SADCWater PT Chemistry workshop 2018 – Part 2: Quality Control Charts

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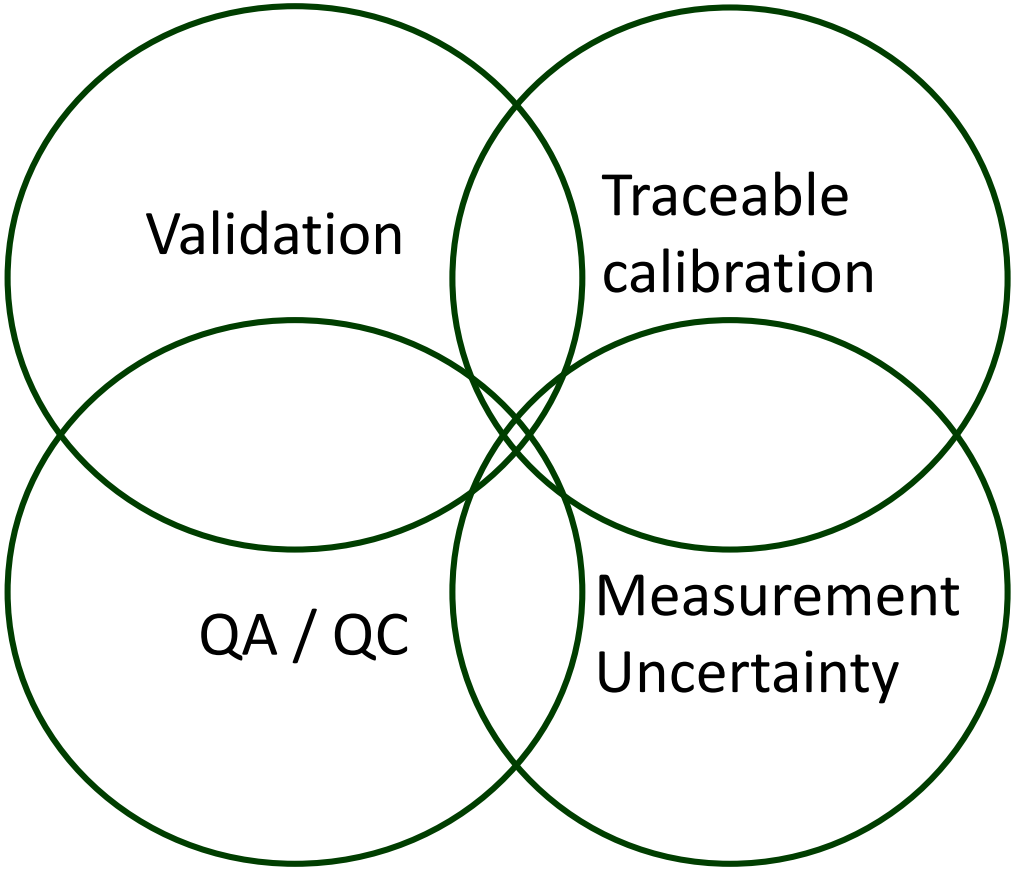
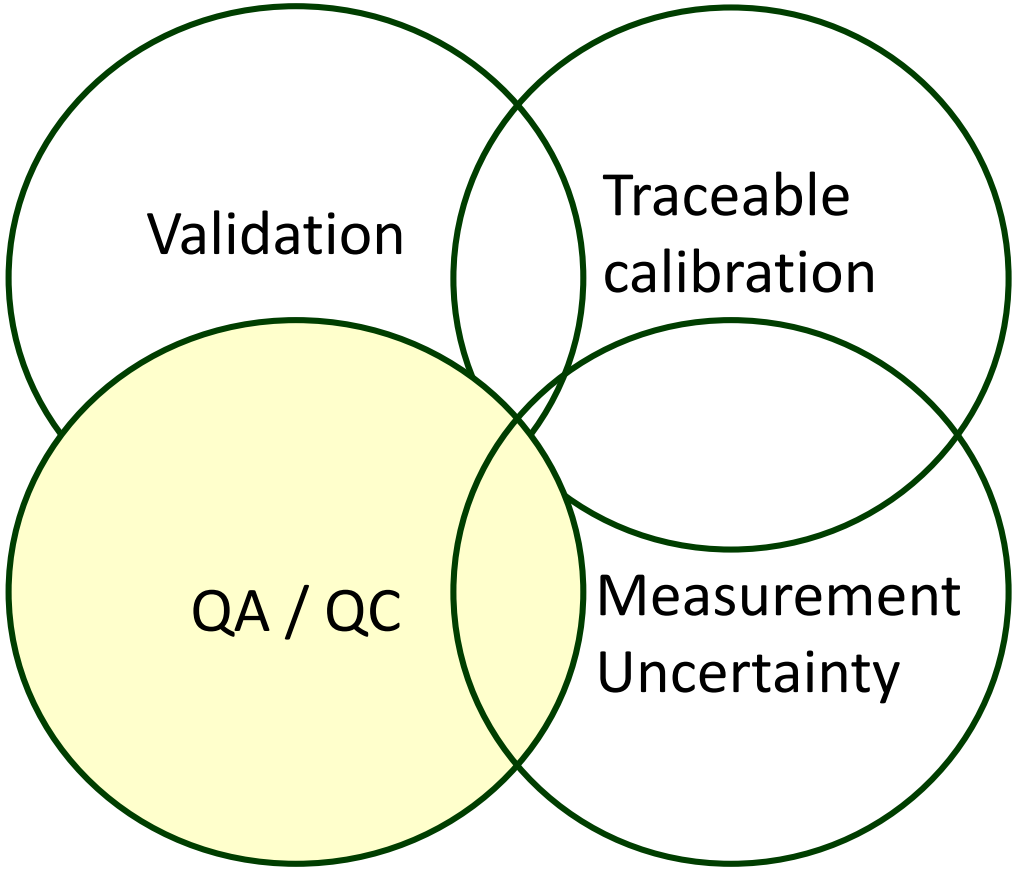
26-27 November 2018

Ensuring valid Analytical Measurements



Ensuring valid Analytical Measurements



Overview

- General concepts and statistical background
- Type of control charts
- Quality control samples
  - Types
  - Requirements
  - Advantages & Disadvantages
- Setting up an Internal Quality control program
  - Setting control limits
- Evaluation of Quality control charts

Introduction: Quality control

- Quality control program
  - Measures to ensure that a validated method remains “in control”
  - Continuous evaluation of laboratory’s methods and working routines
  - Cover the complete analytical process:
    - Physical sample preparation, e.g. drying, milling, etc.
    - Chemical sample preparation, e.g. digestion, extraction, dilution, etc.
    - Analysis, e.g. wet chemistry, instrumental analysis
    - Reporting

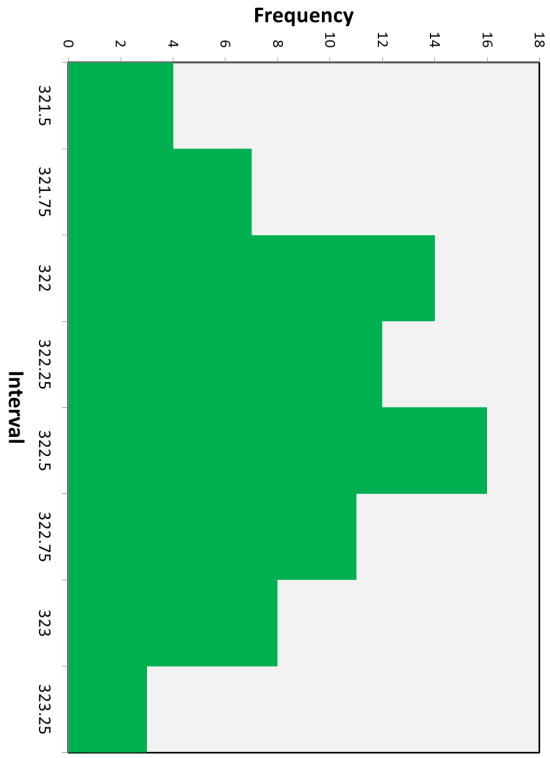
Laboratory Quality control

- External quality control
  - Proficiency testing
    - Reproducibility & Bias checks
- Internal quality control
  - Statistical process control (SPC) charts: Used for daily quality control of routine analytical work
    - Simple graphical tools
    - Very powerful - changes in quality can be detected quickly
  - Monitors:
    - Bias
    - Within Laboratory Reproducibility
    - Repeatability

Statistical basis for QC

Repeated measurements

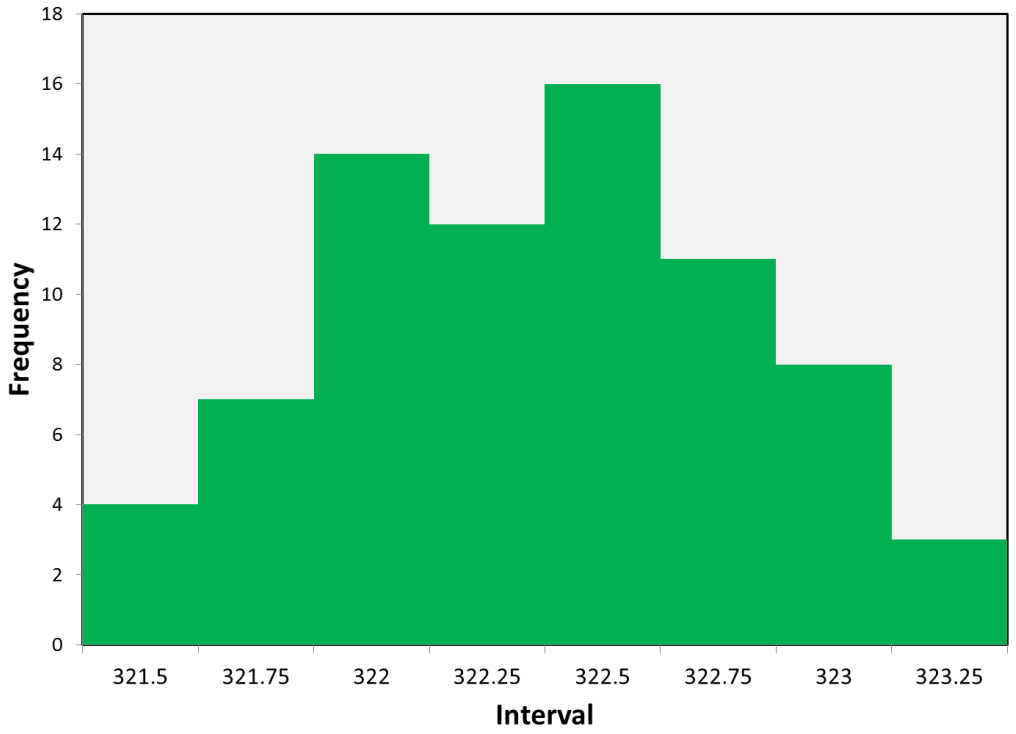
322,23	321,68	1
322,49	321,75	
322,18	321,76	3
322,07	321,97	
321,67	322,07	
321,76	322,17	4
321,75	322,18	
322,17	322,23	
322,56	322,36	
321,68	322,40	3
322,36	322,49	
322,40	322,56	1



Statistical basis for QC

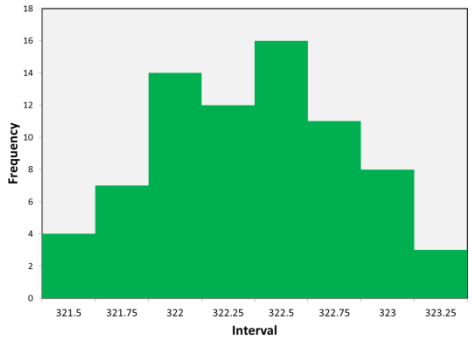
Variations are always present.

