot arm activate the drive mechanism?
- when the draft shield is manually operated can the proposed robot arm reliably open and close the draft shield?
- if safety shielding is in place around the whole system is a draft shield necessary?

13.3 Balance pan

Most electronic balances will be supplied with a balance pan that is either circular or square in shape. For some balances an adapter is supplied to allow under the bench suspension weighings to be performed. For many automation systems involving pick and place operations a shaped holder is preferable to the supplied balance pan. This will ensure the accurate placement and correct alignment of the sample.

If a modified balance pan is required the following points must be considered:

- is the weight of the modified pan within the manufacturer's permitted range
- will the material used ensure an earth continuity to be maintained?

- will the material used ensure that any environmental temperature change does not create adverse effects on the balance operation?

13.4 CE stamping

All weighing devices sold in the European Union must be supplied with a CE (Conformance Europenne) stamp that indicates that the manufacturer has tested that the unit complies with all relevant European Union directives. For balances this includes the low voltage and radio frequency interference directives but does not include the Non-Automatic Weighing Instrument Directive (Chapter 3.1) which uses the supplementary M stamp.

If an automation system is created, e.g. a balance, robot and spectrophotometer, although each of the individual units will be supplied by the manufacturer with a CE stamp this does not automatically generate a CE approval for the system.

If an automation system is provided through a third party supplier then it is the responsibility of the supplier to ensure that all appropriate testing of the system has been performed and the appropriate certificate(s) has been issued. If the system is built in-house from the individual units then currently there is no need for the system to be CE approved provided that the individual units have been approved.

14 Statistical process control

Statistical Process Control (SPC) was developed in the 1940s as a means of reducing process waste as a result of material being produced that was out of specification. The results of the sampling measurements being performed allowed meaningful decisions to be made on controlling the process.

In the early days of SPC the measurement data was plotted by the technician using a variety of graphical presentations, e.g. a Shewart chart. The visual presentation of the data allowed the technician to readily see trends in the data and to use this information to make meaningful adjustments of the process.

Today many software packages exist that allow data collection to be performed, appropriate calculations to be performed and graphical representations to be generated. Some software packages may allow automatic adjustment of the manufacturing machine to be performed and others may display recommendations of the changes required to the operator.

In the Pharmaceutical industry very little use is made of SPC. This has been a result of a historical process where the main argument has centred on the relatively short size of manufacturing runs in the industry and in many cases the regular change of equipment to different product sizes and types.

The Pharmaceutical industry generates very large quantities of measurement data during the manufacturing process that is solely used as a pass / fail decision. The remainder of the information in the data about the performance of the manufacturing process is ignored. The use of simple SPC techniques such as Shewart charts and

Process Capability measurements would allow greater information on the process to be understood.

14.1 Shewart chart

The simplest Shewart chart is the plot of the mean of subsequent sample groups and this combined with the range allows ready understanding of the control of the process.

