PDA®
Parenteral Drug Association

Professional sampling in Quality Control Laboratories

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Agenda:

➢ **Responsibility of a QP**

➢ **Type of errors**

➢ **Sampling errors**

➢ **Samples purpose**

➢ **Sample size**

➢ **Sampling plan**

➢ **Sampling and documentation**

What is an error?

An error is defined as:

"The difference between the measured value and the actual value."

If two people use the same measuring instrument to perform the same test, it is not essential that they get the same results. There may arise a difference between their measurements.

This difference is referred to as an "ERROR".

The difference between the measured value and the true measurement value is composed of a systematic and a random element.

The systematic element can be determined by identification of its causes and their (constant) influences
eg. temperature.

The random element can be calculated from a sufficient number of single values by using statistical methods.

Type of errors

Consequently errors can be divided into two categories:

(1) Systematic Error

(2) Random Error

Systematic Error (determinate error)

Systematic errors (also called systematic bias) can be seen as reproducible inaccuracies that are consistently in the same direction. They are consistent and associated with faulty equipment or a flawed experiment design.

The error is reproducible and can be discovered and corrected.

Systematic Error (determinate error)

1) Instrument errors - failure to calibrate, degradation of parts in the instrument, power fluctuations, variation in temperature, etc.
Can be corrected by calibration or proper maintenance of instruments

2) Method errors - errors due to no ideal physical or chemical behavior - completeness and speed of reaction, interfering side reactions, **sampling problems**
Can be corrected with proper method development.

3) Personal errors - occur where measurements require judgment, result from prejudice, color acuity problems.
Can be minimized or eliminated with proper training and experience.

Random error

Random errors (also called unsystematic error, system noise or random variation) are statistical fluctuations (in either direction) in the measured data due to the precision limitations of the measurement device.

Random errors usually result from the experimenter's inability to take the same measurement in exactly the same way to get the exact same number.

You can't predict random error and these errors are usually unavoidable.

Example:

You measure the mass of a tablet three times using the same balance and get slightly different values:

57.452 mg, 57.454 mg, 57.453 mg

Propagation of uncertainty (or propagation of error)

Only a few physical parameters can be determinated directly, eg. temperature, weight or length.

Very often we are facing the situation that we need to measure two or more quantities, each with their individual uncertainties, and then combine the information from these quantities in order to come up with a final result.

This final result will contain errors from all quantities that were used.

$$D \quad\quad a \quad\quad C$$
$$b \quad\quad\quad b$$
$$A \quad\quad a \quad\quad B$$

Example:
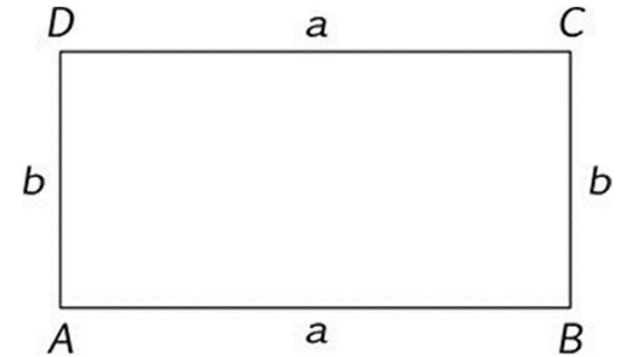
The surface of a rectangle can only be calculated by measuring the side length a and b and multiplication afterwards. *f = a*b*

Each measured result for side a and side b will include an individual error that is transmitted to the final result of the surface.

The more complex an analytical method is, the bigger the cumulated error will be.

Example:

Assay of Dexamethasone from an eye ointment by HPLC-method

Sample preparation is done by liquid extraction

Analytical method:
➢ isocratic elution
➢ reversed-Phase-coloum
➢ *external standard*

Process parameter with individual errors that will influence the final result

- weighing, pipetting
- dissolution in volumetric flask
- HPLC
- calculation

Standard solution 1:

<u>Acid 1:</u>	pipetting, dissolution	2x error
<u>Acid 2:</u>	pipetting, dissolution	2x error

Weight of sample taken + dissolution   2x error

<u>From this:</u>

1ml + acid 1 -> dissolution   2x error

Extraction:

Weighing of ointment, dissolution	2x error
Stirring 10 min in water bath (60°C)	1x error
Freeze for 15 min	1x error
Filtration to Erlenmeyer flask	
(repeat 2 times)	(3x error)
Final rinse and filling up	1x error

HPLC:

column	1x error
flow rate (pump)	1x error
detection (wave length)	1x error
injection volume	1x error

Over all you can find in total more than 20 sources of errors in this analytical method. The final result will be influenced by all of those.

Sampling and the main calculation are not included yet.

Sampling

Regulatory requirements for the sampling process are given in the EU-GMP guideline:[1]

EU-GMP-Guideline Part I, Chapter 6.11 to 6.14 „ Sampling"

EU-GMP-Guideline, Annex 8   „ Sampling of starting and packaging materials„

EU-GMP-Guideline Part II, Chapter   7.3:   Sampling and Testing of Incoming
                                              Production Materials
                              8.3:   In-process Sampling and Controls
                             11.7:   Reserve/Retention Samples

Sampling

Sampling defines the process of taking a representative portion of a material or product to test it.

The aim is to determine the quality or composition of a defined starting material.

There is the option to analyse single samples, to combine samples to a mixed sample or to divide a taken sample.

Overall objective is to generate a sample that is as meaningful as possible and representative for the total amount or the whole population.

Sampling in the pharmaceutical industry

During the sampling process of incoming goods you take a random sample of packaging materials, raw materials or finished goods.

All those samples serve as a basis for the testing in the quality control units.

The correct and professional sampling is an essential part of the quality control process because only representative and authentic samples will give an answer about the quality, condition or composition of the received materials.

Sampling errors will have a deep impact on the final result of the analytical testing and cannot be corrected later.

Sampling errors normally exceed the error of the following analytical testing.

They have to be taken into consideration when the result of the test is evaluated.

Sampling errors should not exceed three-quarters of the total error of the analysis.[2]

What is a sampling error?

A sampling error is a statistical error that occurs when an analyst does not select a sample that represents the entire population of data and the results found in the sample do not represent the results that would be obtained from the entire population.

Sampling error is the deviation of the selected sample from the true characteristics, traits, behaviors, qualities or figures of the entire population.

Why Does This Error Occur?

- A sampling process error occurs because analysts draw different subjects from the same population but still, the subjects have individual differences.

