ICHQ14, AQbD, Method Life Cycle Management –

What does this all mean for my CE method development?

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SEPARATION SCIENCES

ICH harmonisation for better health

ICHQ14: Analytical Procedure Development

Guideline Objectives – Q14

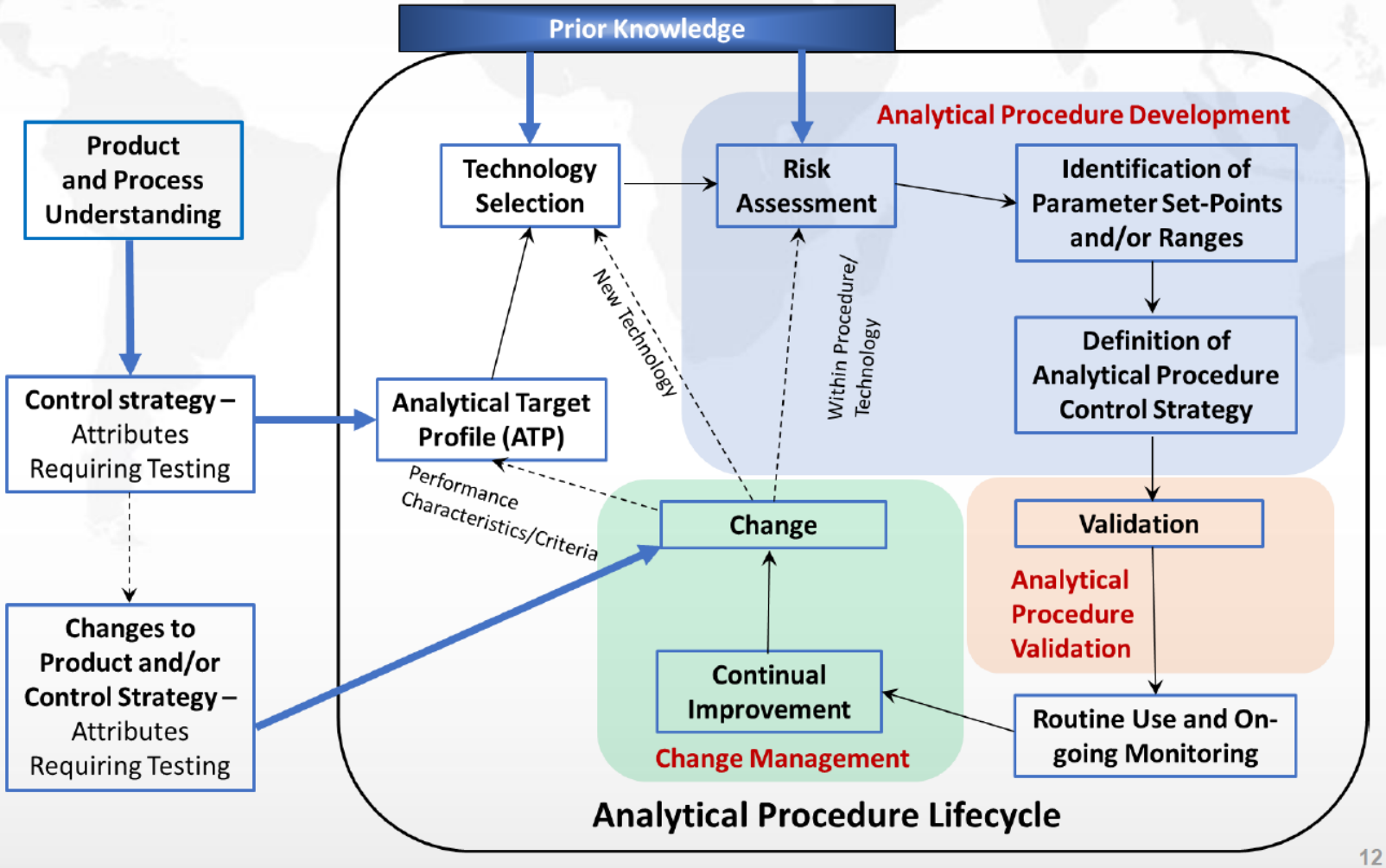
- Describes science and risk-based approaches for developing and maintaining analytical procedures fit for intended use, in line with the systematic approach suggested in ICH Q8 and using principles of ICH Q9.
- Specifies a minimal approach and elements of an enhanced approach for analytical procedure development.
- Describes considerations for the development of multivariate analytical procedures and for real time release testing (RTRT).
- Provides principles to support change management of analytical procedures based on risk management, comprehensive understanding of the analytical procedure and adherence to predefined criteria for performance characteristics.
- Includes submission considerations of analytical procedure development and related lifecycle information in the Common Technical Document (CTD) format.