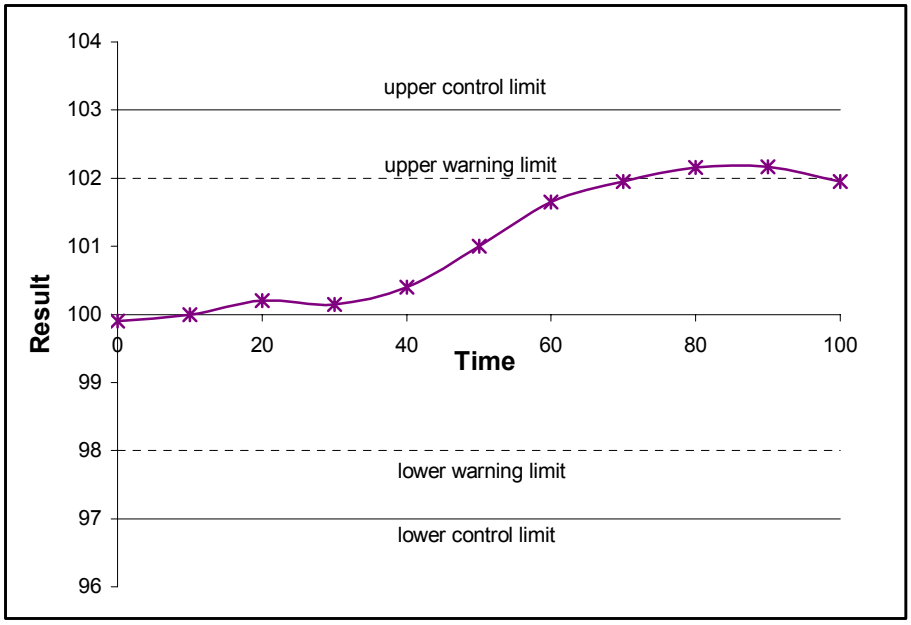


Figure 3: Example of a Shewart chart

14.2 Process capability

The Process Capability, Cp, was one of the original process values. The value for a batch is calculated as follows:

$$Cp = (UCL - LCL) / 6\sigma$$

Where: Cp = Process capability
UCL = Upper Control Limit
LCL = Lower Control Limit
σ = batch standard deviation

The Cp is a very useful measure when the mean of a batch is very close to the target value. For a batch where the mean is not centred on the target value the Cpk value should be used and this is calculated from the following equations:

$$A = (UCL - mean) / 3\sigma$$
$$B = (mean - LCL) / 3\sigma$$
Cpk is the lower value of A and B

As with any statistical sampling the process can only be applied if the sample population follows an appropriate distribution. Process capability measurement

assumes that the sample distribution is normally distributed. In the early days of SPC a process capability of 1 was considered a capable process. As manufacturing and measurement technology improved the definition of a capable process increased to 1.3 and this equates to a 3σ process with a defect rate of 3 units in a 1000. In recent years the 6σ process, with a defect rate of 1 unit in a 1,000,000 is seen as the ultimate target and this equates to a process capability of 3. Note: true process capability values are calculated from upper and lower control limits. If process permitted limits are used as control limits to calculate process capability very high but meaningless Cp and Cpk values can be obtained. Control limits should be calculated from the capability of the manufacturing process and would normally be expected to lie well within the process permitted limits.

15 Uncertainty of measurement

15.1 Introduction

When making measurements there is always an element of uncertainty in the result. We cannot know 'true' values – there are limitations in our knowledge and in the performance of the instruments we are using. Therefore a measurement is not complete without an estimate of the doubt that surrounds it (the uncertainty) and the confidence we have in that estimate. This chapter gives an introduction to the terminology and some of the main sources of uncertainty, plus a brief summary of the process for calculating the uncertainty and associated confidence level. All calculations are performed in accordance with the ISO Guide to the Expression of Uncertainty in Measurement [8] also known as the GUM.

15.2 The measurement

Although perhaps an obvious point, before starting it is worth confirming precisely what the measurements are aimed at determining. The following need to be considered:

- Which measurements and calculations will be required to enable you to establish the mass value and the uncertainty in its determination? For example, will you need to determine air density?
- How many measurements do you need to take? (The more measurements you take the more representative the mean (average) value becomes, although there is a reduction in benefit as the number of measurements increase beyond a certain point. Ten measurements is a common choice and statistically valid but not always practical – eg for economic reasons. One way of dealing with this problem is to use some data from previous measurements to determine the performance of the balance and then take a smaller number of measurements for the particular calibration in hand.)
- How to take your measurements and calculate a mass value.

When any measurement is performed on an electronic balance, or any other piece of equipment, it is very easy to make the assumption that the result shown on the display is the true value. In reality all measurements have an associated uncertainty. All

measurements and measurement processes should be assessed and the uncertainty assigned to the result.

When calculating measurement uncertainty two types, correctly known as Type A and Type B must be assessed and combined.

15.3 The uncertainty budget

Once you have determined the mass value you are ready to start calculating the uncertainty in the measurement. The following table is a typical layout for an uncertainty budget for weighing. It can be in the form of a computer spreadsheet – to make repeated calculations easier - or it can be a paper table completed by hand using a calculator. Each column in the table is dealt with separately below.

Symbol	Source of uncertainty	Value	Probability distribution	Divisor	Sensitivity coefficient	Standard uncertainty	v_i or v_{eff}

15.3.1 Symbol

The symbol used in to denote the input quantity or the influence factor.