- Keep in mind that when you take a sample, it is only a subset of the entire population; therefore, there may be a difference between the sample and the population.
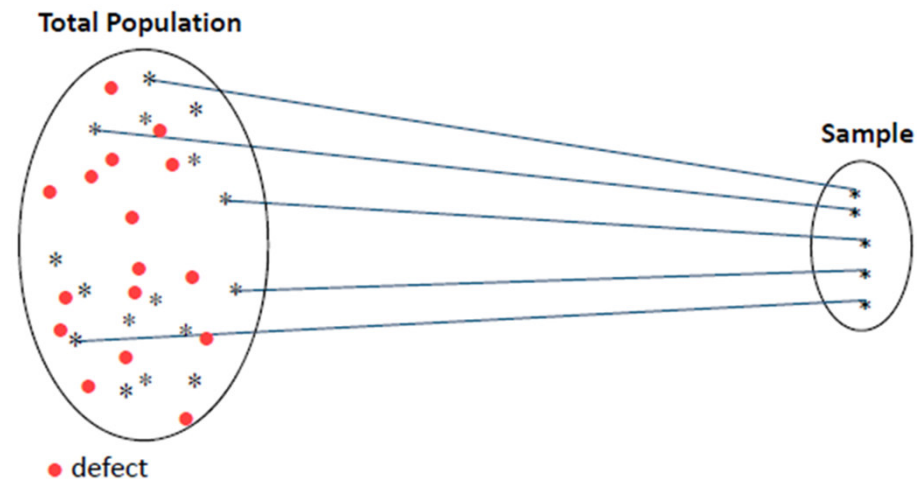
The sampling process comprises several stages:

- Defining the aim of your sampling and the population of concern

- Specifying a sampling method

- Determining the sample size

- Implementing the sampling plan

- Sampling and data collecting

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Main problem when preparing a sampling:

Without an explicit formulation of a question there cannot be a correct sampling.

You generate only data. [3]

Before you start sampling you have to define the aim of the test. Sampling must focus on this aim.

Example:

For illustration, consider a site map
for a dry lagoon formerly fed by a pipe.

The analytical results of soil samples
drawn from randomly located sites A, B,
and C may be representative if the objective is to address whether
the pipe has released a particular contaminant.

However, these data are not representative if the objective is to
estimate the average concentration level of the entire old lagoon. For
that estimation, random sampling locations should be generated from
the entire site of the old lagoon (for example, perhaps including
samples at D, E, and F).

Location of pipe

Area where output of pipe was expected to accumulate

Dry lagoon
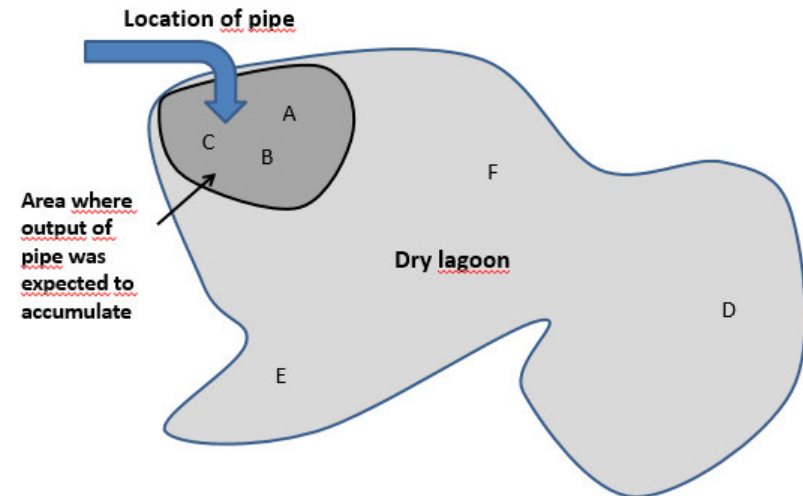
Example:

QC testing of incoming goods

Question:

How should I take a sample of a raw material container?

Should I take a sample from the surface (influence of Oxygen) or only a sample from a deeper layer?

What is the purpose of this sampling?

For a test of identity a sample from the surface layer would be ok.

A determination of the peroxide value would need a sample from a deep layer.

The sampling process comprises several stages:

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Different factors will influence the choice of the sample method

➢ Type and quality of sample material

➢ Access to additional information about the material (eg. certificates)

➢ Regulatory requirements about accuracy of sample method

➢ Type of analytical method (identity vs. assay)

➢ Economic factors (costs)

Normally you have to take the physical state of your component into account.

Within a QC testing of incoming goods you will be faced with each state of aggregation.

Solids: (API, plastic material)

Liquids: (excipiants, water)

Gases: (Nitrogen, pressurized air)

Also the way of shipment and the delivered amount can have an influence on your way of sampling and should be kept in mind.

Different types of sampling:

Targeted sample:

This is a risk-orientated sampling type. You take the sample at a location where you expect a contamination. This is the most sensible type of sampling if the aim is to detect illegal abuse (eg. drug screening test in urine or blood) .

Random sample:

Simple random sampling is the basic sampling technique in which each sample has an equal probability of being chosen. Each unit is chosen entirely by chance and each unit of the population has an equal chance of being included in the sample. A sample chosen randomly is meant to be an unbiased representation of the total population.

An excellent example of an incorrect random sample can be found in the **Literary Digest Desaster** which happened in 1936.[4]

In this case a distorted random sample provocated a totally wrong election forecast.

This mistake formed the basis for the development of new and modern systems for election forecasts and prognoses.

The Literary Digest was an influential American general interest weekly magazine.

Beginning with early issues, the emphasis was on opinion articles and on an analysis of news events. Established as a weekly news magazine, it offered condensations of articles from American, Canadian and European publications.

The Literary Digest was one of the most respected magazines of the time and had a history of accurately predicting the winners of presidential elections that dated back to 1916.

For the 1936 US presidential election, the Literary Digest conducted a poll to predict the winner of the election.

Alf Landon, the Republican Governor of Kansas, or the Democrate Franklin D. Roosevelt.

The magazine sent out more than 10 million straw vote ballots and over 2,3 million ballots were returned. An impressive number but representing less than a 25% participation rate.