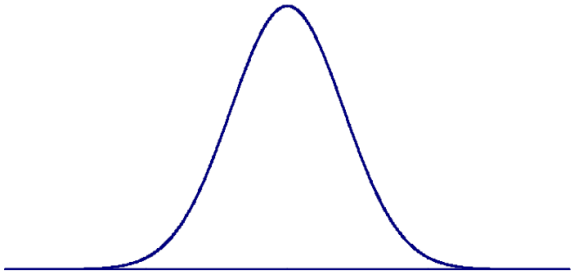
322,23
322,49
322,18
322,07
321,67
321,76
321,75
322,17
322,56
321,68
322,36
322,40



Population vs. Sample

Sample	Population
A selection of 1000 inhabitants of a town	All inhabitants of a town
Any number of measurements of salinity in samples from the Indian Ocean	*Not possible*

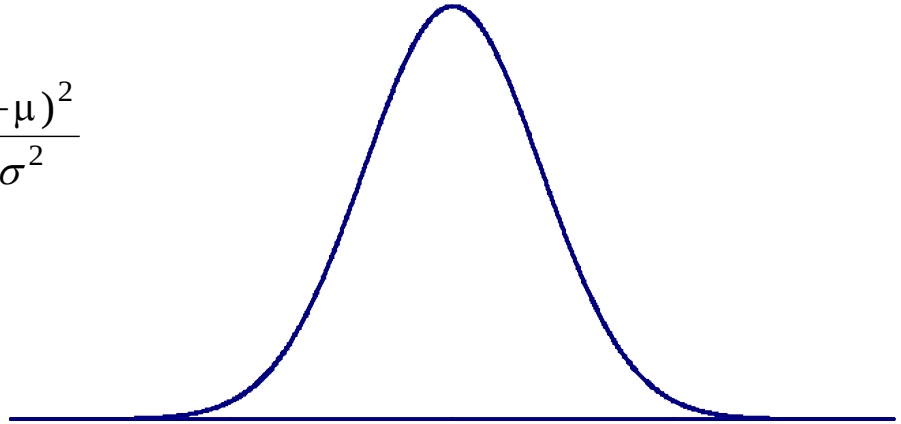




Normal Distribution

- The curve is symmetrical about μ
- The greater the value of σ the greater the spread of the curve
- Completely determined by μ and σ

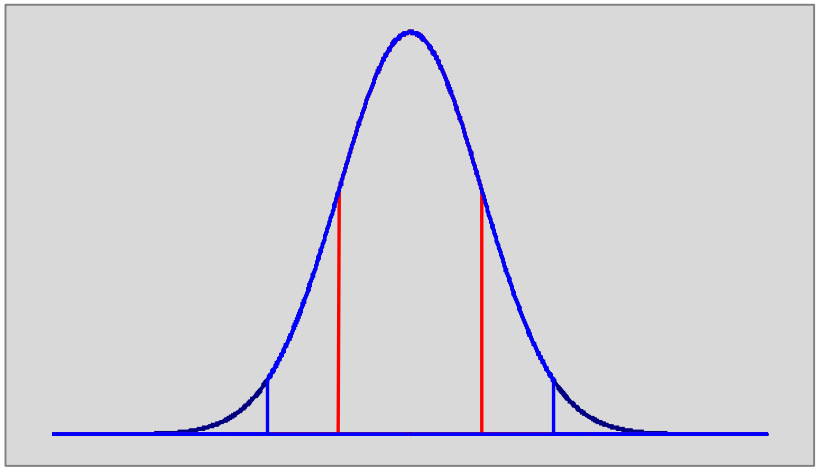
$$y = \frac{1}{\sigma\sqrt{2\pi}} e^{\frac{(x-\mu)^2}{2\sigma^2}}$$



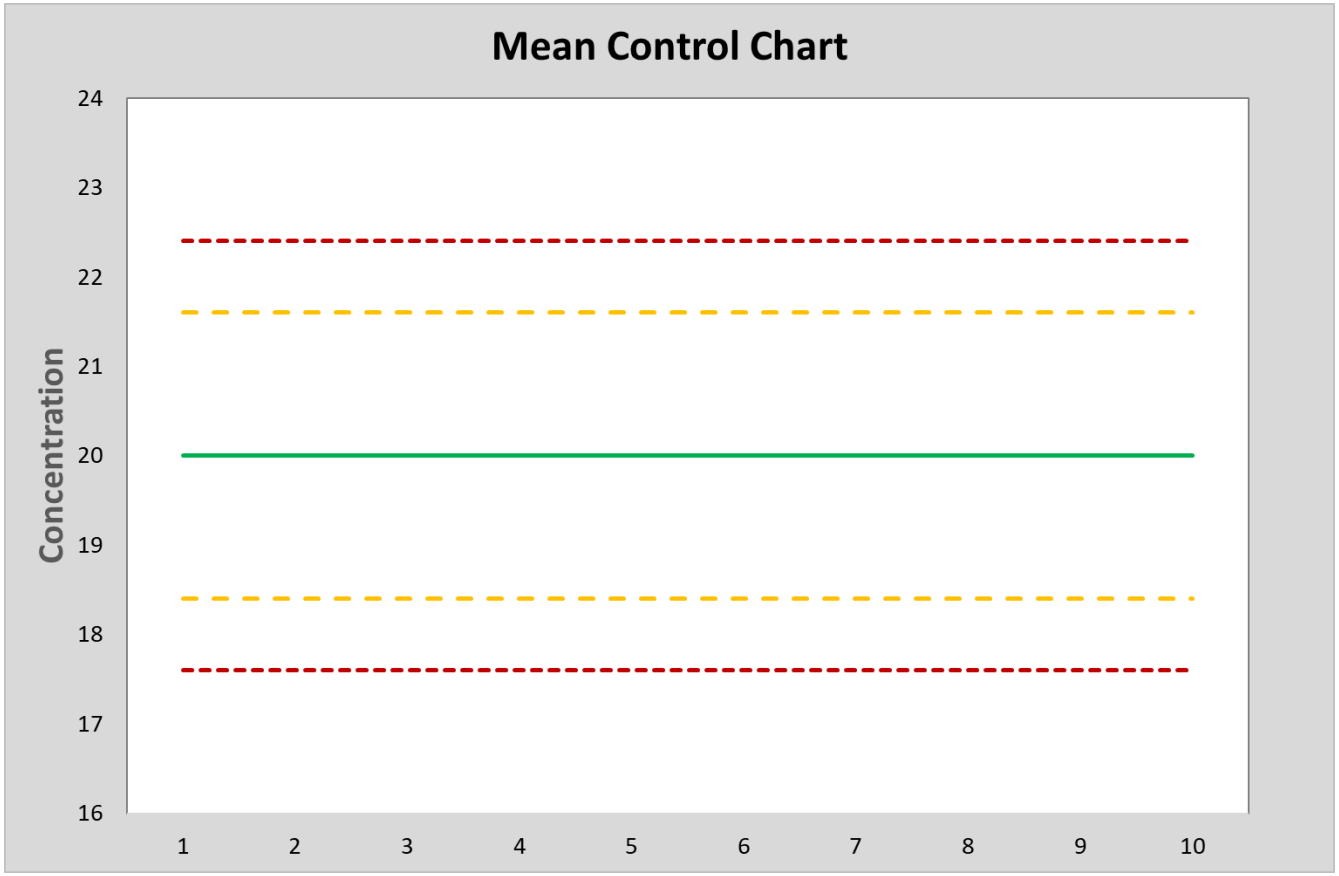
Normal Distribution

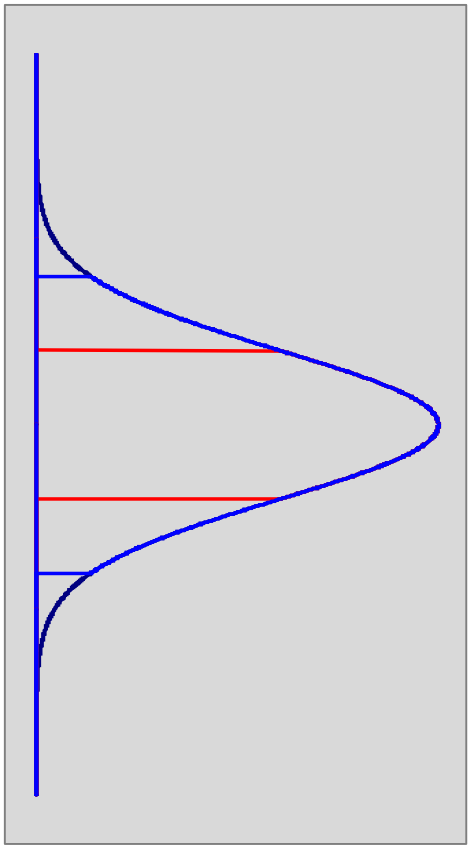
Important Properties

- Approximately 68% (68,27%) of the data lie within $\mu \pm 1\sigma$
- Approximately 95 % (95,45%) of the data lie within $\mu \pm 2\sigma$
- Approximately 99,7 % (99,73%) of the data lie within $\mu \pm 3\sigma$