15.3.2 Sources of uncertainty

The sources of the uncertainty are dependent on the measurement process and equation used - as defined in your procedures and by your laboratory environment. Here we consider the most common sources.

Each of the *input quantities* in the measurement equation used to calculate the mass value has an uncertainty. For example if the equation you are using is:

$$Wx = Ws + \Delta W + Ab$$

where Wx is the unknown mass
Ws is the mass of the standard
ΔW is the difference in the balance readings
Ab is the correction for air buoyancy

then there is an uncertainty associated with each of the input quantities Ws, ΔW and Ab. The uncertainty in ΔW depends on uncertainty due to other influence factors:

- Rounding errors in the comparator readings (δI_d)
- The uncertainty due to less-than-perfect repeatability of the readings (W_R)
- The value associated with comparator linearity (δC)

Another influence factor to be considered is

- The drift of the standard with time (Ds)

Symbol	Source of uncertainty	Value	Probability distribution	Divisor	Sensitivity coefficient	Standard uncertainty	v_i or v_{eff}
Ws	Calibration of mass standard						
δC	Comparator linearity						
Ab	Air buoyancy						
Ds	Uncorrected drift of the standard						
δI_d	Digital rounding error						
W_R	Repeatability						

15.3.3 Values

The values associated with the sources of uncertainty are either measured, calculated or come from *a priori* (previous) knowledge.

In our example:

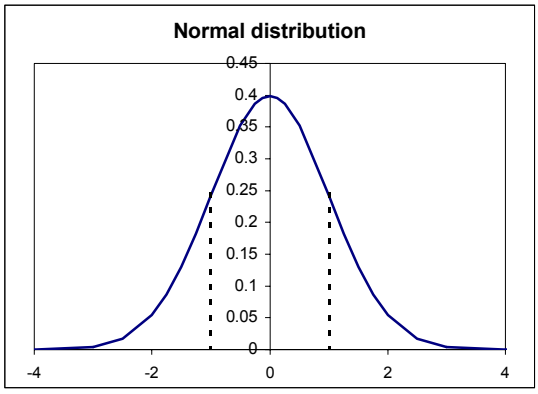
Symbol	Uncertainty source	The value
Ws	Calibration of mass standard	The uncertainty in the mass standard is taken from its calibration certificate.
δC	Comparator linearity	Estimated from previous measurements according to your procedures.
Ab	Air buoyancy	A calculated uncertainty based on the air buoyancy correction equation ie $(Vs - Vx)(\rho_a - 1.2)$ (see paragraph 15.4) In this example the volumes have not been measured and the uncertainty in the volume difference is based on the values given in the OIML recommendation R111 (if the volumes are measured the uncertainty can be less) but the value of air density has been measured.
Ds	Uncorrected drift of the standard	The uncertainty quoted on the mass standard's calibration certificate will not include any contribution for drift in its mass value. The evaluation of this effect is normally the responsibility of the weight's owner as they are best placed to evaluate how much its mass changes between calibrations. Drift is usually determined by considering how much a particular artefact has changed its mass value over a recent period and extrapolating the figure to cover the period up to its next calibration. In this example no previous calibration knowledge is assumed and the uncertainty in the current mass value calibration is also used to estimate the limits of drift.
δI_d	Digital rounding error	Each reading is subject to a rounding error. It is taken to be ± half the resolution of the comparator. Such errors occur in the comparator reading of the standard mass and the unknown mass.
W_R	Repeatability	This is an uncertainty component which is a measure of the 'spread' of the repeated readings. It is estimated by determining the experimental standard deviation of the mean (see *Further reading*). In this example a previous evaluation of repeatability of the measurement process (from ten comparisons between a mass standard and an unknown mass) were used to establish a standard deviation of 0.00017 mg which was then divided by √n, where n is the number of readings in the current measurement – in this case three).

15.3.4 Probability distributions

A probability distribution is a statistical description of how results behave. There are three distributions commonly used in mass uncertainty budgets: *normal* (sometimes called *Gaussian*), *rectangular* (sometimes called *uniform*) and *triangular*. The following graphs illustrate these distributions where the zero value on the horizontal axis represents the mean value of a number of readings, the vertical axis is the probability of a particular value occurring and the broken lines represent plus and minus one standard deviation (k=1) - encompassing approximately 68% of the measurement values (ie 68% of the area under each curve).