On the basis of the returned ballots the Literary Digest's prediction was that Landon would get 57% of the vote against Roosevelt's 43%
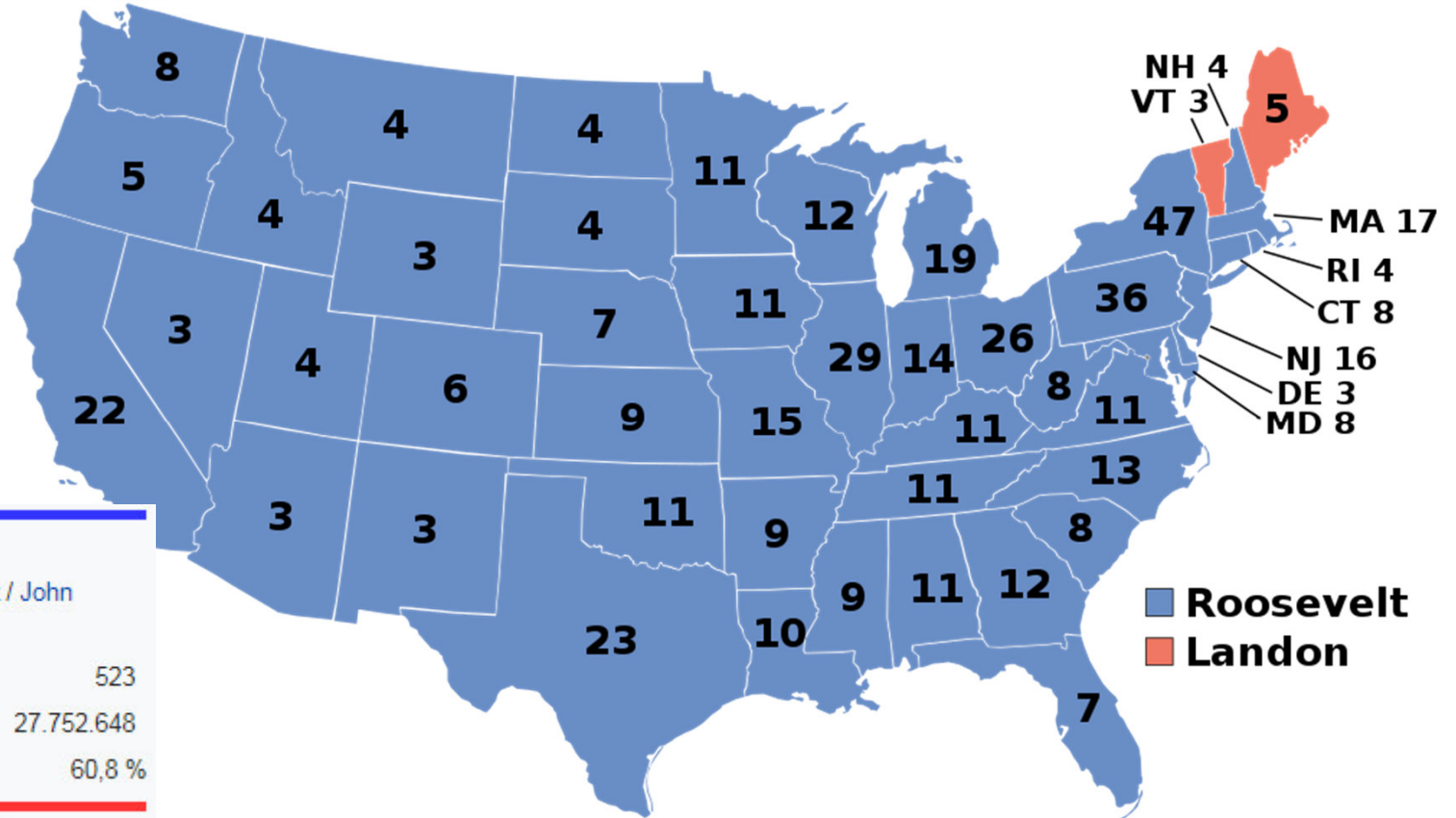
Demokratische Partei	
Franklin D. Roosevelt / John Nance Garner	
Wahlmänner	523
Stimmen	27.752.648
	60,8 %

Republikanische Partei	
Alf Landon / Frank Knox	
Wahlmänner	8
Stimmen	16.681.862
	36,5 %

■ Roosevelt
■ Landon

[5] Präsidentschaftswahl in den Vereinigten Staaten 1936

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What had happen?

The reason for this big discrepancy between election forecast and final result can be found in a typical sample error. Their sample, although large, was not representative of the population of voters.

The Literary Digest's poll had sampled voters by using telephone directories, magazine subscriber lists, and voter lists, primarily.

Own readers of the magazine were surveyed first, a group with disposable incomes well above the national average of the time, shown in part by their ability still to afford a magazine subscription during the depths of the Great Depression.

Also it was not recognized that registered automobile owners and telephone users were wealthier than the average American at the time.

The sampling process comprises several stages:

- Defining the aim of your sampling and the population of concern

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Sample size

Larger sample sizes generally lead to increased precision when estimating unknown parameters.

For example, if we wish to know the proportion of a certain species of fish that is infected with a pathogen, we would generally have a more precise estimate of this proportion if we sampled and examined 200 rather than 100 fish.

In some situations, the increase in precision for larger sample sizes is minimal, or even non-existent. This can result from the presence of systematic errors or strong dependence on the data, or if the data follows a heavy-tailed distribution.

Example: Environmental soil contamination

You take soil samples to detect
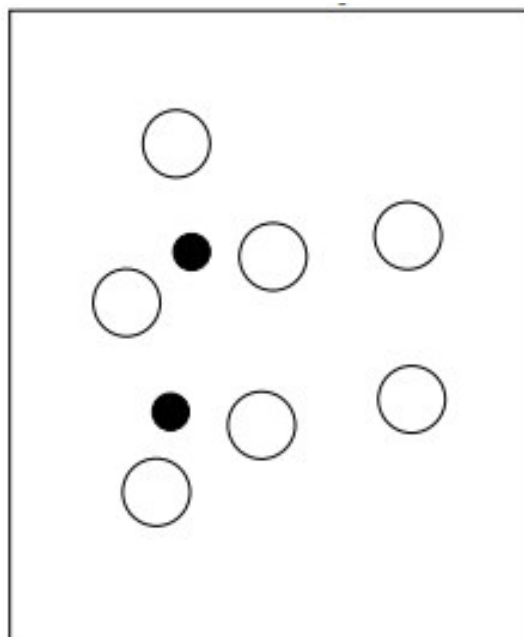an environmental pollution.
E.g. oil spillage in an agricultural area

The success of your investigation
depends on the sample size and
sample number
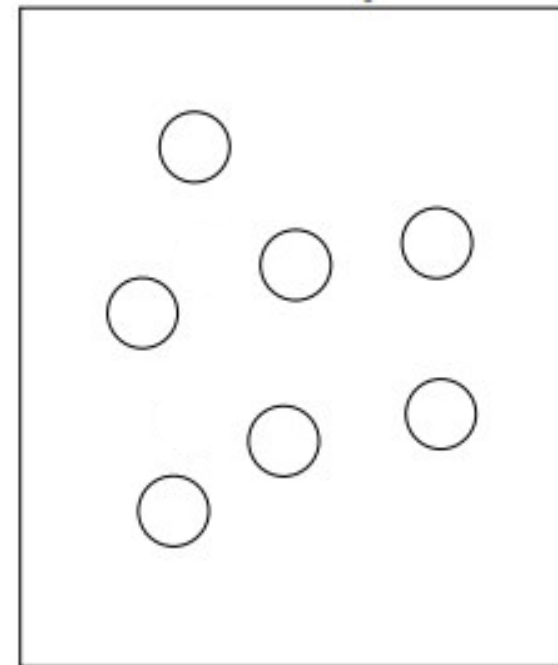
○　= location of sample points