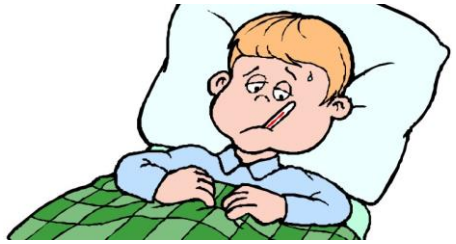
www.ich.org
www.uspnf.com

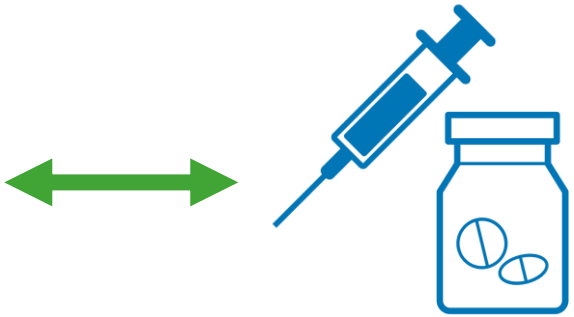
<1220> Analytical Procedure Life Cycle

This general chapter holistically considers the validation activities that take place across the entire life cycle of an analytical procedure and provides a framework for the implementation of the life cycle approach. The procedure life cycle approach described here is consistent with the quality by design concepts described in International Council for Harmonisation (ICH) guidelines. The procedure life cycle approach emphasizes the importance of sound scientific approaches and quality risk management for the development, control, establishment, and use of analytical procedures.

Chapter 2.2: Analytical Procedure Lifecycle







Expectations:

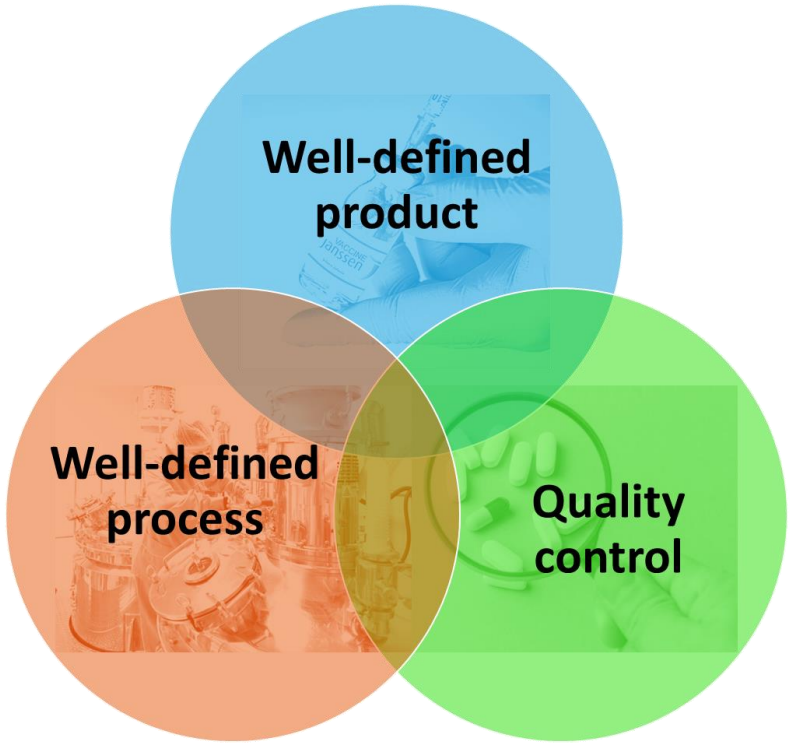
Effective: cure, relieve

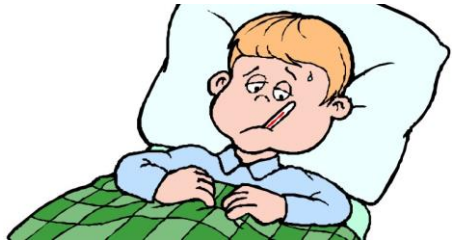
Effective: consistently right substance at right dose

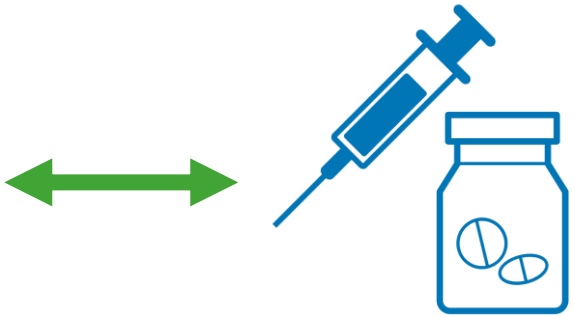
Safe: pure, stable, free from contamination

Available

Reliable medicines: quality







Expectations:

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Effective: consistently right substance at right dose