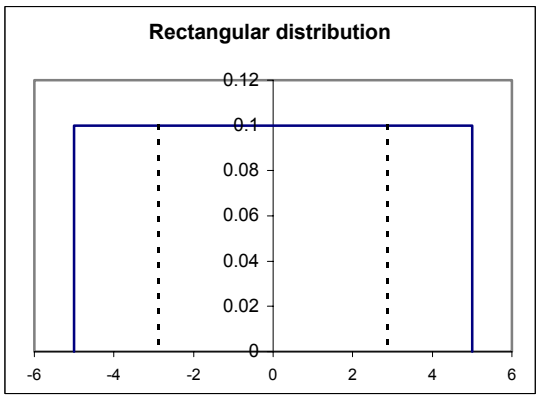
15.3.4.1 Normal distribution

This represents a group of measurements where the values are more likely to fall closer to the mean value than further away from it. Repeated measurements are an example of this type of distribution. The graph shows normally distributed data with a mean value of zero and a standard deviation of ±1.



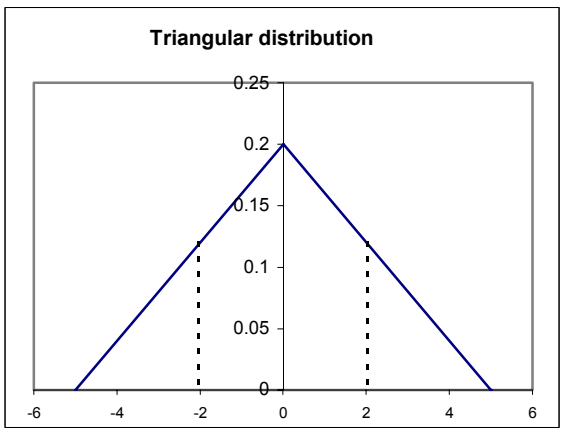
15.3.4.2 Rectangular distribution

This represents a group of measurements where the values are evenly spread between two limits and never fall outside these limits. An example is when using an assumed air buoyancy correction (as opposed to a measured or calculated value). The graph shows a rectangular distribution, again with a mean value of zero, but limits of ±5. In this case one standard deviation is ±2.89.



15.3.4.3 Triangular distribution

This is the distribution you get when adding two rectangular distributions. An example is the uncertainty due to rounding errors. The graph shows a triangular distribution, again with a mean value of zero and limits ±5. In this case one standard deviation is ±2.04.



15.3.5 Divisor

In order to eventually sum all the individual input quantities they must be quoted with the same confidence level. This is done by establishing a number by which the input quantity uncertainty value is divided to convert it to one standard deviation and is dependent on the distribution as shown in the table below.

Distribution	Divisor
Normal	1 or 2
Rectangular	$\sqrt{3}$
Triangular	$\sqrt{6}$

The normal distribution has a divisor of either 1 or 2 depending on the confidence level of the value quoted. For example on a certificate of calibration the uncertainty might be quoted as 'k = 1' (~68%) or 'k = 2' (~95%) in which case the divisor is the 'k' number. Other values are sometimes used, for example k = 3.

15.3.6 Sensitivity coefficient (c_i)

This is a multiplication factor which converts the uncertainty in the value of an input quantity to a corresponding uncertainty in the output quantity (it sometimes has to convert both *quantity* – such as temperature or pressure - to mass and also the right *units*). In the example being discussed all the input quantities are already expressed in the quantity *mass* and using the sub-unit *milligram* so the sensitivity coefficient is 1.

An explanation of the air buoyancy correction calculation is in paragraph 15.4.

15.3.7 Standard uncertainty in units of measurand, $u_i(W_i)$

In order to add all the components together we need them in the same units and the values for this column are simply calculated from

$$\text{Value} \div \text{Divisor} \times \text{Sensitivity coefficient } (c_i)$$

15.3.8 Degrees of freedom v_i

The number of degrees of freedom is "…in general the number of terms in a sum minus the number of constraints on the terms of the sum"[8]. Before considering this further it is necessary to first appreciate that measurement uncertainties are considered to fall into one of two categories, known as *Type A* and *Type B*.