Example: Environmental soil contamination

small "hot spots"   large "hot spots"
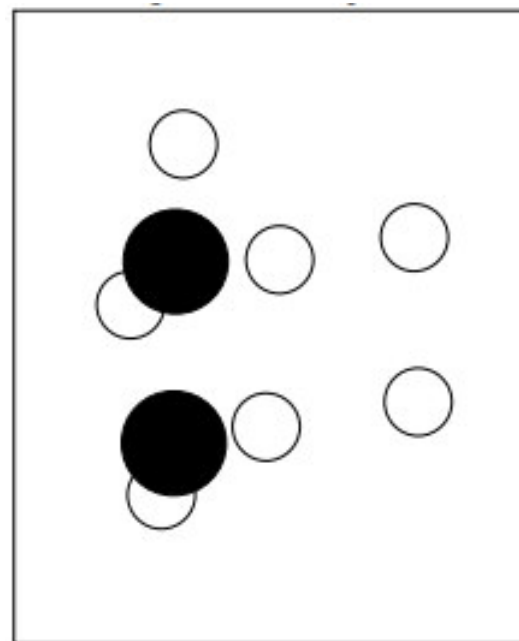
○ = sampling point   ● = "Hot spot" (contamination)

Example: Environmental soil contamination

low number of samples   high number of samples
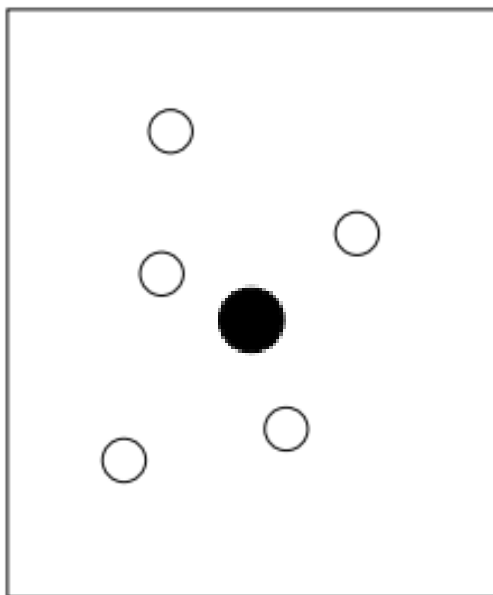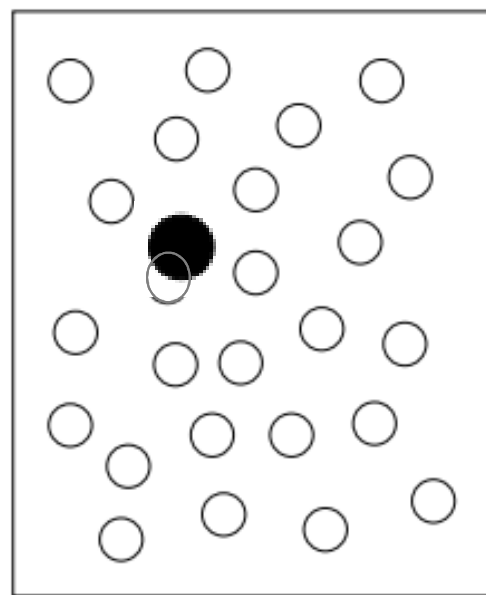
○ = sampling points   ● = "Hot spot" (contamination)

Sample size

Sampling errors can be eliminated when the sample size is increased and also by ensuring that the sample adequately represents the entire population.

Sample size

In quality control labs the sample size is often chosen by:

- experience in your production process

- statistical calculation

- standards and guidelines

Established general practice of sampling in QC labs:

Each container of incoming goods has to be checked for:

- integrity of container
- correct labeling
- identity of material

Material that is delivered in damaged containers should be rejected.

Material with missing label on container has to be rejected in each case.

Identity check:

EU GMP Guideline Part 1 Chapter 5.3

All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.

EU GMP Guideline Annex 8

2. The identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labelled.

Sample size

Determination of sample sizes can be done by using the

n, p, r - Plan of the WHO Guideline for starting materials [6]

Especally the number of units to be tested for a reduced identity check can be calculated.

Sample size

This WHO Guideline sampling plan is focusing on three different scenarios.

1. The sample is homogeneous and the material is purchased from a well known and qualified supplier. The main interest is the identity check.

2. The sample is not homogeneous and/or the supplier is unknown and/or an herbal medicinal product is used as starting materials

3. The sample is homogeneous and the material is purchased from a well known and qualified supplier. (reduced sampling plan)

n, p, r- plan

The number of units to be sampled depends on different assumptions and three possible plans

Table 1
Values of n, p or r for the N sampling units[a]

Value of n, p or r	Values of N		
	n plan	p plan	r plan
2	up to 3	up to 25	up to 2
3	4–6	26–56	3–4
4	7–13	57–100	5–7
5	14–20	101–156	8–11
6	21–30	157–225	12–16
7	31–42		17–22
8	43–56		23–28
9	57–72		29–36
10	73–90		37–44

p - plan

The "p plan" may be used when the material is uniform, is received from a recognized source and the main purpose is to test for identity.

The p plan is based on the formula $p = 0.4\sqrt{N}$, where N is the number of sampling units.

The figures for p are obtained by rounding up to the next highest integer.

According to this plan, samples are taken from each of the N sampling units of the consignment and placed in separate sample containers.

These original samples are transferred to the control laboratory, visually inspected and tested for identity. If the results are concordant, p final samples are formed by appropriate pooling of the original samples.

Example

Consider a consignment of 40 containers of a starting material.

Assuming a uniform material from a recognized source with the main purpose of checking the identity

Value of n, p or r	p plan
2	up to 25
3	26–56
4	57–100
5	101–156
6	157–225
7	
8	
9	
10	

Using the *p plan, samples would be taken from each container.*

The appearance and identity of each of these samples is checked. If the results are concordant, the samples are appropriately combined to form three final, composite samples to be used for retention (or full testing if required).

r - plan

The "r plan" may be used when the material is suspected of being non-uniform and/or is received from a source that is not well known. The r plan may also be used for herbal medicinal products used as starting materials.

The p plan is based on the formula r = 1.5 $\sqrt{N}$, where N is the number of sampling units.

The figures for r are obtained by rounding up to the next highest integer.

According to this plan, samples are taken from each of the N sampling units of the consignment and placed in separate sample containers.

r - plan

These original samples are transferred to the control laboratory and **each container** is tested for identity.

If the results are concordant, *r samples are randomly selected and* individually subjected to testing.

If these results are concordant, the *r* samples are combined for the retention sample.

Example

Consider a consignment of 20 containers of an herbal starting material.

Because it is an herbal excipient we have to assume that the material is not homogeneous.

Using the *r plan, samples would be taken from each container. The* appearance and identity of each of these samples is checked. If the results are concordant, 7 samples are selected at random and individually subjected to full testing.

Value of *n, p* or *r*	*r* plan
2	up to 2
3	3–4
4	5–7
5	8–11
6	12–16
7	17–22
8	23–28
9	29–36
10	37–44

n - plan

The "n plan" should be used with great caution and only when the material to be sampled is considered uniform and is supplied from a recognized source.

Samples can be withdrawn from any part of the container
(usually from the top layer).

The n plan is based on the formula n = 1 + √N, where N is the number of sampling units in the consignment .

A minimum number of containers needs to be sampled, e.g. if N is less than or equal to 4, then every container is sampled.

Note:
The n plan is not recommended for use by control laboratories of manufacturers who are required to analyse and release or reject each received consignment of the starting materials used to produce a drug product.