Safe: pure, stable, free from contamination

Available

R&D, GMP, QC

Science

Knowledge sharing

Traceability

Fit-for-purpose

Fit

Define purpose

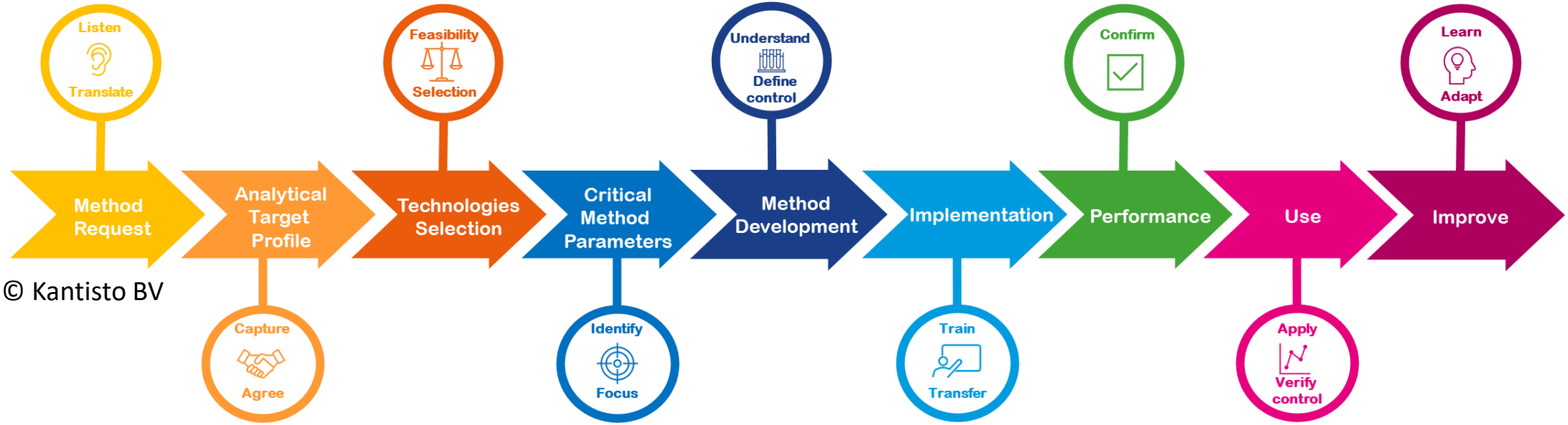
E.g. assay, purity, potency, stability

Specifications

Method requirements

Towards our AQbD approach

Our AQbD approach

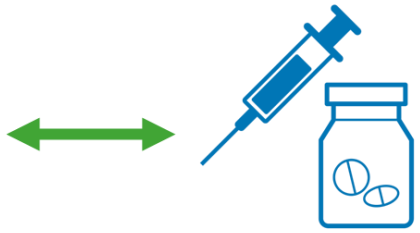


Nota Bene:

- Equal length does not mean equal time or equal effort
- The actual process is not linear, there are many reiterations at different levels
- This sketches the full process, but these steps are not always performed in one time frame or by the same people

Understand the question behind the question:

- Background information
- What need of knowledge will be filled, what is already known?
- What will be done with the analytical result?



Expectations:

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Effective: consistently right substance at right dose

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Available

- Why – What – In what – What range – When ?

Adenovirus vaccine production

Process hold

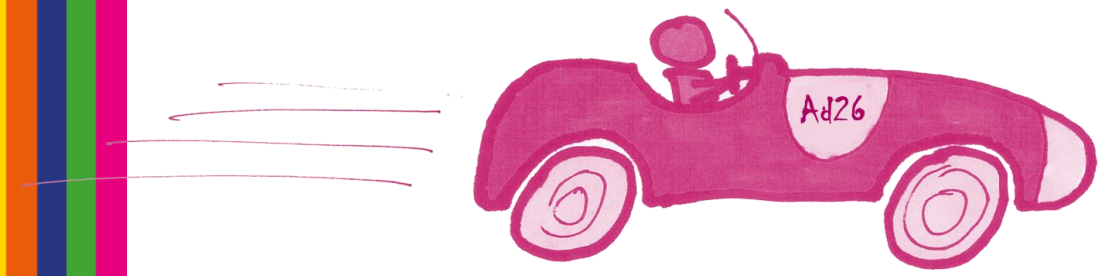
Cell and Virus Bank

Bioreactor

DNA removal

AEX-filtration

Sterile filtration

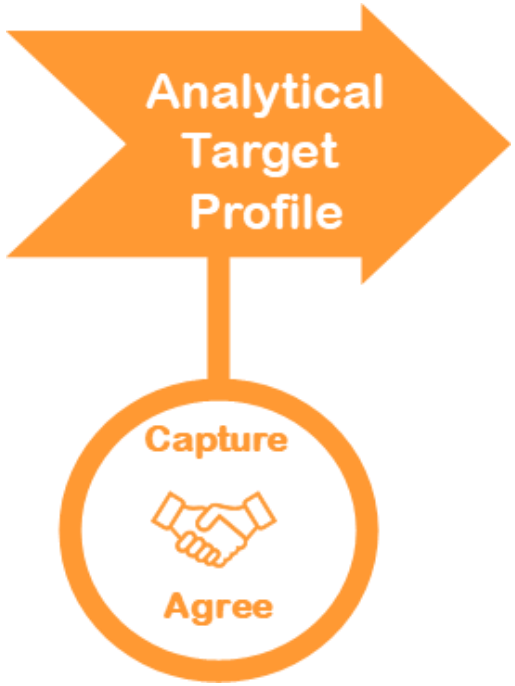


In-process control test on BCH defines DSP steps

The IPC result is used to determine

- The number of purification cycles for the AEX chromatography
- The dilution of the diafiltration product with formulation buffer to achieve the target concentration of the final drug substance

BCH Bulk Clarified Harvest
DSP Down-stream process
IPC In-process control
AEX Anion-exchange



- A list of prioritized method requirements from the
  - Requester
  - Method developer
  - End-user
  - Future end-user

- Method fit-for-purpose
  - Analytical methods are used to provide data/information to **make decisions**
    - Provide monitoring of product quality and process performance
    - Distinguish between product quality and analytical uncertainty:
      - Can this batch be released and given to the patient?