- Type A uncertainties are those that are evaluated by statistical methods. For example, uncertainty due to less-than-perfect repeatability of a measurement can be reduced by calculating a mean value from several measurements.

- Type B uncertainties are evaluated by other means. They cannot be reduced by taking more measurements – the uncertainty quoted on a certificate of calibration cannot be made lower by repeatedly reading the certificate for example!

The degrees of freedom, v_i, for individual uncertainty contributions are given by:

Type A	v_i = n-1 where n is the number of measurements used to evaluate the type A contribution
Type B	v_i is usually taken to be infinite

15.3.9 Adding it all up

15.3.9.1 Combined standard uncertainty u(Wx)

To obtain an uncertainty in Wx, the mass value of the unknown weight, the components have to be added to obtain a *combined standard uncertainty*. As it is unlikely that all the errors will have been at their maximum value in any one measurement it is inappropriate to add them in arithmetically. The recognised way to address this issue is to arithmetically add the squares of the standard uncertainties and then take the square root of the result – this process is know variously as taking the *root sum of the squares* (RSS) or *quadrature summation*.

In the example we are considering the summation is:

$$u(Wx) = \sqrt{0.0250^2 + 0.0115^2 + 0.0216^2 + 0.0289^2 + 0.0020^2 + 0.0001^2}$$

$$= 0.0454 \text{ mg}$$

The resulting probability distribution will be a normal distribution unless one rectangular distribution is much larger than the other components.

15.3.9.2 Effective degrees of freedom v_{eff}

In general the effective degrees of freedom, $v_{eff,}$ will not need to be calculated if the type A uncertainty is less than half of the combined standard uncertainty, there is only one type A component and at least three measurements have been taken. Otherwise the effective degrees of freedom will have to be calculated to ensure that the k-factor of 2 will indeed give a confidence level of ~95%.

The effective degrees of freedom for the combined standard uncertainty will depend on the magnitude of the degrees of freedom for the type A contributions in relation to the type B. If the type B uncertainties are all taken to have infinite degrees of freedom the relationship is shown using the simplified Welsh-Satterwaite equation:

$$v_{eff} = \frac{u_c^4(y)}{\left(\frac{u_i^4(y)}{v_i}\right)}$$

where $u_c(y)$ is the combined standard uncertainty
$u_i(y)$ is the individual type A uncertainty contribution
v_i is the degree of freedom in $u_i(y)$

therefore in our example:

$$v_{eff} = \frac{0.0454^4}{\left(\frac{0.0001^4}{9}\right)} \qquad \text{thus} \qquad v_{eff} = 3.8\text{E+}11$$

In this example v_{eff} is a very large number which can be taken to be infinity. If this value had been less than 100 a k-factor would have been calculated from a distribution other than a normal distribution.

15.3.9.3 Expanded uncertainty

The expanded uncertainty U(Wx) is the combined standard uncertainty u(Wx) multiplied by a k-factor which will give an uncertainty value with a confidence level of approximately 95%, in this case 2.

The final uncertainty budget for our example is shown below.

Symbol	Uncertainty source	Value ±mg	Probability distribution	Divisor	Sensitivity coefficient	Std. uncertainty ± mg	v_i or v_{eff}
Ws	Calibration of standard weight	0.0500	Normal	2	1	0.0250	∞
δC	Comparator linearity	0.0200	Rectangular	√3	1	0.0115	∞
Ab	Air buoyancy	0.0216	Normal	1	1	0.0216	∞
Ds	Uncorrected drift of the standard	0.0500	Rectangular	√3	1	0.0289	∞
δI_d	Digital rounding error	0.0050	Triangular	√6	1	0.0020	∞
W_R	Repeatability	0.0001	Normal	1	1	0.0001	9
u(Wx)	Combined standard uncertainty		Normal			0.0454	>500
U(Wx)	Expanded uncertainty		Normal k=2			0.0908	>500