Example

Consider a consignment of 40 containers of a starting material.

Assuming a uniform material from a recognized source where there is a high degree of confidence in the source

Value of n, p or r	n plan
2	up to 3
3	4–6
4	7–13
5	14–20
6	21–30
7	31–42
8	43–56
9	57–72
10	73–90

Using the n plan, samples would be taken from seven containers selected at random. The appearance and identity of each of these seven samples is checked. If the results are concordant, the seven samples are combined to produce a single, composite sample from which an analytical sample is prepared for full testing.

Sample size

The procedure of sample size calculation should be standardized and defined in a special SOP.

Use of flow diagrams may be beneficial.

Probezug für die Untersuchungen im Labor

Anlage

Wareneingang

Wirkstoff? — Nein → Hilfsstoff? — Nein → Kunststoff-granulat? — Nein → fremdgefertigter Buk/FW? — Nein → Packmittel?

Wirkstoff? — Ja → Probe aus **jedem** Gebinde der Charge

Hilfsstoff? — Ja → Probe aus **jedem** oder $\sqrt{n} + 1$ Gebinde d. Charge

Kunststoffgranulat? — Ja → Probe aus $\sqrt{n} + 1$ Gebinden

fremdgefertigter Buk/FW? — Ja → Probe mitgeliefert?
- Nein → Probezug laut Anweisung
- Ja → Probe wird vom Lieferanten zusammen gestellt

Packmittel? — Ja → Probe mitgeliefert?
- Nein → Probezug laut Probezug-anweisung
- Ja → Probe wird vom Lieferanten zusammen gestellt

Sample size

If sampling is needed to evaluate a specific failure or damage, the sample size has to be calculated in a different way.

In those cases the Acceptable Quality Limit oder Acceptance Quality Limit (AQL) is the method of choice.

AQL is a standardized method that is often used in quality control laboratories to define a sufficient sample size and to specify individual acceptance criteria. [7]

AQL

Acceptance sampling was originally applied by the U.S. military for testing bullets during World War II. The dilemma was, if every bullet was tested in advance, no bullets would be able to be shipped on time.

If, on the other hand, no bullets were tested, malfunctions might occur on the battlefield, with potentially catastrophic results.

(We are facing exactly the same dilemma in the pharmaceutical industry during production of sterile pharmaceuticals)

AQL

The "AQL tables" are statistical tools at the disposal of buyers (for product inspections). They are an industry standard. Most suppliers involved in international trade are using it.

They help determine two key elements:

- How many samples should be picked and inspected among a batch of product or parts?

- Where is the limit between acceptability and refusal, when it comes to defective products?

How to determine the AQL value

- Identify the lot size

- Assess the inspection level

- Define the AQL level
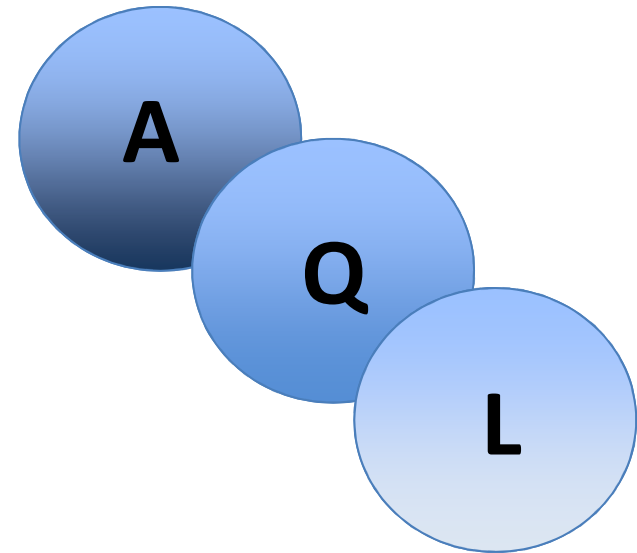
Determination of AQL values is discribed in DIN ISO 2859-1.

Inspection level

Three general and four special inspection levels are provided.

The general inspection levels (I to III) are commonly used for non-destructive inspection. Level II is considered the norm (except for small sample sizes).

Level I requires only 40 percent of inspection level II and can be used where less discrimination is needed.

Level III equals 160 percent of the amount of inspection Level II. Level III will give a lower risk of accepting a lot with an excessive number of defects. However, inspection of larger samples is required.

 Unless otherwise specified, inspection Level II will be used.

[7]

Inspection level

Special Levels S-1, S-2, S-3 and S-4 may be used where relatively small sample sizes are necessary or large sampling risks can be taken.

Examples of this are inspections involving destructive or costly (time consuming) types of inspection, or where large lots are involved, small sample sizes are desired and large risks can be tolerated such as repetitive processes (screw machine, stamping, bolting operations, etc.) performed by a quality supplier.

Larger sample sizes are for inspection levels increasing from S-1 to S-4.

Code letter for sample plan

The sample size will be determined by using a code letter.

To identify the correct code letter for the sample size, table 1 of DIN 2859-1 must be used.

[7]

Losumfang			Spezielle Prüfniveaus				Allgemeine Prüfniveaus		
			S-1	S-2	S-3	S-4	I	II	III
2	bis	8	A	A	A	A	A	A	B
9	bis	15	A	A	A	A	A	B	C
16	bis	25	A	A	B	B	B	C	D
26	bis	50	A	B	B	C	C	D	E
51	bis	90	B	B	C	C	C	E	F
91	bis	150	B	B	C	D	D	F	G
151	bis	280	B	C	D	E	E	G	H
281	bis	500	B	C	D	E	F	H	J
501	bis	1 200	C	C	E	F	G	J	K
1 201	bis	3 200	C	D	E	G	H	K	L
3 201	bis	10 000	C	D	F	G	J	L	M
10 001	bis	35 000	C	D	F	H	K	M	N
35 001	bis	150 000	D	E	G	J	L	N	P
150 001	bis	500 000	D	E	G	J	M	P	Q
500 001	und mehr		D	E	H	K	N	Q	R

[7] DIN ISO 2859-1

<u>Defect category:</u>

Each defect should generally be classified as either major, minor or critical. (The following definition can be seen as an example)

Critical – Any condition found which poses the possibility of causing injury or harm to, or otherwise endangering the life or safety of, the end user of the product or others in the immediate vicinity of its use.

An example of a critical defect might be a sharp plastic bur that has potential to scratch or otherwise harm people. The AQL (acceptable quality level) is generally 0.10 here so any critical defects noted would result in a rejected inspection.

Defect category:

Major – Any condition found adversely affecting the product's marketability and salability or adversely affecting its required form, fit or function and which is likely to result in the end user returning it to the source from which it was purchased for replacement or refund.

An example of a major defect might be a burn off loss in the plastic material of a plastic bottle. The AQL is generally tighter for major defects noted, so less is acceptable in a general sample size to achieve a passing result.

Defect category:

Minor – Any condition found which, while possibly less than desirable to the end user of the product, does not adversely affect its required marketability, salability, form, fit or function and is unlikely to result in its return to the source from which it was purchased.