Control Charts: General Concepts





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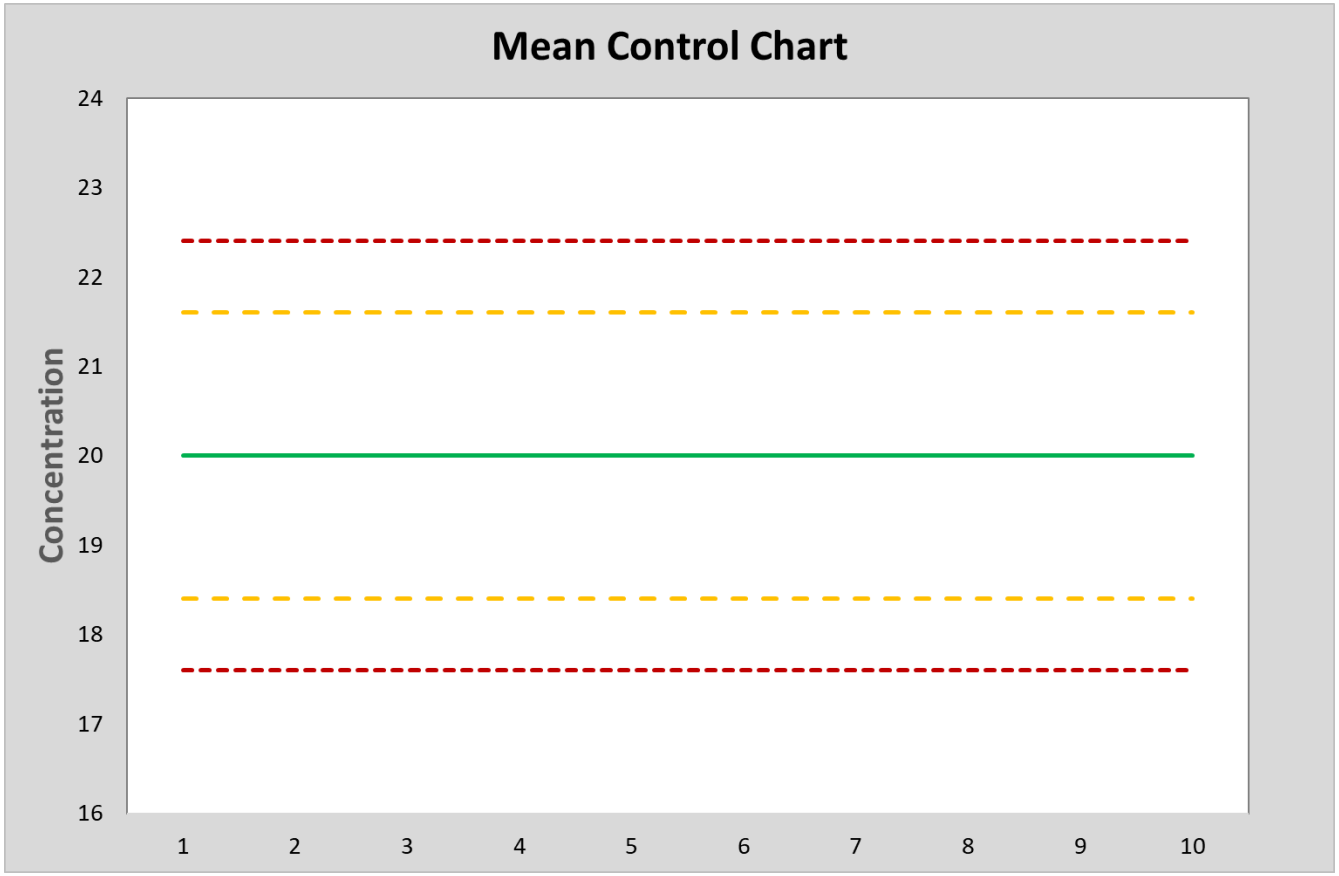


Upper Action Limit

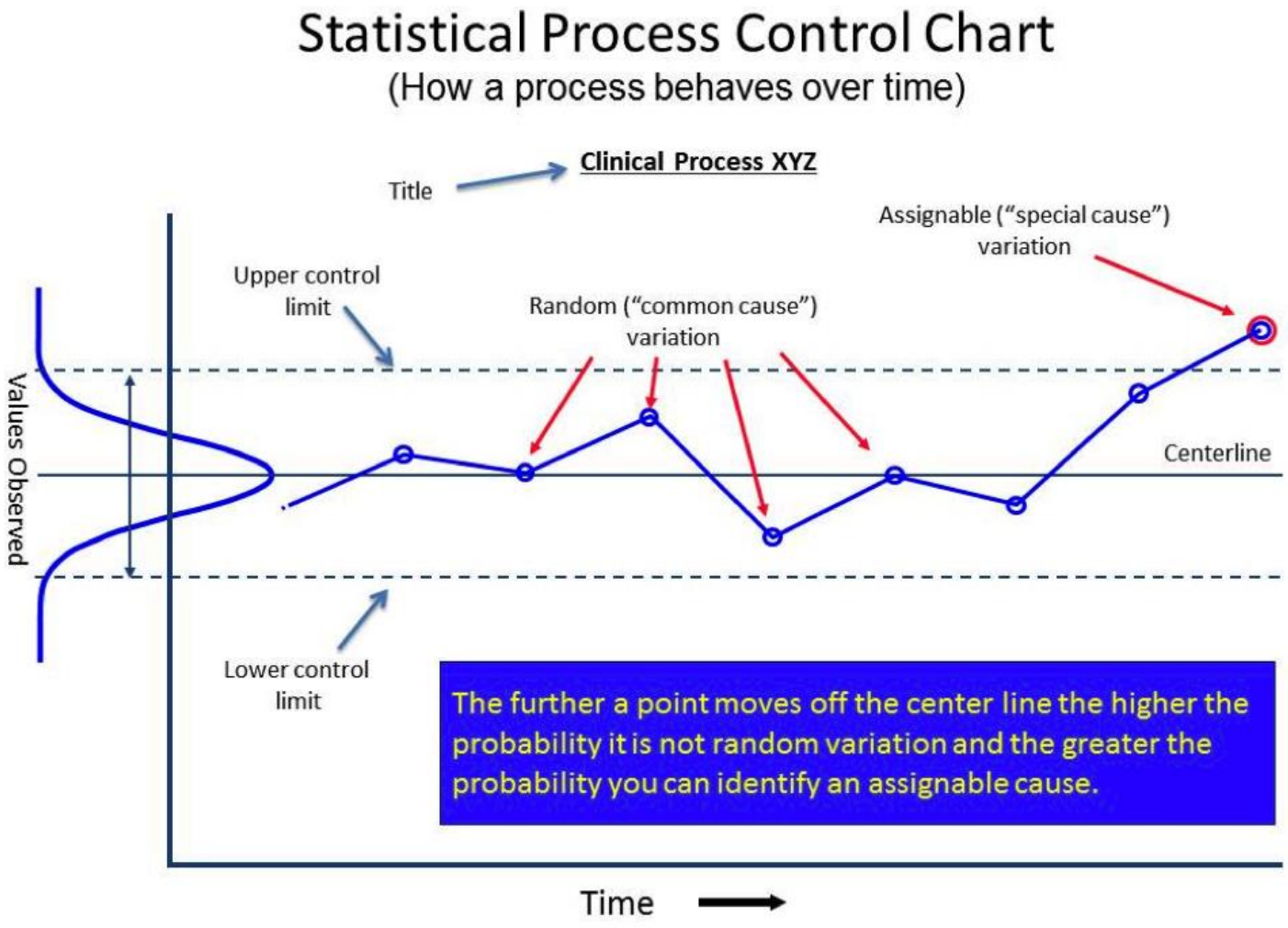
Upper Warning Limit

Target value

Lower Warning Limit

Lower Action Limit

Control Charts: General Concepts

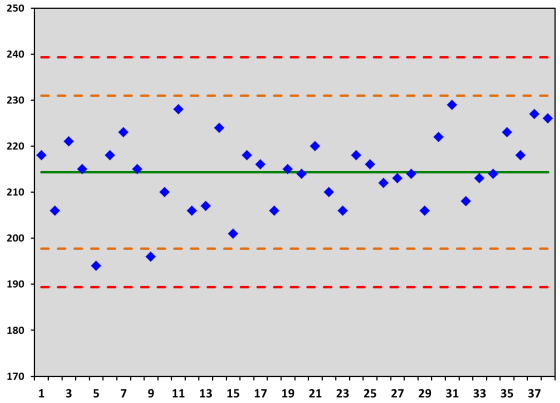


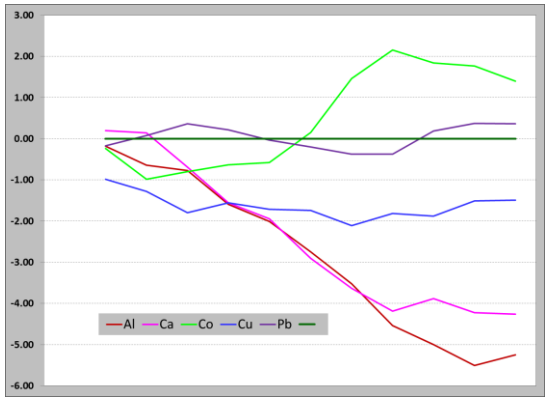
Control Charts - General concepts

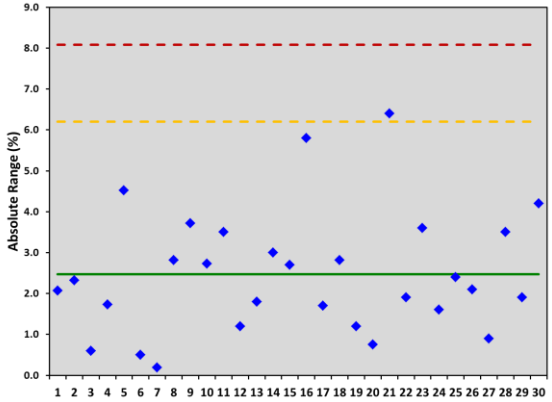
- Displays results vs. time
- Target value / Central line (CL)
  - Mean
  - Reference value
- Control Limits
  - Warning limit
    - Upper and Lower: CL ± 2s
    - 95 % of results should be within this limit, i.e. 5% of correct results can be expected to exceed this limit
  - Action Limit
    - Upper and Lower: CL ± 3s
    - 99.7 % of results should be within this limit, i.e. only 0.3% of correct results can be expected to exceed this limit – very unlikely