15.4 Air buoyancy uncertainty budget

In order to calculate the uncertainty in the air buoyancy correction for entry into the main uncertainty budget an additional uncertainty budget has to be completed. Air buoyancy (Ab) is dependent on the volumes of the weights and the air density with the following relationship:

$$Ab = (Vs - Vx)(\rho_a - 1.2)$$

where (Vs - Vx) is the difference in volume between the standard and the unknown weight
(ρ_a - 1.2) is the difference between measured density of the air and the standard air density

There are two ways to calculate an uncertainty value for Ab, either working in relative values or calculating the sensitivity coefficient directly. In our example the volumes have not been measured so the value of (Vs - Vx) is taken to be the largest difference possible according to the OIML recommendations [6] when comparing E_2 and F_1 weights – that is 1.3 cm^3 with an uncertainty of ±1.3 cm^3. This uncertainty is treated as a rectangular distribution because the real value may lie anywhere between these limits and thus the standard uncertainty (u(V)) is equal to ±(1.3 ÷ √3). In this example the air density, ρ_a, has been measured as being 1.22 kg/m^3 with an uncertainty of ±10% - thus the uncertainty in (ρ_a – 1.2), that is u(ρ), is ±0.012 kg/m^3. Thus:

$$Ab = (1.3)(1.22 - 1.2) = 0.026$$

15.4.1.1 Relative uncertainty

The relative uncertainty in the air buoyancy, u(Ab)/Ab, is given by:

$$\frac{u(Ab)}{Ab} = \sqrt{\left(\frac{u(V)}{(Vx - Vs)}\right)^2 + \left(\frac{u(\rho)}{(\rho_a - 1.2)}\right)^2}$$

inserting the values gives:

$$u(Ab) = Ab\sqrt{\left(\frac{1.3 \div \sqrt{3}}{1.3}\right)^2 + \left(\frac{0.012}{1.22 - 1.2}\right)^2}$$

$$u(Ab) = 0.0216$$

This method of calculation works well for an equation where the only operators are multiplication or division.

15.4.1.2 Partial differentiation

The other method, partial differentiation, sounds more complicated but is actually quite straightforward for this type of equation.

Using the same equation, Ab = (Vs - Vx)(ρ_a - 1.2), and the same values as above, we calculate the sensitivity coefficients - the numbers by which values of u(V), expressed here in cm^3, and u(ρ), expressed here in kg/m^3, should be multiplied to calculate their effect on the output quantity expressed in grams.

The partial derivative of a simple equation, such as the one we are looking at, is simply the multiplier for the term for which we wish to calculate the partial derivative. For example, if our equation is A = B × C then the partial derivative of B is C and the partial derivative C is B.

In our air density problem the partial derivative of (Vs - Vx) is (ρ_a - 1.2) and the partial derivative of (ρ_a - 1.2) is (Vs - Vx). In the correct terminology this is expressed as :

$$\frac{\partial(\mathrm{Ab})}{\partial(\mathrm{Vs} - \mathrm{Vx})} = (\rho_a - 1.2) = 0.02$$

$$\frac{\partial(\mathrm{Ab})}{\partial(\rho_a - 1.2)} = (\mathrm{Vs} - \mathrm{Vx}) = 1.3$$

The values 0.02 and 1.3 are entered directly into the sensitivity coefficient column of the uncertainty budget and the remaining calculations are the same as for the main uncertainty budget.

Symbol	Source of uncertainty	Value ±mg	Probability distribution	Divisor	Sensitivity coefficient	Std. uncertainty ± mg	v_i or v_{eff}
Vs – Vx	Difference in volumes	1.3	Rectangular	$\sqrt{3}$	0.02	0.0150	∞
ρ_a – 1.2	Diff. in air density	0.012	Normal	1	1.3	0.0156	∞
Combined standard uncertainty			Normal			0.0216	∞

The combined standard uncertainty is the same as in the previous method.

Partial differentiation is more difficult when the equation is more complex.

15.5 Reporting the results

In general calculations should not be rounded until the final result is calculated. The uncertainty should be quoted to 2 significant figures and the result quoted to the same number of decimal places. In the worked example the result would be reported in the form:

100.000 71 g ±0.10 mg

and would be accompanied by a statement explaining how the uncertainty and its confidence level are calculated such as:

> The reported expanded uncertainty is based on a standard uncertainty multiplied by a coverage factor k = 2, providing a level of confidence of approximately 95%. The uncertainty evaluation has been carried out in accordance with UKAS requirements.