An example of a minor defect might be a small scratch on the label of the product.

Defect category:

Defect category	AQL value
Critical	0,010
Major	0,015 – 0,1
Minor	> 0,1

<u>Acceptance criteria</u>:

By using the determined code letter and the defined AQL value an applicable acceptance criteria can be picked from table 2, 3 and 4 of the DIN.

Tabelle 2-A — Einfach-Stichprobenanweisungen für normale Prüfung (Leittabelle)

Annehmbare Qualitätsgrenzlage, AQL, in Anteil fehlerhafter Einheiten in Prozent und Anzahl Fehler je 100 Einheiten (normale Prüfung)

Legende der Zellwerte: jede AQL-Spalte enthält die Werte **Ac Re** (Annahmezahl / Rückweisezahl); Pfeile ↓/↑ siehe Fußnoten.

Kennbuchstabe für den Stichprobenumfang	Stichprobenumfang	0,010	0,015	0,025	0,040	0,065	0,10	0,15	0,25	0,40	0,65	1,0	1,5	2,5	4,0	6,5	10	15	25	40	65	100	150	250	400	650	1000
A	2	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31
B	3	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45
C	5	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45	↑
D	8	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45	↑	↑
E	13	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45	↑	↑	↑
F	20	↓	↓	↓	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑
G	32	↓	↓	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑
H	50	↓	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑
J	80	↓	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑
K	125	↓	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
L	200	↓	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
M	315	↓	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
N	500	↓	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
P	800	↓	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Q	1 250	0 1	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
R	2 000	↑	↓	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑

⇓ = Man wende die erste Stichprobenanweisung unter dem Pfeil an. Ist der Stichprobenumfang gleich dem Umfang des Prüfloses oder größer, wende man 100%-Prüfung an.
⇑ = Man wende die erste Stichprobenanweisung über dem Pfeil an.
Ac = Annahmezahl
Re = Rückweisezahl

[7] DIN ISO 2859-1

Example

Your manufacturing department has produced a lot of 100,000 eye drop units.
During QC inspection the following issue comes up.

You have to decide how to proceed with the batch.

Losumfang			Spezielle Prüfniveaus				Allgemeine Prüfniveaus		
			S-1	S-2	S-3	S-4	I	II	III
2	bis	8	A	A	A	A	A	A	B
9	bis	15	A	A	A	A	A	B	C
16	bis	25	A	A	B	B	B	C	D
26	bis	50	A	B	B	C	C	D	E
51	bis	90	B	B	C	C	C	E	F
91	bis	150	B	B	C	D	D	F	G
151	bis	280	B	C	D	E	E	G	H
281	bis	500	B	C	D	E	F	H	J
501	bis	1 200	C	C	E	F	G	J	K
1 201	bis	3 200	C	D	E	G	H	K	L
3 201	bis	10 000	C	D	F	G	J	L	M
10 001	bis	35 000	C	D	F	H	K	M	N
35 001	bis	150 000	D	E	G	J	L	N	P
150 001	bis	500 000	D	E	G	J	M	P	Q
500 001	und mehr		D	E	H	K	N	Q	R

[7] DIN ISO 2859-1

Tabelle 2-A — Einfach-Stichprobenanweisungen für normale Prüfung (Leittabelle)

Kenn-buchstabe für den Stichproben-umfang	Stichproben-umfang	Annehmbare Qualitätsgrenzlage, AQL, in Anteil fehlerhafter Einheiten in Prozent und Anzahl Fehler je 100 Einheiten (normale Prüfung)																								
		0,010	0,015	0,025	0,040	0,065	0,10	0,15	0,25	0,40	0,65	1,0	1,5	2,5	4,0	6,5	10	15	25	40	65	100	150	250	400	650	1 000
		Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re

⇓ = Man wende die erste Stichprobenanweisung unter dem Pfeil an. Ist der Stichprobenumfang gleich dem Umfang des Prüfloses oder größer, wende man 100%-Prüfung an.

⇑ = Man wende die erste Stichprobenanweisung über dem Pfeil an.

Ac = Annahmezahl

Re = Rückweisezahl

[7] DIN ISO 2859-1

Exemple

You have to draw 500 random samples and inspect them.

If you find 10 units or less with this failure you can release the batch.

If you find more than 10 samples showing the failure you have to reject it.

The sampling process comprises several stages:

- Defining the aim of your sampling and the population of concern

- Specifying a sampling method

- Determining the sample size

- Implementing the sampling plan

- Sampling and data collecting

Sampling plan

A sampling plan is a detailed outline of:

- which measurements will be taken at what times,
- on which material,
- in what manner, and
- by whom.

Sampling plans should be designed in such a way that the resulting data will contain a representative sample of the parameters of interest and allow for all questions, as stated in the goals, to be answered.
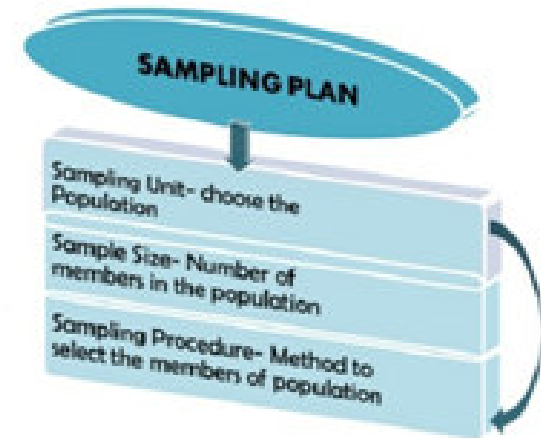
Sampling plan

The sampling plan for packaging materials should take account of at least the following:

- the quantity received,
- the quality required,
- the nature of the material (e.g. primary packaging materials and/or printed packaging materials),
- the production methods,
- and what is known of the Quality Assurance system of the packaging materials' manufacturer based on audits.

The number of samples taken should be determined statistically and specified in a sampling plan.

(Annex 8 – EU GMP Guideline)

The following points should be taken into account and must be defined in a SOP:

- personnel that is performing the sampling;
- sampling area;
- the method of sampling;
- the equipment to be used;
- the amount of the sample to be taken;
- instructions for any required sub-division of the sample;
- the type and condition of the sample container to be used;
- the identification of containers sampled;
- any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
- the storage conditions;
- instructions for the cleaning and storage of sampling equipment.

The sampling process comprises several stages:

- Defining the aim of your sampling and the population of concern

- Specifying a sampling method

- Determining the sample size

- Implementing the sampling plan

- Sampling and data collecting

Documentation

Documentation of sampling activities is done in a sampling protocol that should reflect all points that have been defined in the sampling plan.

In practice you will find often combined documents (sampling plan/sampling protocol) that are automatically created by the ERP-System (Enterprise-Resource-Planning eg. SAP) or the LIMS (Laboratory Information System) after material is booked by the receiving logistic department.

If special returning points are mentioned in a separate SOP it is not necessary to include them in each sampling plan or protocol.