Types of Control Charts

- X-chart (Shewart / Mean control chart)
- Range-chart (R or r%)
- Cumulative charts



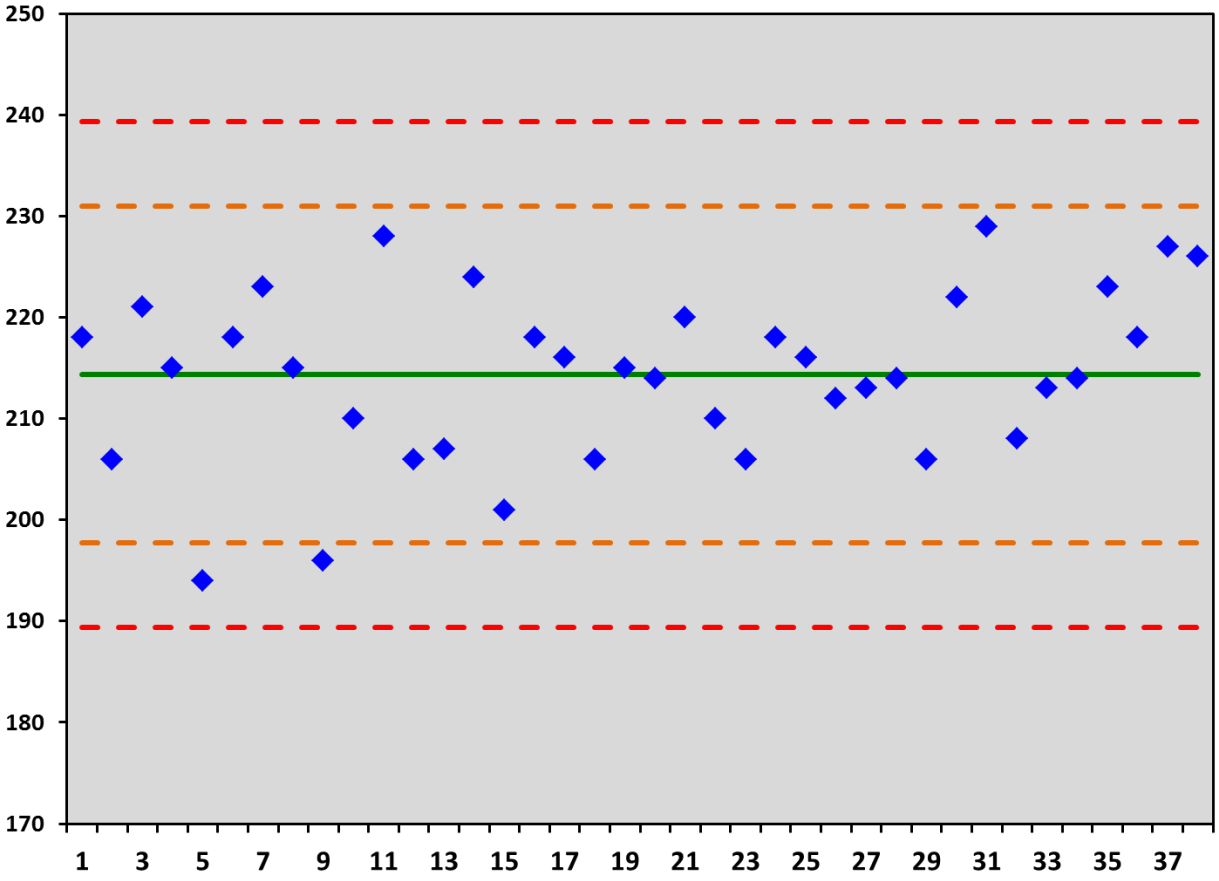




Mean / X-control chart

- Characterised by mean, upper and lower warning and control limits
  - Shows distribution of control values around a central value (mean or reference value)
  - Monitor systematic and random effects
- Control samples
  - Reference material (CRM / RM)
  - Test sample / Inhouse control sample
  - Blank
    - Reagent blank
    - Sample matrix blank
  - Standard solution

Mean Control Chart



- **Action limit:**

  Mean ± 3s

- **Warning limit:**

  Mean ± 2s

- **Central line:**

  Mean

Mean / X-control chart

- QC information available from X-control charts
  - QC / CRM sample
    - Intermediate precision
    - Changes in systematic error
    - Trueness (if CRM is used)
  - Blank
    - Reagents
    - Potential environmental contamination

Range Control Chart

- Monitors repeatability
- Range = Difference (Max-Min) of replicate analysis of randomly selected test samples
  - Typically proportional to concentration (at levels above LOD/LOQ)
  - At levels close to LOD/LOQ, range no longer proportional to concentration so recommended to use absolute range
- Characterised by central line and upper warning and control limits
- Important to perform same number of measurements for test samples as for control samples

Range Control Chart

- Real samples analysed in duplicate/triplicate/ etc.
- Calculate
  - %Absolute Range
  - Mean %Range
  - Standard deviation

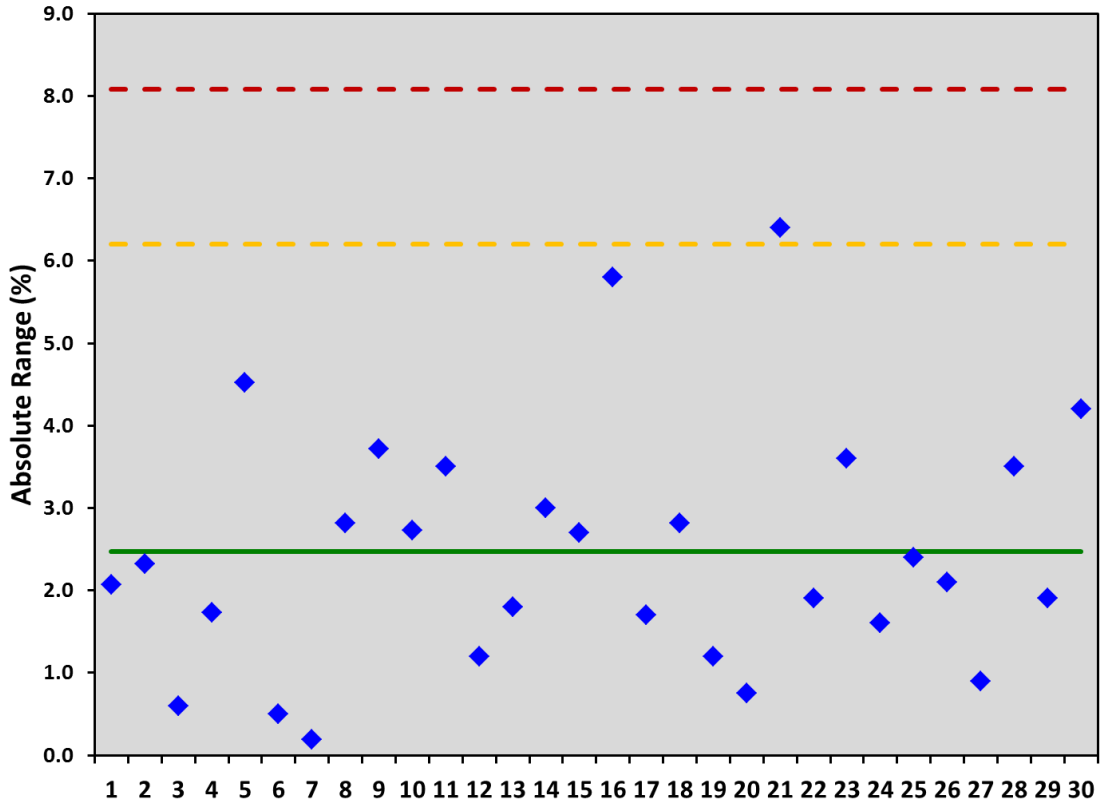
$$\%Range(i) = \frac{Max - Min}{Mean} \times 100$$

$$s = \frac{MeanRange}{d_2}$$

Number of replicate measurements (n)	d_2
2	1.128
3	1.693
4	2.059
5	2.326

Range Control Charts

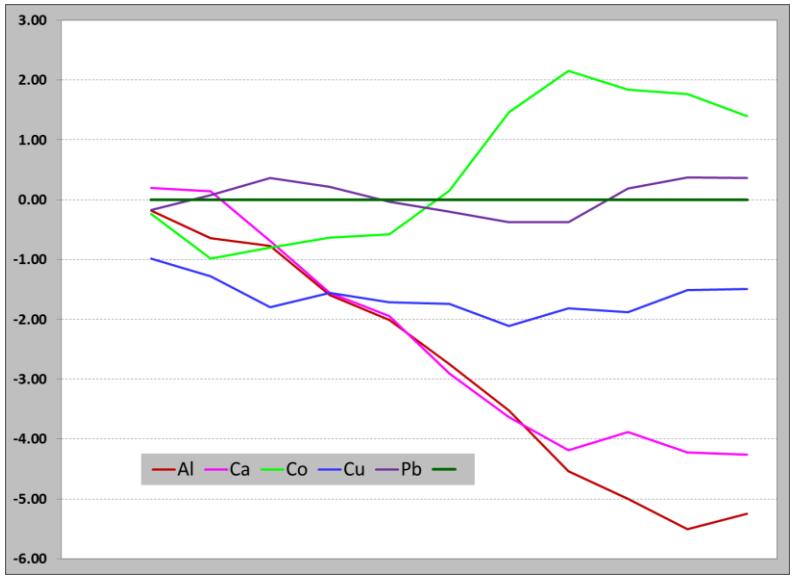
- Replicate analysis of routine test samples



- **Action limit:**
  Mean ± 3.69s
- **Warning limit:**
  Mean ± 2.83s
- **Central line:**
  Mean Range

Control Charts

- CUSUM chart
  - Cumulative sum of all errors from one target value
    - Difference between target value and measurement result is added to the sum of all the previous differences
  - Faster detection of change in process
  - Can identify point at which process went out of control