This statement was taken from the UKAS document [9].

The uncertainty has been rounded to 0.10 mg; uncertainties should always be rounded up rather than down to ensure that the value remains within the 95% confidence limit.

15.6 Multiple units

In a laboratory analysis the weighing can only be a small part of the measurement process. The process may also involve the use of analytical glassware, e.g. volumetric flasks or a pipette, and a final measurement using a spectrophotometer. The individual effects of the balance, the glassware and the spectrophotometer could be assessed in g, ml and absorbance units. It is not possible to combine different units when performing an uncertainty calculation. In an example such as this a common unit must be chosen when calculating the overall measurement uncertainty.

15.7 Effect of uncertainty on the result

If a result is displayed graphically on a typical control chart as in Figure 4 the result will be shown as the measured value with the measurement uncertainty overlaid as a bar. The true value of the measurement can be anywhere between the upper and lower limit of the bar.

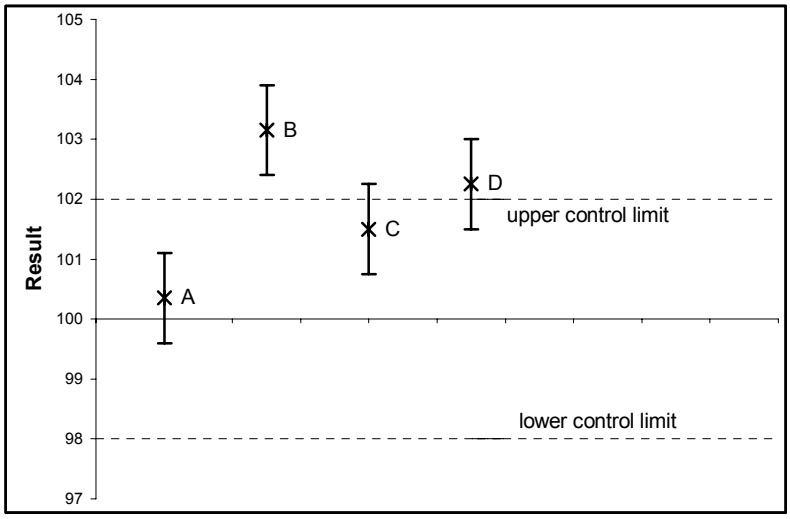


Figure 4: Example of control chart.

In the chart above measurement A shows a value close to the target value, the uncertainty bar maintaining the result within the permitted upper and lower control limits. In an analytical test this sample would be classed as satisfactory. Measurement B shows a measured value and the associated uncertainty above the upper control limit. In an analytical test this sample would be rejected and classed as unsatisfactory.

Measurement C shows a measured value within the upper and lower control limits but the associated uncertainty bar crosses the upper control limit. Measurement D shows a measured value above the upper control limit but the associated uncertainty bar crosses the upper control limit. If the control chart had been plotted without uncertainty bars measurement C would automatically have been accepted and measurement D rejected. However as the true value can lie anywhere within the uncertainty bar how should the results of measurements C and D be classified.

In the Pharmaceutical industry very few measurement processes have a calculated uncertainty. To overcome the problem associated with measurements C and D in the previous example a typical industry solution is to assign control limits to the process that are tighter than required by legislation. This would result in measurement C being classed as satisfactory and measurement D as rejected. Although the true value of measurement C may exceed the process upper control limit it would still be within the legal limits for the product. Measurement D would typically be tested using extra replicate samples and if the result was still as shown, the product would be rejected.

15.8 Understanding the measurement process

By performing an assessment of the measurement uncertainty it is possible to gain an improved understanding of the measurement process. By determining which of the effects has the greatest effect on the overall measurement uncertainty efforts at improving the process can be targeted. In the examples above the measurement repeatability of a balance can be improved by installing a balance with a better repeatability of measurement, temperature variation within the laboratory can be reduced and better quality glassware can be purchased. In the example of an operator failing to fully extract a sample this can be improved by operator training and an assessment of the operator using controlled samples.

16 References

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