Determining the product quality or the analytical uncertainty?

- The analytical variation should be well below the product variability
- Relation between analytical precision and product acceptance criteria for n = 3

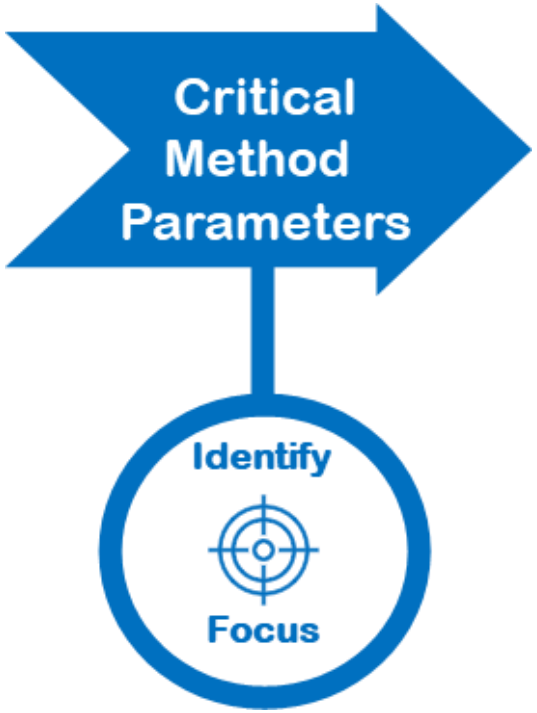
Product acceptance limits in percentage of the nominal value (%)	Maximal total analytical method relative standard deviation (% RSD)
95.0 – 105.0	1.9
90 – 110	5
85 – 115	10
70 – 130	20

- Evaluate potential techniques that might adhere to ATP requirements and business urgency
  - As a first step, identify as many technologies as possible that might be suitable
  - Prioritize the ATP requirements
  - Score for every potential technique for each requirement
    - Score the certainty/uncertainty of the knowledge
    - If uncertain, perform feasibility experiment
  - Select the best technologies (plural!) for further development

Intact VP determination - find techniques fitting the ATP

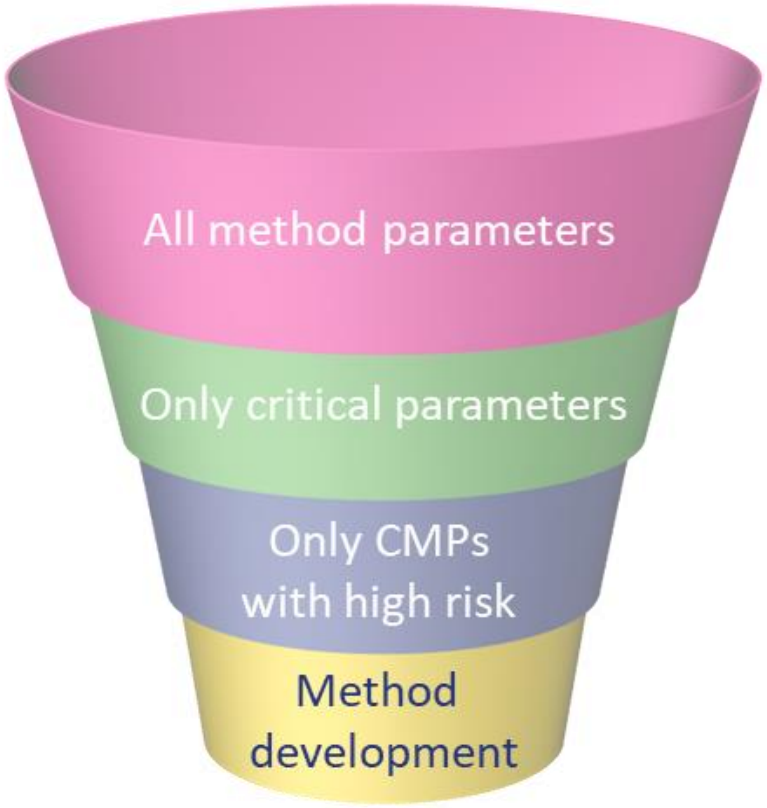
Analytical target profile (ATP)			Technology selection					
Requirements	**Priority**	**Targets**	**Q-PCR**	**CZE**	**AEX-HPLC**	**HP-SEC**	**RP-HPLC**	**OD260**
Purpose and reportable value Product	1	Virus particle concentration determination in (VP/ml) Adenovirus types 26 and 35 particle	Indirect: encapsulated DNA from virus particle	Direct: Virus particles	Direct: Virus particles	Direct: Virus particles	Indirect: Specific virus proteins	Unspecific absorbance
Production process intermediates Matrix	1	• Crude harvest • Lysed harvest • Clarified harvest → in-process control (IPC) • Anion exchange product • Diafiltration product • Drug substance • Drug product → final product The matrix contains cell debris, residual DNA, high salt concentrations, proteins, and/or formulation buffer dependent on the production process intermediate	All	All	Only purified samples: Diafiltration product, Drug substance, and Drug product	Only purified samples: Diafiltration product, Drug substance, and Drug product	Only purified samples: Diafiltration product, Drug substance, and Drug product	Only purified samples: Diafiltration product, Drug substance, and Drug product
Time to result	2	< 4 h for IPC	1 – 3 days	<4h	1 – 2 days	<4h	<4h	<2h
Precision	2	< 10% CV	10% – 35%	10%	10% – 20%	10%	20%	20%
Bias	3	< 10%	< 30%	< 10%	< 20%	< 15%	< 25%	< 20%
Concentration range	3	> 10^{10} VP/ml	> 10^{7} VP/ml	> 10^{10} VP/ml	> 6 x 10^{9} VP/ml	> 5 x 10^{10} VP/ml	> 5 x 10^{10} VP/ml	> 10^{10} VP/ml
Expected sample load per month	3	320 samples	Maybe	Yes	Maybe	Maybe	No	Yes
Equipment available	3	NA	Available	Available	Available	Available	Available	Available