Quality Control samples

- Requirements:
  - Ideally control sample should go through the whole measurement procedure
  - Should be representative of typical samples, i.e. must be similar in matrix and concentration to test samples
  - Homogeneous
  - Sufficient quantities (more than a year)
  - Stable / Long term stability

Type of Quality control samples

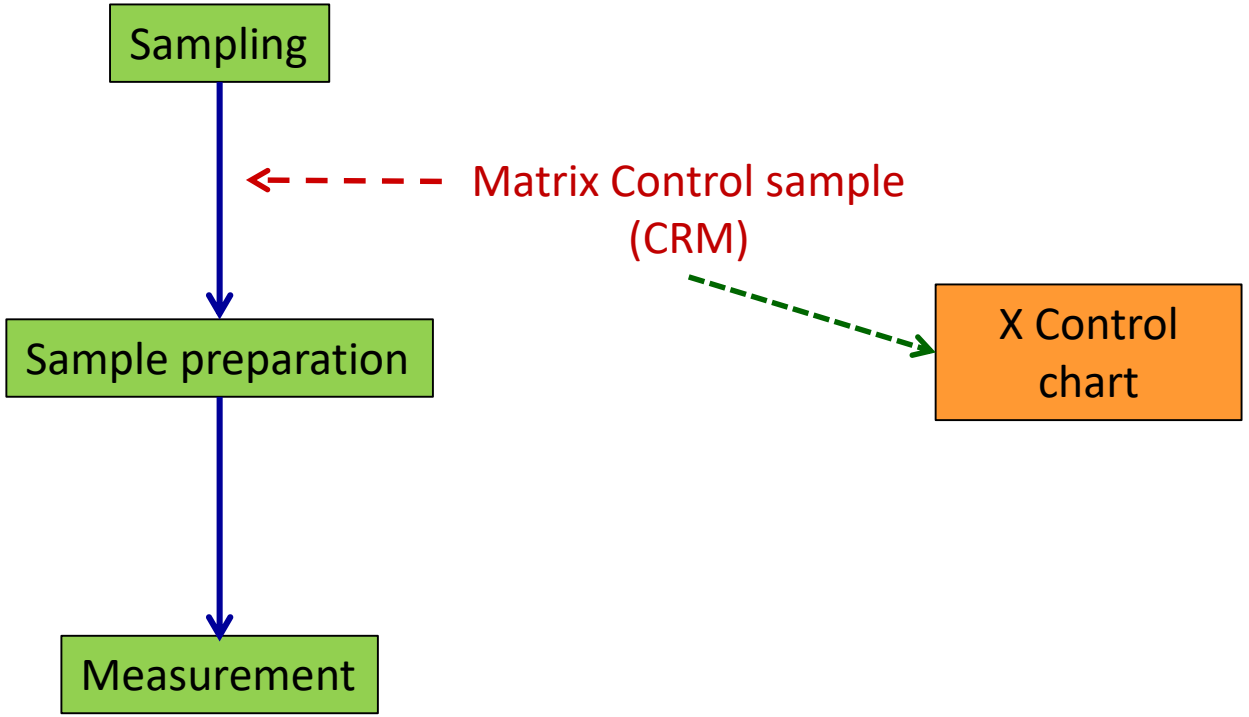
- CRM: Certified reference material
- RM: Reference material
- Standard solutions / appropriate calibration material
- In-house control sample
- Test samples
  - Replicate analysis of routine test samples
- Blank samples
  - Standard / Reagent blank
  - Matrix blank

Control sample type I: Matrix CRM

- Pro's
  - Excellent way to monitor for Bias (systematic effect)
  - Stability and homogeneity is guaranteed
  - Control data can be used to determine uncertainty
- Con's
  - Homogeneity of CRMs are often better than test samples' homogeneity, so will tend to give an overly optimistic estimate of within laboratory reproducibility
  - Very difficult to closely match matrix and analyte concentration
  - Expensive
- Mean control chart

Control chart vs Laboratory Process

- Control sample covering the whole analytical process

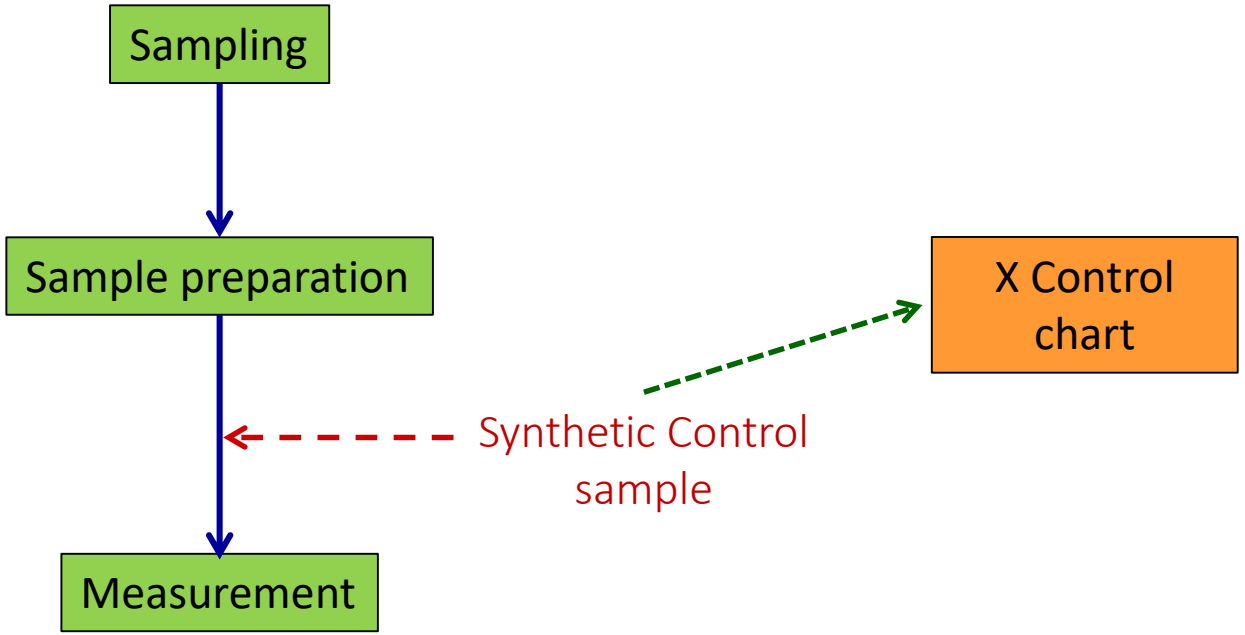


Control sample type II:

- Standard Solutions prepared by the laboratory
  - Prepared from pure standards / chemicals and solvents
  - Critical that different source of traceability
    - Different manufacturer
    - K-salt instead of Na-salt (e.g. NO_3 standard)
  - Expanded Uncertainty should not be more than 20 to 25% of target standard deviation of control chart
- Pro's:
  - Easy to prepare and readily available
  - Effective approach to monitor Bias (systematic effect)
- Con's
  - Depending on method, only partially monitors within laboratory reproducibility / repeatability (doesn't cover the complete analytical process)
- Mean control chart

Control chart vs Laboratory Process

- Control sample not covering the whole process, matrix different

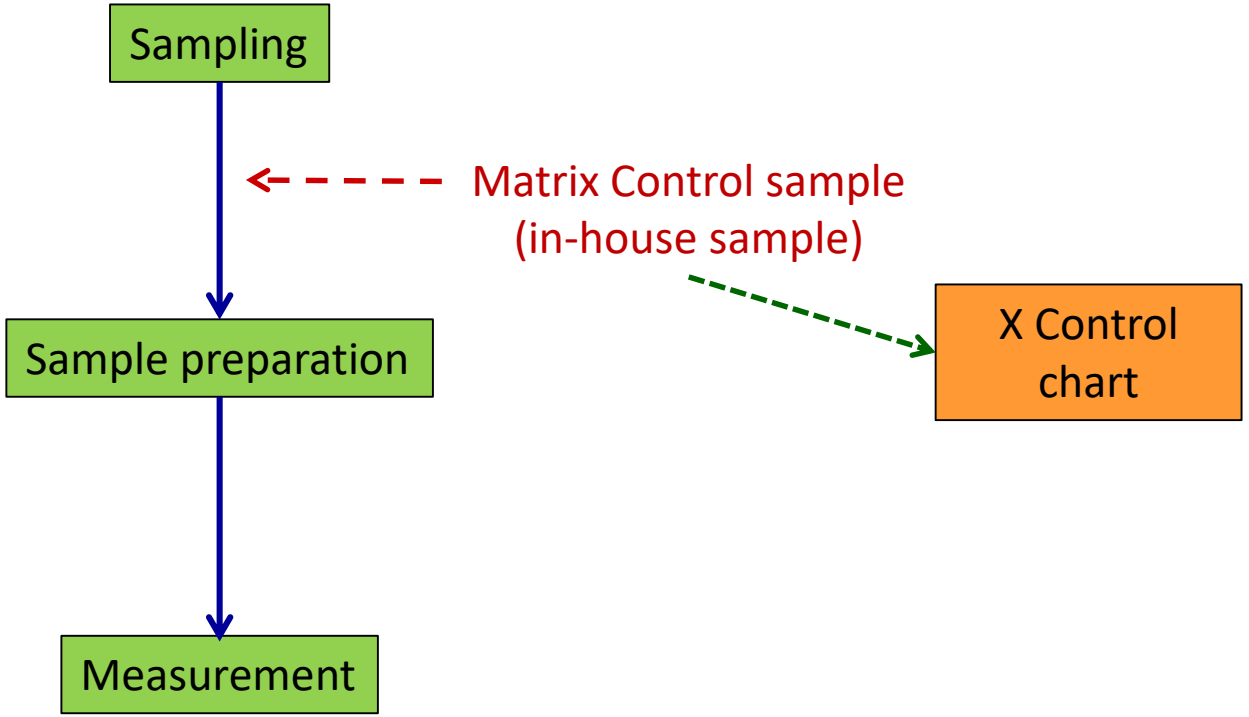


Control sample type II (cont)

- In-house material (ISO Guide 80)
  - Collected by the laboratory or selected from samples received
    - Sufficient quantities for at least a year
    - Homogeneity testing
    - Stability testing
- Pro's
  - Exactly matches test samples
  - Cheap
  - Excellent way to monitor within laboratory reproducibility (covers the whole analytical process)
- Con's
  - Laboratory has to ensure stability and homogeneity itself
  - No reference value (i.e. only partial bias evaluation)
- Mean control chart