In the pharmaceutical industry sampling is performed in all clean room areas (unclassified to class A)

| Sampling type	Material	Place	Requirement
incoming goods	raw materials	sampling cabinet	class C, laminar flow (LF)
	raw material (sterile)	micro lab, production	class A
	packaging material	warehouse, supplier	Unclassified
IPC	bulk, semi finished goods	production	class E-A
	finished product	production	class E
media	compressed air, nitrogen	utility rooms	unclassified

Qualified sampling requests specific requirements to the place where samples should be taken.

- The whole area must be clean, dry and dustless.

- A smooth surface structure allows a good and easy cleaning and disinfection (cave! material resistance)

- Temperature and humidity must be monitored and a sufficient ventilation must be assured.

- The working area is sufficiently illuminated

- Access to sampling areas is controlled.

Usually sampling cabinets are located directly in the warehouse where goods are received and no additional transport is needed.
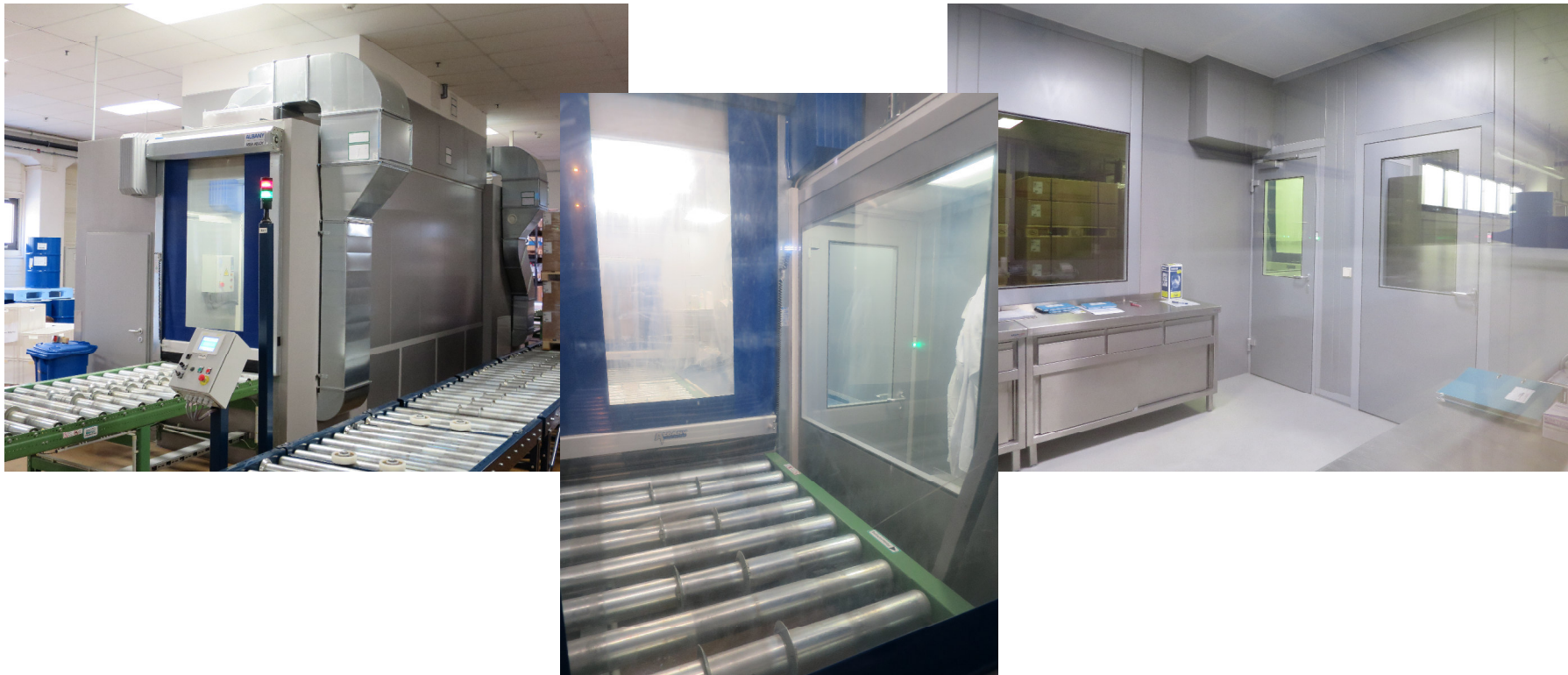
Example: Sampling cabinet is located in the warehouse
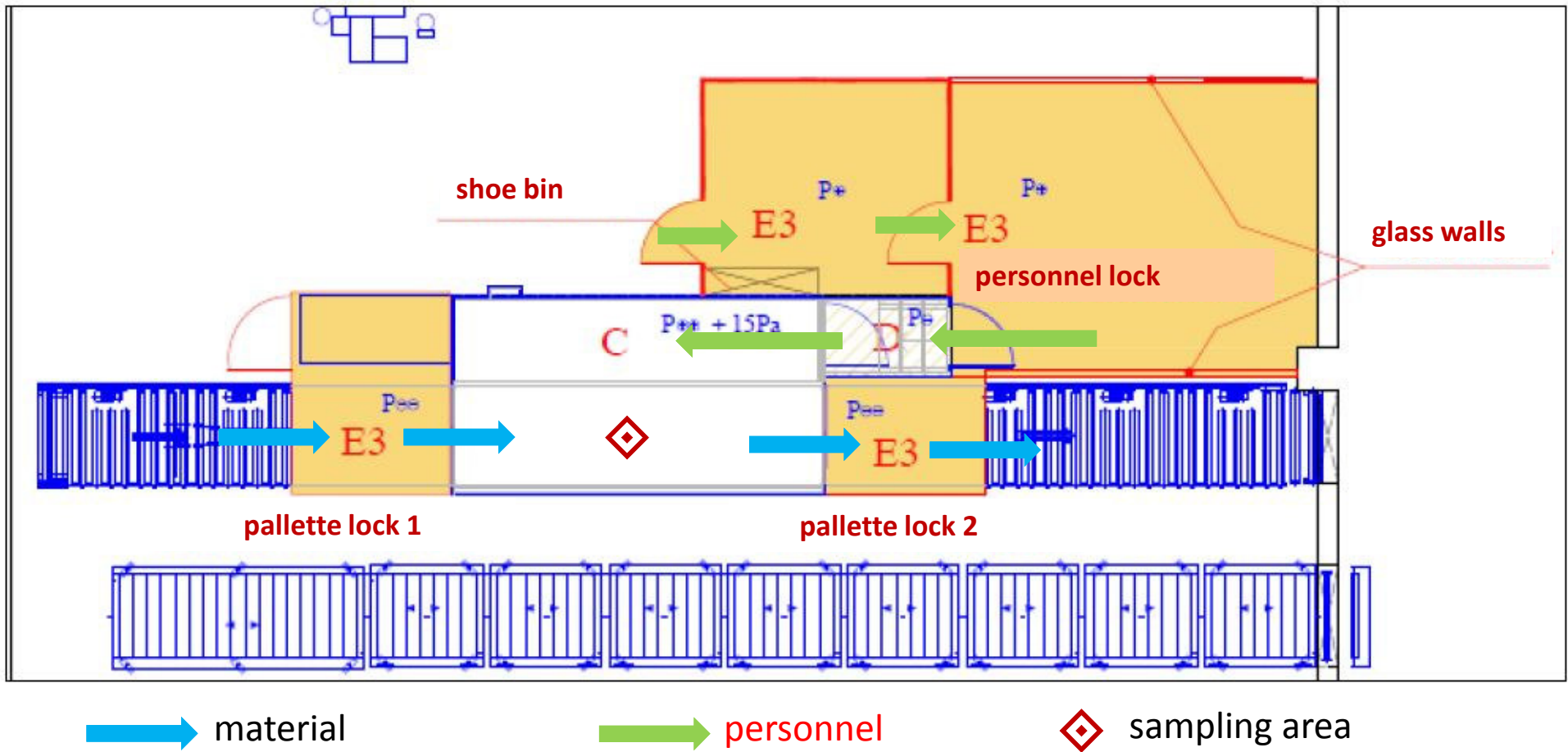
Sampling equipment:

Needed sampling equipment is based on the nature and condition of the sampling material.[6]

| material	Possible container	equipment
liquids	tank trucks, kegs, bottles...	liquid collectors
Bulk cargo (powder, granulates ...)	bags, barrels, big bags...	single and multi-zone-sampler, lances, spoons, shovels
semi-solid goods (ointment bases...)	barrels...	ladle, spoon, spatula
solid goods (tablets, capsulas...)	container, bags...	shovels, scoops, spoons, spatula

Sampling equipment - liquids

liquid receiver

plunging siphon

[8] Fa. Bürkle GmbH - www.buerkle.de

Sampling equipment - liquids
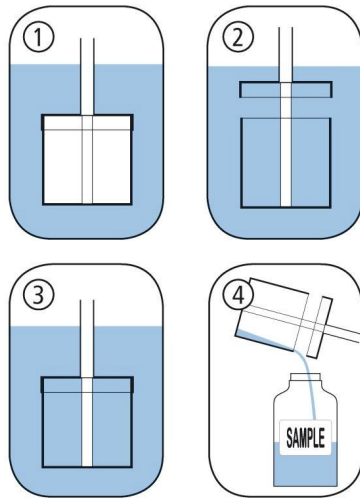
cup sampler

scoop

[8] Fa. Bürkle GmbH - www.buerkle.de

Sampling equipment – bulk material

zone-sampler

lance

[8] Fa. Bürkle GmbH - www.buerkle.de

Sampling equipment – bulk material

shovels

spoons

[8] Fa. Bürkle GmbH - www.buerkle.de

Sampling equipment

**plastic or glass wideneck
cans for powder or granulates**

**plastic or glas bottles for
liquids**

[8] Fa. Bürkle GmbH - www.buerkle.de

Sampling equipment

**plastic jars for solid and
semi-solid materials**

**sample bags (Steri bag)
for sterile samples**

[8] Fa. Bürkle GmbH - www.buerkle.de

Type, condition and identification of sample container

Sample containers should be adequate for the type of sample (size, material, closure…)

Sample containers should bear a label indicating:

- the contents,
- the batch number,
- the date of sampling and
- the containers from which samples have been drawn.

They should be managed in a manner to minimize the risk of mix-up and to protect the samples from adverse storage conditions.

Storage conditions

Segregated areas should be provided for the storage of
rejected, recalled or returned materials or products.

- Highly active materials or products should be stored in safe and secure areas.

- Printed packaging materials are considered critical to the conformity of the medicinal product and special attention should be paid to the safe and secure storage of these materials.

Storage conditions

Segregated areas should be provided for the storage of
rejected, recalled or returned materials or products.

- Highly active materials or products should be stored in safe and secure areas.

- Printed packaging materials are considered critical to the conformity of the medicinal product and special attention should be paid to the safe and secure storage of these materials.

Storage conditions

- Collected samples should be packed, transported, and stored in a manner that prevents any deterioration, contamination, or adulteration.

- Samples should be stored in accordance with the manufacturer's recommended storage instructions for the respective drug.

- Closures and labels should be tamper evident, that is, of such a type that unauthorized opening can be detected.

- When opening a sample container, the analyst or the person who opens it must date and initial it.

Personnel

Personnel who take samples should receive initial and on-going regular training in the disciplines relevant to correct sampling.

This training should include:

- sampling plans,
- written sampling procedures,
- the techniques and equipment for sampling,
- the risks of cross-contamination,
- the precautions to be taken with regard to unstable and/or sterile substances,
- the importance of considering the visual appearance of materials, containers and labels,
- the importance of recording any unexpected or unusual circumstances.

References:

[1] EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and
    Veterinary Use

[2] Analytische Chemie - Matthias Otto, Wiley-VCH Verlag GmbH & Co. KGaA

[3] Akkreditierung und Qualitätssicherung in der Analytischen Chemie –
    Prof. Dr. H. Günzler, Springer; Auflage: 1994

[4] Literary Digest Desaster - Marktforschungs-Wiki, abgerufen am 02.07.2017

[5] Präsidentschaftswahl in den Vereinigten Staaten 1936 – Wikipedia, abgerufen am
    02.07.2017

[6] World Health Organization WHO Technical Report Series, No. 929, 2005,
    Annex 4-WHO guidelines for sampling of pharmaceutical products and
    related materials

[7] DIN ISO 2859-1 "Annahmestichprobenprüfung anhand der Anzahl fehlerhafter
    Einheiten oder Fehler (Attributprüfung) – Teil 1: Nach der annehmbaren Qualitätslage
    (AQL) geordnete Stichprobenpläne für die Prüfung einer Serie von Losen

[8] Fa. Bürkle GmbH - www.buerkle.de

Guidelines and standards:

Richtlinie 2003/94/EG zur Festlegung der Grundsätze und Leitlinien der Guten Herstellungspraxis für Humanarzneimittel und für zur Anwendung beim Menschen bestimmte Prüfpräparate

EU-GMP-Leitfaden Teil I, Kapitel 6 „ Probenahme"

EU-GMP-Leitfaden, Annex 8 „Ergänzende Leitlinie für die Probenahme von Ausgangsstoffen und Verpackungsmaterial „

EU-GMP-Leitfaden Teil II, Kapitel 7.3: Probenahme und Prüfung eingehender Materialien für die Produktion

8.3: Inprozessprobenahme und –kontrollen

11.7: Rückhalte-/Rückstellmuster

World Health Organization WHO - Technical Report Series, No. 929, 2005,
Annex 4-WHO guidelines for sampling of pharmaceutical products and related materials

DIN ISO 2859-1 "Annahmestichprobenprüfung anhand der Anzahl fehlerhafter Einheiten oder Fehler (Attributprüfung) – Teil 1: Nach der annehmbaren Qualitätslage (AQL) geordnete Stichprobenpläne für die Prüfung einer Serie von Losen

Thank you for your attention