Techniques of Choice



- Identify and focus on the technique (method) parameters that matter
  - Find and determine the critical method parameters, the knowledge gaps, and potential failure modes/risks
    - Tools to help identify, sort, and document
  - Method optimization of **CMPs** have priority
- The method parameters are re-evaluated on criticality every time more knowledge of experience is gained

Critical Method Parameters CMPs



- Identifying the CMPs helps to focus
  - Many analytical procedures consist of > 50 parameters that could be optimized and that could possibly impact the ATP requirements
    - Only possible with endless budget, time, and patience

- How?
  - Mindmap/Fishbone diagram
  - List all method parameters
  - Criticality assessment: score on impact on the ATP and score on how certain you are on this assessment of impact
  - Risk assessment: only with CMPs and pCMPs
    - Impact x Probability x Detectability = Risk Priority Number
  - Sort and optimize highest risk CMPs
  - Redo when new info comes available

Risk assessment - FMEA example

				Risk score before mitigation					Risk score after mitigation		
#	CMP	ATP requirement impacted	Possible cause of impact	Impact (1-10)	Probability (1-10)	Score (before mitigation	Proposed experiments	Mitigation	Impact (1-10)	Probability (1-10)	Score (after mitigation
1	Capillary type and coating	Bias and precision	Virus adsorption to the capillary wall could impact bias and precision	10	8	80	Test multiple capillaries and coatings and select capillary + coating with good virus recovery	A PVA coated capillary was selected to prevent adsorption of the adenovirus	10	2	20
2	Buffer pH	Bias	A pH that is too low or too high could cause virus degradation	10	8	80	Find the optimal pH range in regards with adenovirus stability	The optimal pH range was determined at 6.0 – 8.5.	10	1	10
3	Buffer pH	Specificity / selectivity	The pH of the BGE could impact the selectivity and therefore the separation of the adenovirus from its matrix components	7	10	70	Screen several buffer types (with different pH) to evaluate the impact on the selectivity. Select a BGE + pH and perform a robustness design	A BGE containing 200 mM tris and 200 mM tricine was selected at pH 7.6. This BGE and pH allowed for baseline separation of all peaks and was robust.	10	1	10
4	Buffer pH	Precision	Variations in the BGE pH might impact the migration time precision of the method	6	10	60	Prepare the BGE in such a way that the pH is reproducible	Tris and Tricine are weighted (instead of titrated) to reduce the pH variation	6	1	6
5	Sample type and matrix	Bias and precision	The sample matrix components like DNA, protein and salts could impact the precision and bias	10	8	80	Evaluate whether a sample treatment is required for a set of representative samples from DSP and USP	A sample treatment was implemented for crude samples to remove residual DNA. The precision and bias were determined and acceptable for three representative samples: CH, AEX, and DS	10	3	30
6	Detection wavelength	LOD and LOQ	If the wrong detection wavelength is selected than this could result in low absorbance or low S/N values.	10	8	80	Evaluate and select a wavelength that allows for adenovirus detection and quantification	A wavelength of 214 nm was selected to analyze adenovirus.	10	1	10

Mitigation: The background electrolyte (BGE)

- Buffer: pH determines charge on the analyte
  - Maintain pH, even when electrolysis occurs
  - High concentration, close to pK_a gives best buffering capacity
    - In addition, reduces electromigration dispersion
  - Use low-conducting buffers if possible

- Mobility matching of BGE co-ion with analytes
  - Reduce electromigration dispersion