Control chart vs Laboratory Process

- Control sample covering the whole analytical process

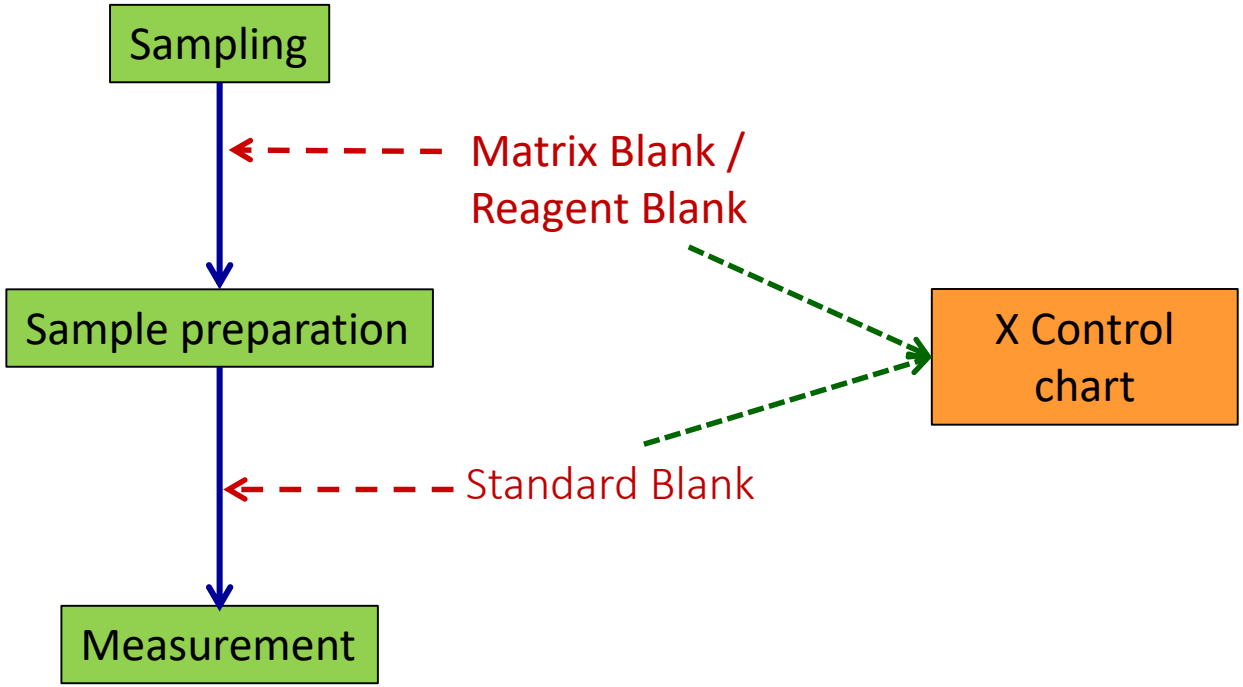


Control sample Type III

- Blank sample
  - Calibration, preparation or matrix blank
  - Monitors:
    - Limit of Detection (LOD)
    - Limit of Quantification (LOQ)
    - Contamination
    - Reagent quality
- Mean control chart

Control chart vs Laboratory Process

- Blank covering / not covering the whole process

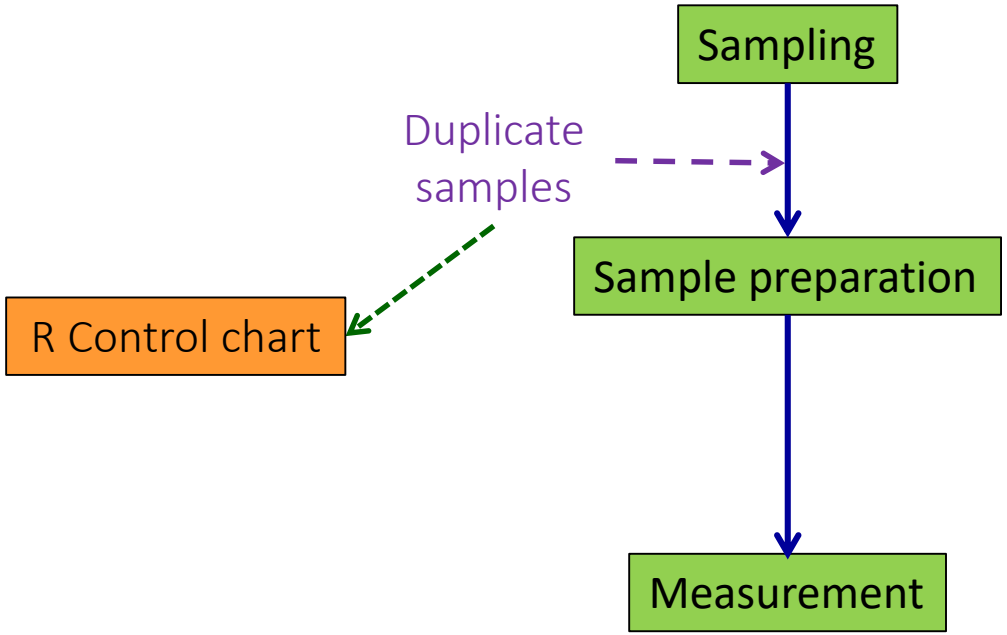


Control sample Type IV

- Randomly selected test samples run in replicate (typically duplicate)
- Pro's
  - True reflection of sample matrix, homogeneity and concentration
  - Useful where test samples are not stable, i.e. no mean control chart possible
- Con's
  - No long term precision information
  - Cannot monitor potential systematic effects (Bias)
- Range control chart

Control chart vs Laboratory Process

- No stable control sample, only duplicate / triplicate test sample analysis



Setting up Internal quality control program

- Determine:
  - Type of Control chart(s)
  - Control sample(s)
    - Type
    - Frequency
    - Concentration range
  - Control limits
    - Central line
    - Warning and Action limits
    - Initially base on method validation information
- General Recommendations:
  - Record one more significant digit than for test results
  - Report values below LOD
  - Report negative values

Setting up Internal quality control program

- Type of Control chart
  - Mean / x-control chart
  - Range control chart
- Control sample
  - Type:
    - CRM
    - Inhouse sample
    - Synthetic sample
    - Replicate test samples
    - Blank
  - Concentration range
    - Number of QC samples: Low, medium and/high concentration

Setting up Internal quality control program

- Control sample:
  - Frequency
    - Minimum 1/batch
    - Typically 5% of batch
    - Lower for high sample throughput
    - 20-50% possible for complex procedures or non-routine analysis
    - Depend on nature, criticality, batch size, frequency with which method is employed and complexity of the method

Control charts – Setting limits

- Central value (CL)
  - Based on analytical performance of method
    - Mean from QC data ideally collected over period of at least a year
  - Based on assigned reference value
    - Central line is reference value from CRM or well-characterised material (e.g. RM or PT sample)

Control charts – Setting limits

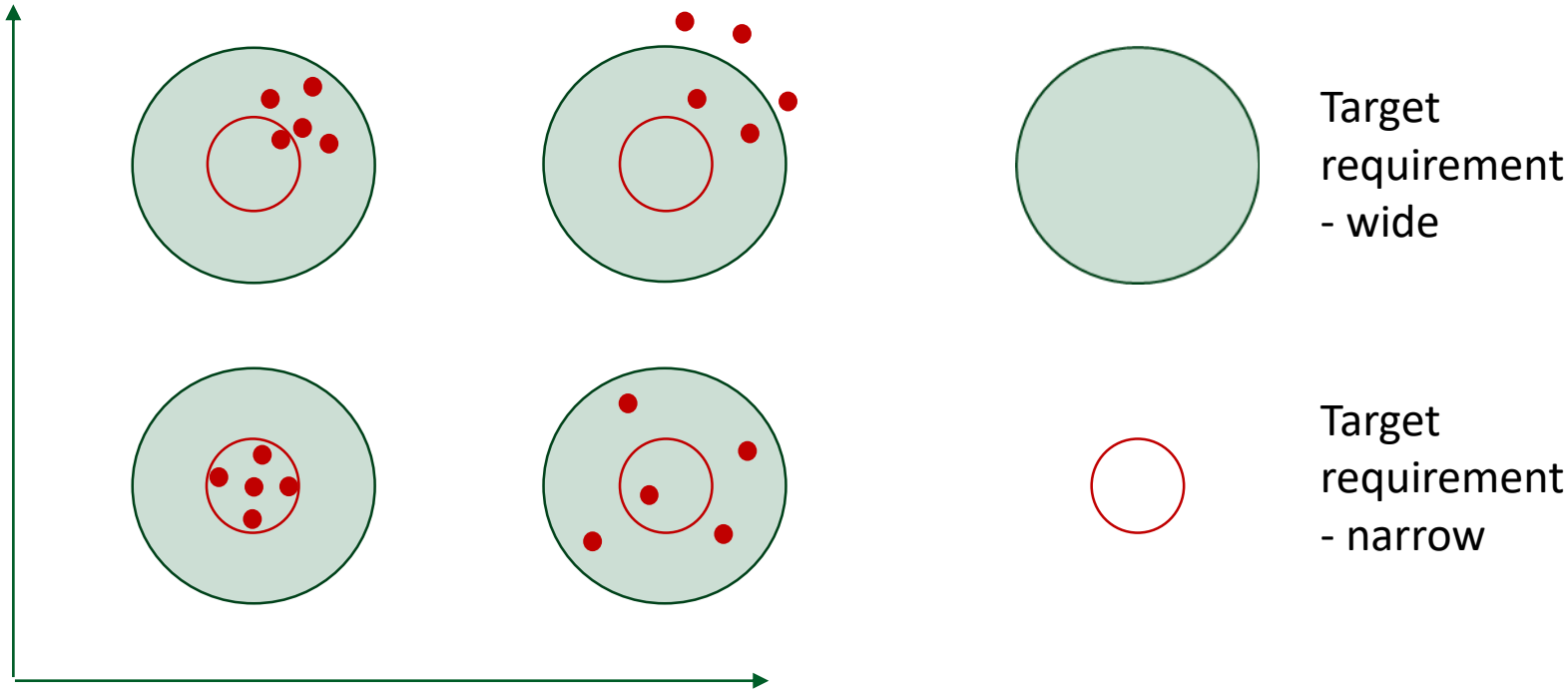
- Control limits
  - Statistical control limits (s_R): Based on method performance
    - Based on routine analysis, i.e. typical precision
      - Repeatability: Too narrow limits
      - Reproducibility: Too wide limits
      - Within laboratory reproducibility (S_{Rw})
  - Target control limits: Independent quality criteria
    - Customer requirements
    - Regulatory requirements

Control charts – Setting limits

- Statistical control limits
  - Within laboratory Reproducibilty (s_{Rw})
    - Based on analytical performance of method
      - Standard deviation (s_{Rw}) of data ideally collected over period of at least a year
      - WL = CL ± $2s_{Rw}$
      - AL = CL ± $3s_{Rw}$
  - Target control limits
    - Based on fit-for-purpose analytical requirement
      - s_{Rw} = Analytical requirement (e.g. legislation, production requirement, client specification)
      - WL = CL ± $2s_{Rw}$
      - AL = CL ± $3s_{Rw}$

Setting QC targets

- Fit for purpose



Determination of Pb in water with ICP-MS

- Laboratory collected a sufficiently large quantity of a lake water sample and preserved it in HNO_3.
- Target limits based on statistical limits from experimental data collected over a period of 3 months (n=30)
  - Mean concentration = 0.294 µg/L
  - Standard deviation = 0.008 µg/L
- The within laboratory precision requirement from the client for this analysis is 5%

Determination of Pb in water with ICP-MS

- Quality control plan:
  - Mean control chart
  - Control sample Type II: In-house control sample
    - Monitors potential bias (partially) and within laboratory reproducibility
  - Central line = Mean = 0.294 µg/L
  - Statistical control limits
    - Warning limits = Mean ± 2*Rw = 0.294 ± 0.018 µg/L
    - Action limits = Mean ± 3*Rw = 0.294 ± 0.024 µg/L
  - **Vs**
  - Target control limits
    - Warning limits = Mean ± 2*5% = 0.294 ± 0.029 µg/L
    - Action limits = Mean ± 3*5% = 0.294 ± 0.044 µg/L

Setting control limits: R-chart

- Only Upper limits
- Statistical control limits
  - Data collected over extended period of time, e.g. 1 year
  - CL = Mean range
  - Standard deviation =
    - Mean range/1.128
    - Pooled standard deviation
  - Warning limit = CL + 2.83 s
  - Control limit = CL + 3.69 s
- Target control limits
  - Based on repeatability requirement
  - CL = 1.128*s
  - Warning limit = CL + 2.83 s
  - Control limit = CL + 3.69 s

Determination of N-NH_4 in water with indophenol blue method

- Laboratory prepared a 20 µg/L synthetic solution from NH_4SO_4 (different source from calibration standards) which is analysed with every batch of water samples analysed
  - Mean = 19.99 µg/L
  - Standard deviation = 0.521 µg/L
- The laboratory also analyse one test sample in duplicate for every batch of 20 samples received
  - Mean range = 0.559 µg/L
- All test samples analysed are typically close to the LOQ of the method

Determination of $N\text{-}NH_4$ in water with indophenol blue method

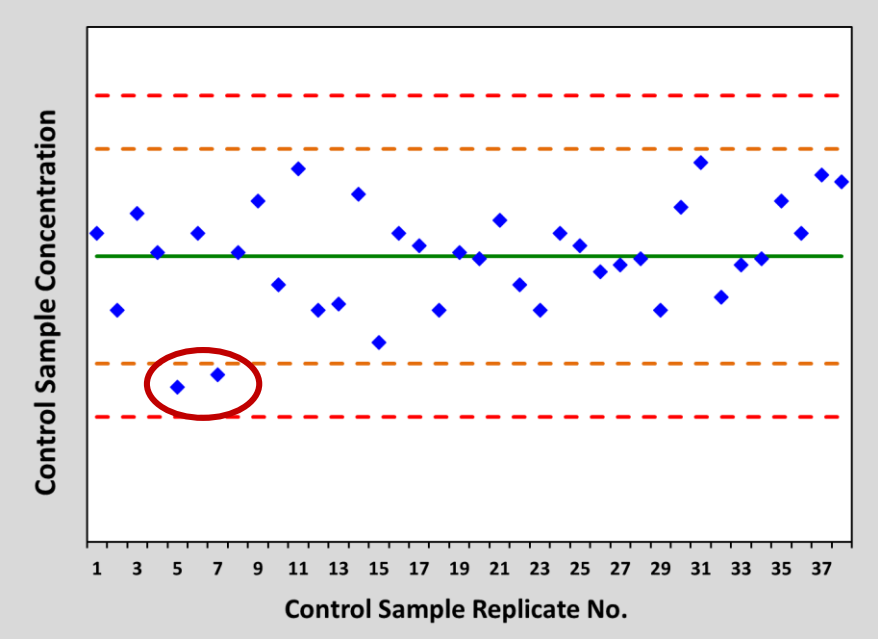
- Mean control chart
  - Central line = Mean = 19.99 µg/L
  - Statistical control limits
    - Standard deviation = 0.521 µg/L
    - Warning limits = Mean ± 2*Rw = 19.99 ± 1.042 µg/L
    - Action limits = Mean ± 3*Rw = 19.99 ± 1.566 µg/L
- Range control chart
  - Central line = Mean range = 0.559 µg/L
  - Statistical control limits
    - Standard deviation = Mean range / 1.128 = 0.496 µg/L
    - Warning limits = Mean + 2*s = 0.559 + 0.992 µg/L
    - Action limits = Mean + 3*s = 0.559 + 1.488 µg/L
- All test samples analysed are typically close to the LOQ of the method
  - Work with absolute and not relative scale

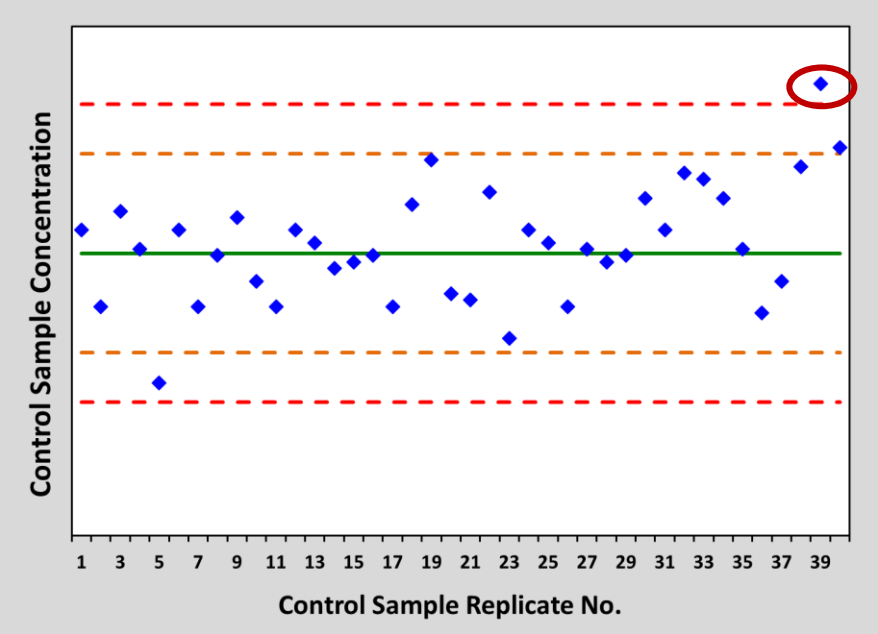
Evaluation of Control charts

- Method in control
  - Control value within warning limits, OR
  - Control value between warning and control limit, but previous 2 values were within warning limits
- Method in control, but out of statistical control
  - Control value within warning limits, BUT
  - 7 consecutive control values are either increasing or decreasing
  - 10 out of 11 consecutive control values above / below central line (if central line is mean)
    - Report but investigate (preventative action). Indications that method is going out of control.
- Method is out of control
  - Control value outside action limits, OR
  - Control value between warning and action limit, but so where one of last two values
    - Do not report. Repeat all analysis performed since previous control sample were analysed.

Interpretation of Control Charts

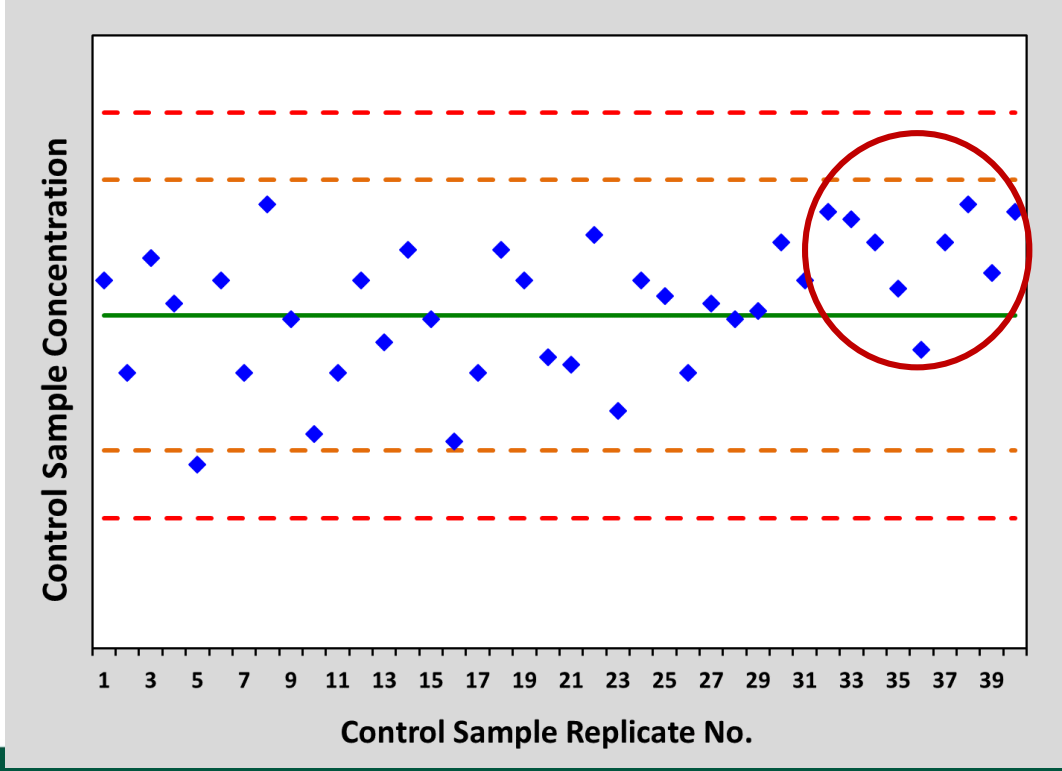
- Indication of “out-of-control” analytical procedure
  - Control limits
    - Warning: 2 out of 3 consecutive values outside limits
    - Action limit: 1 value outside limits