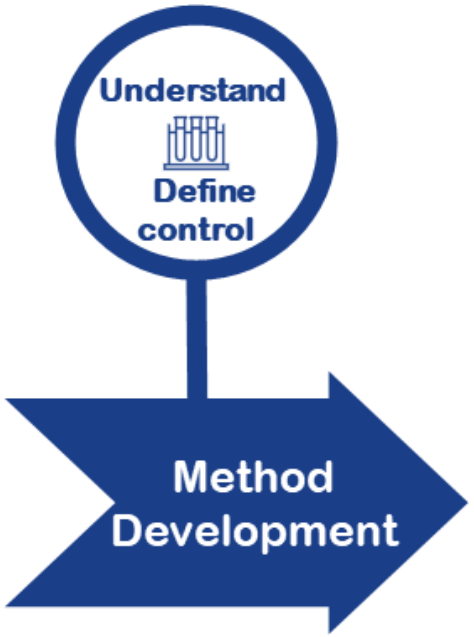
- Current in linear range of Ohm's plot
  - No excessive Joule heating

- Precise recipes, avoid titration to pH
  - Firm control of composition
  - Constant ionic strength, constant current

wikipedia

Mitigation

- Many of the good practice we do stems from mitigation:
  - Sampling
    - No sub-sampling
    - Minimum sample size
  - Sample prep
    - Dissolve/dilute LC sample in eluent
    - Dissolve/dilute CE sample in low-conducting solvent
  - Precision
    - Limited number of dilution steps, no serial dilutions
    - Minimum weight on analytical balance
    - CE: BGE is a buffer and inlet and outlet vials are frequently refreshed
  - Calibration
    - Create calibration line from at least two independent standards
    - Multi-level: At least five levels equally distributed over the range
  - …….



- Design and development of robust and fit-for-purpose method
  - From understanding the principles and best practice
  - Quality is built in, not tested into a method
- Focus on the CMPs
- Use the tools to efficiently gain scientifically sound data, for optimization, and for robustness testing
  - Multivariate Design of Experiments
- Think before you leap…

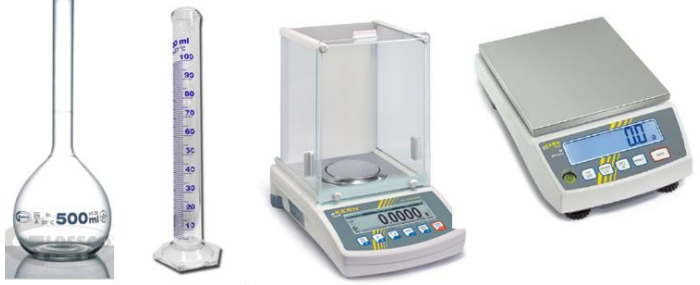
Ad26 CZE: Sample prep vs Capillary costs

- Sample preparation
  - Could cause virus particle degradation and thus erroneous results
  - Takes time
  - Every step in the procedure implies errors/uncertainties
    - The more complex the procedure, the lower the precision
    - The more complex the procedure, the higher the risk for errors being made

- Excluding sample preparation
  - Very dirty samples directly injected onto the capillary
    - Increased risk for adsorption and damaging the capillary coating
    - Extended (automated) conditioning required
    - Can be in control by appropriate system suitability requirements
  - Likely more capillaries required
    - Costs
  - Ease of operation

Use the tools in the right way

Different scenarios for making a 50 µg/ml solution



- Weigh 1 mg, dissolve in 1000 µl and dilute 5 µl with 95 µl with automatic pipettes

$$CV = 100 \times \sqrt{\left(\frac{0.020}{1}\right)^2 + \left(\frac{3}{1000}\right)^2 + \left(\frac{0.3}{5}\right)^2 + \left(\frac{0.3}{95}\right)^2} = 6.3\%$$

- Weigh 5 mg in a 10 ml volumetric flask and dilute 10 µl with 90 µl with automatic pipettes

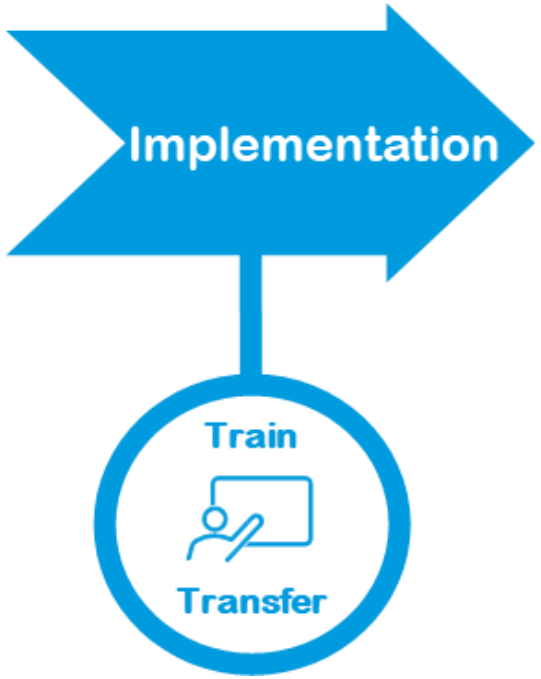
$$CV = 100 \times \sqrt{\left(\frac{0.020}{5}\right)^2 + \left(\frac{0.04}{10}\right)^2 + \left(\frac{0.3}{10}\right)^2 + \left(\frac{0.3}{90}\right)^2} = 3.1\%$$