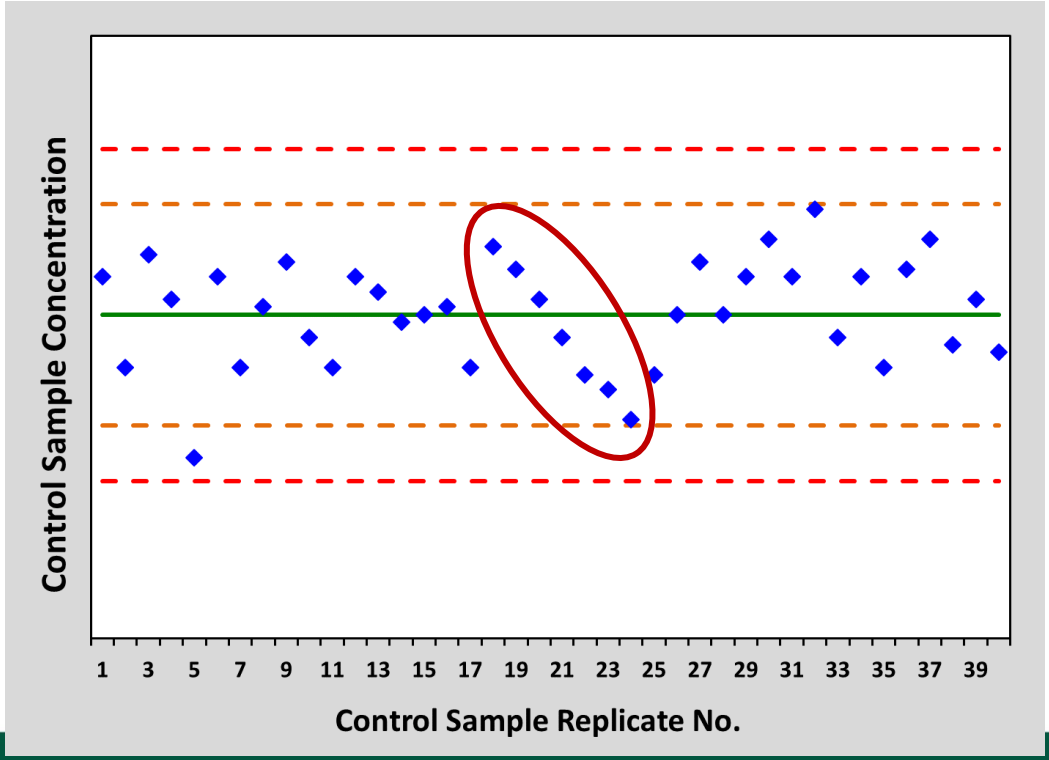
Interpretation of Control Charts

- Method in control, but statistically “out-of-control”
  - Systematic shift / Bias
    - 10 out of 11 consecutive values above or below mean



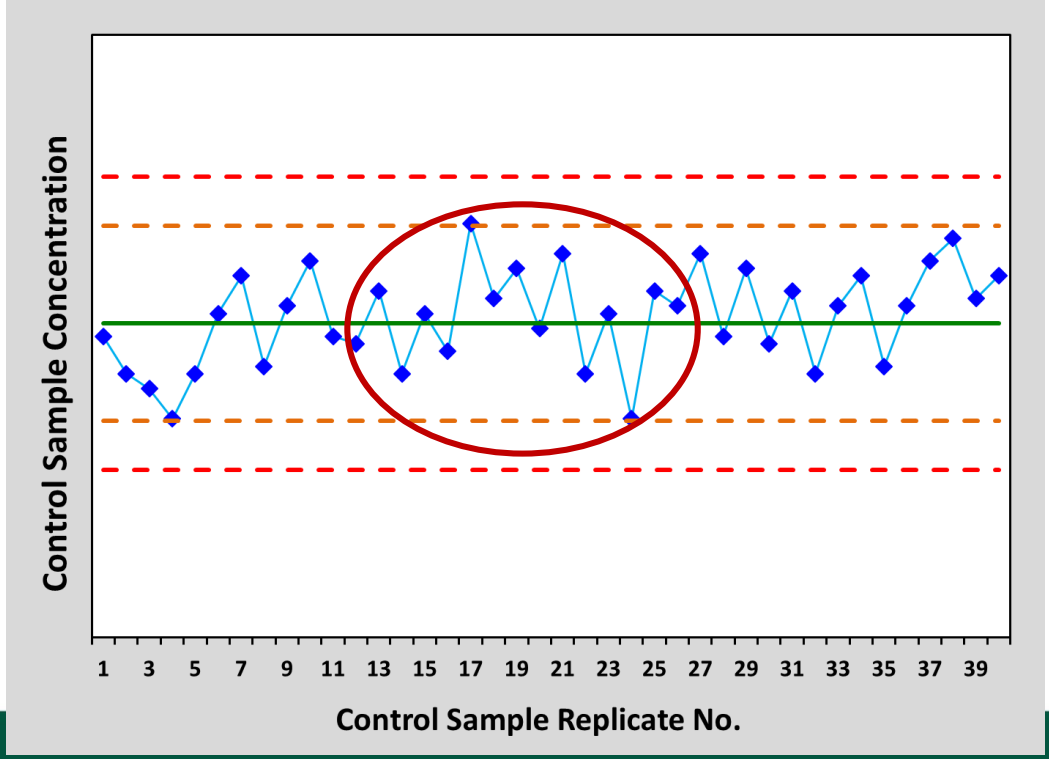
Interpretation of Control Charts

- Method in control, but statistically “out-of-control”
  - Trend
    - 7 consecutive values either increasing or decreasing



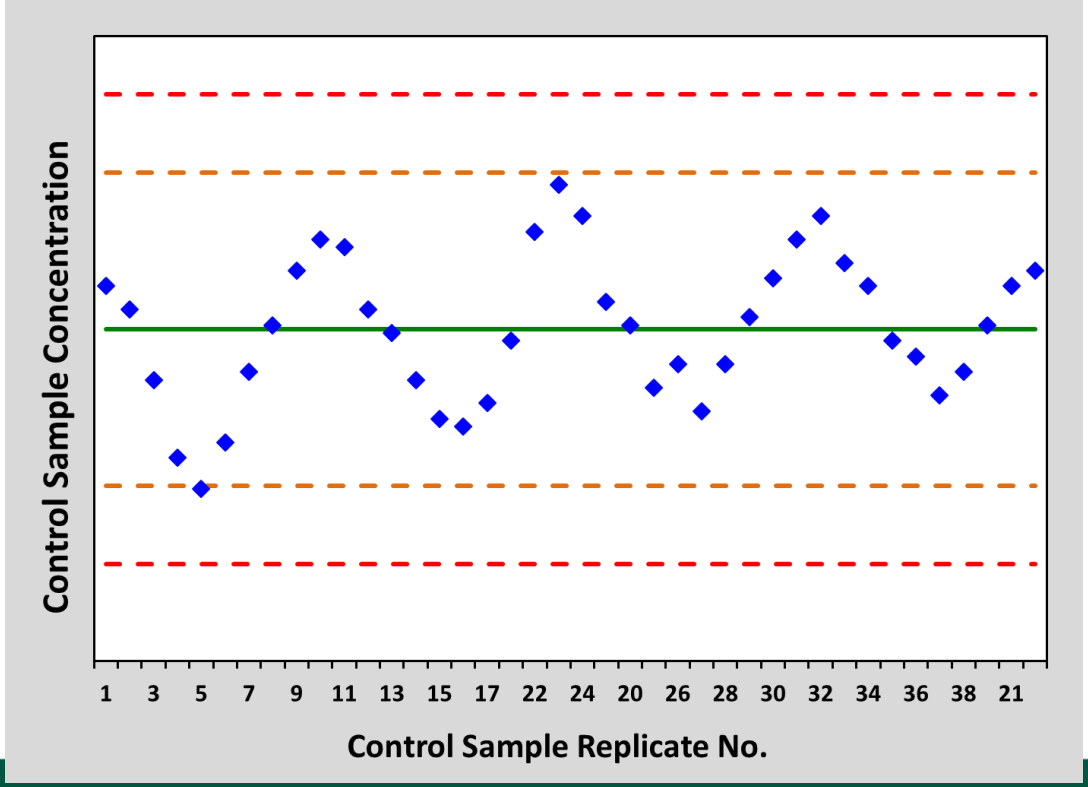
Interpretation of Control Charts

- Method in control, but statistically “out-of-control”
  - Zig-Zag
    - 14 or more consecutive values increasing and decreasing alternatively



Interpretation of Control Charts

- Method in control, but statistically “out-of-control”
  - Cyclical pattern
    - Pattern observed over time



Out-of-control: Action

- Laboratory must clearly define out of control situations and actions, e.g.
  - Repeat control sample analyses
  - Repeat all sample instrumental analysis
  - Repeat sample preparation and analysis
- Critical to maintain good records, to allow root-cause analysis if method goes out of control, e.g.
  - Change in standards, reagents, analysts
  - Instrument problems

Long term Evaluation

- Recommend to review annually (or 60 data points)
- Check for changes in:
  - Mean: t-test
    - Δ Mean > 0,35*s
  - Standard deviation: f-test
    - > 6 outside warning limits
    - < 1 outside warning limits
- Ideally limits and central line should not be changing
  - Control chart limits based on limited method validation data
  - Target control limits may change if customer requirements (or legislation) changes
  - Statistical control limits should not change – unless there has been a system change
  - Central line may be changed if control sample changes

Conclusion

- Very powerful tool to detect changes in quality of analytical results
  - Graphical representation of analysis already being performed in laboratory, e.g. analysis of CRMs, independent calibration standard check, blanks, duplicates.
- Must be Fit for Purpose
  - Number and type of charts
  - Representative QC samples
  - Frequency
  - Evaluation criteria

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We measure what matters

Thank you

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