- Weigh 50 mg in a 100 ml volumetric flask and dilute 10 ml to 100 ml

$$CV = 100 \times \sqrt{\left(\frac{0.020}{50}\right)^2 + \left(\frac{0.020}{10}\right)^2 + 2 \times \left(\frac{0.100}{100}\right)^2} = 0.25\%$$

Error values:

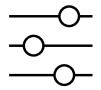
- Weighing on 5-decimal balance $s_w = 0.020$
- 100-ml volumetric flask $s_V = 0.100$
- 10-ml volumetric pipette $s_V = 0.020$
- 10-ml volumetric flask $s_V = 0.04$
- 1000-µl automatic pipette $s_V = 3.0$
- 100-µl automatic pipette $s_V = 0.3$



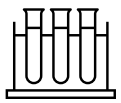
- Define control strategy
  - “An analytical procedure control strategy should ensure that the analytical procedure performs as expected during routine use throughout its lifecycle…
  - … and consists of a set of controls, derived from current understanding of the analytical procedure including development data, risk assessment and robustness.” (ICH Q14)
- Training of operators on method, technique, instrument, best practice
- Transfer to departments that perform the actual testing

Control strategy

- Many common risks are already covered (e.g.: GxP, SOPs, best practices)
- Most method-specific mitigations are defined in the FMEA:

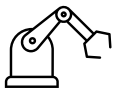


Optimal and robust parameter settings (MD, DoE)



Control samples: blanks, SSC, reference material, internal standards
With acceptance criteria and trending

Prior/during test measurements
E.g.: concentration determination/cell counts/cell viability/brackets, parameter read out,…



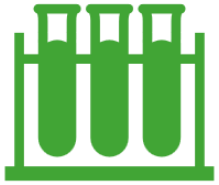
Standardization/automation
E.g.: programming/robots/fill in sheets/proofing/error messaging/etc.

Trending and monitoring

Critical materials

Ad26 CZE System suitability testing

- During method development, the conscious decision was made to offer capillary life time in favour of no sample prep
- SST stringent by choice
  - When the IPC sample is taken, fast analysis is required 
    - SST, including capillary performance, is performed before arrival of IPC sample
      - SST requirements are such that risk of analysis failure on the IPC sample is minimized
      - Reanalysis would cost a lot of time on investigation and paperwork, while the process is on hold
  - Pre-Covid:

> 18000 samples   3 invalids

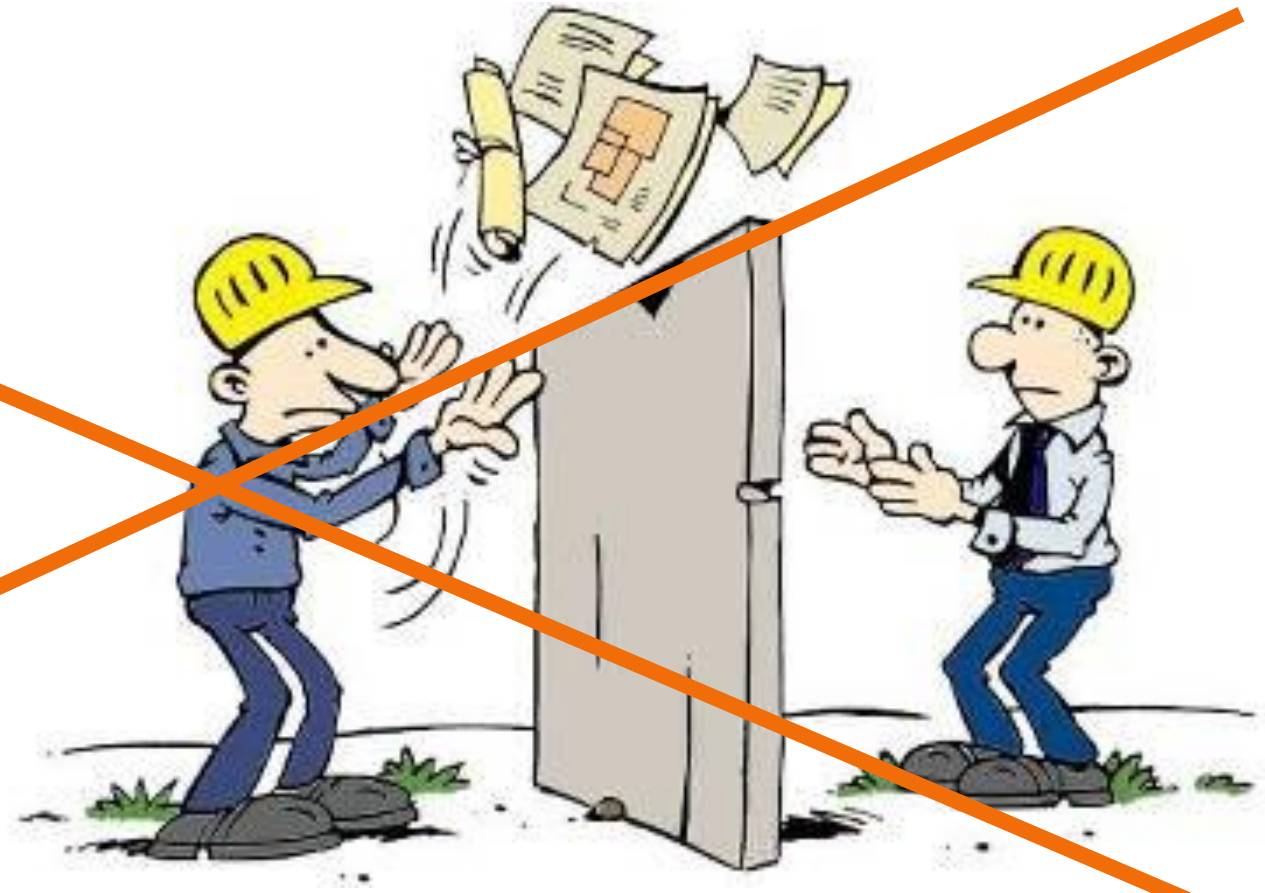
    - SST failure rate was about 20% (3 years of implementation pre-Covid)
    - 0.6% of the sample runs were invalid (3 years of implementation pre-Covid)
    - Causes for failure were monitored and followed up by continuous improvement projects

Van Tricht, Geurink, Sänger et al. "Implementation of at-line capillary zone electrophoresis for fast and reliable determination of adenovirus concentrations in vaccine manufacturing" *Electrophoresis 40* (2019) 2277

Method transfer

~~We are done!~~

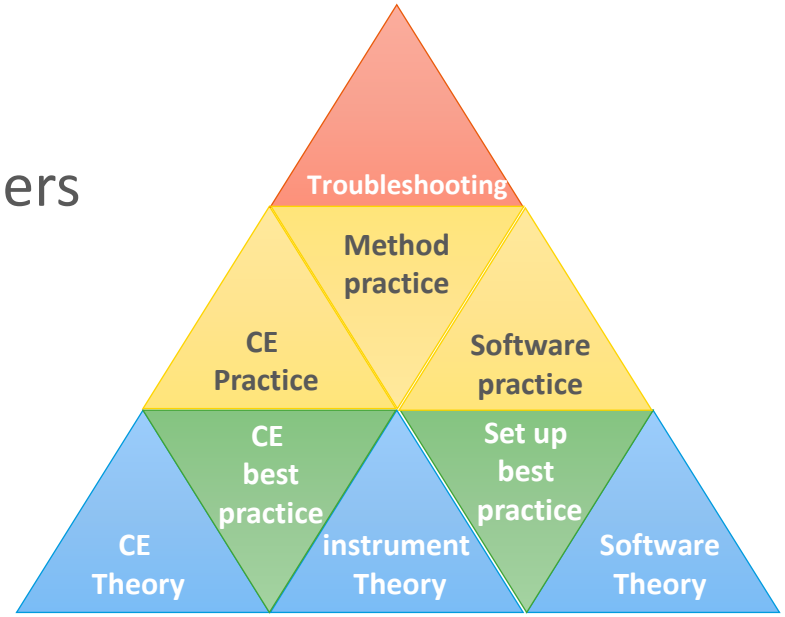
~~Method delivered!~~



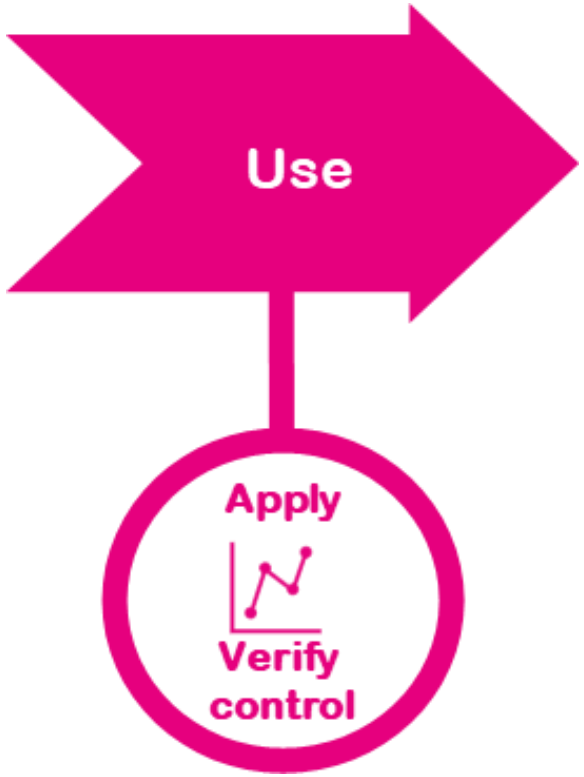
CZE World-wide training while travelling is prohibited

CE: a new technology/instrument/software at all CMOs

- Awareness for operators, management, and project leaders
  - CE is a nano-technology!
  - … and new to most operators
- Online “classroom” trainings
- Feasibility required
  - CE Best practice: capillary handling, cleaning of system
  - Vaccine sample handling (no mAb!)
  - Integration of electropherograms
- Lectures, pictures, movies, animations, Smart-glasses, Teams, explanations, discussions, learning-by-doing, ….
  - Observation and guiding of the operators in the CMO labs rather than continuous demonstrations

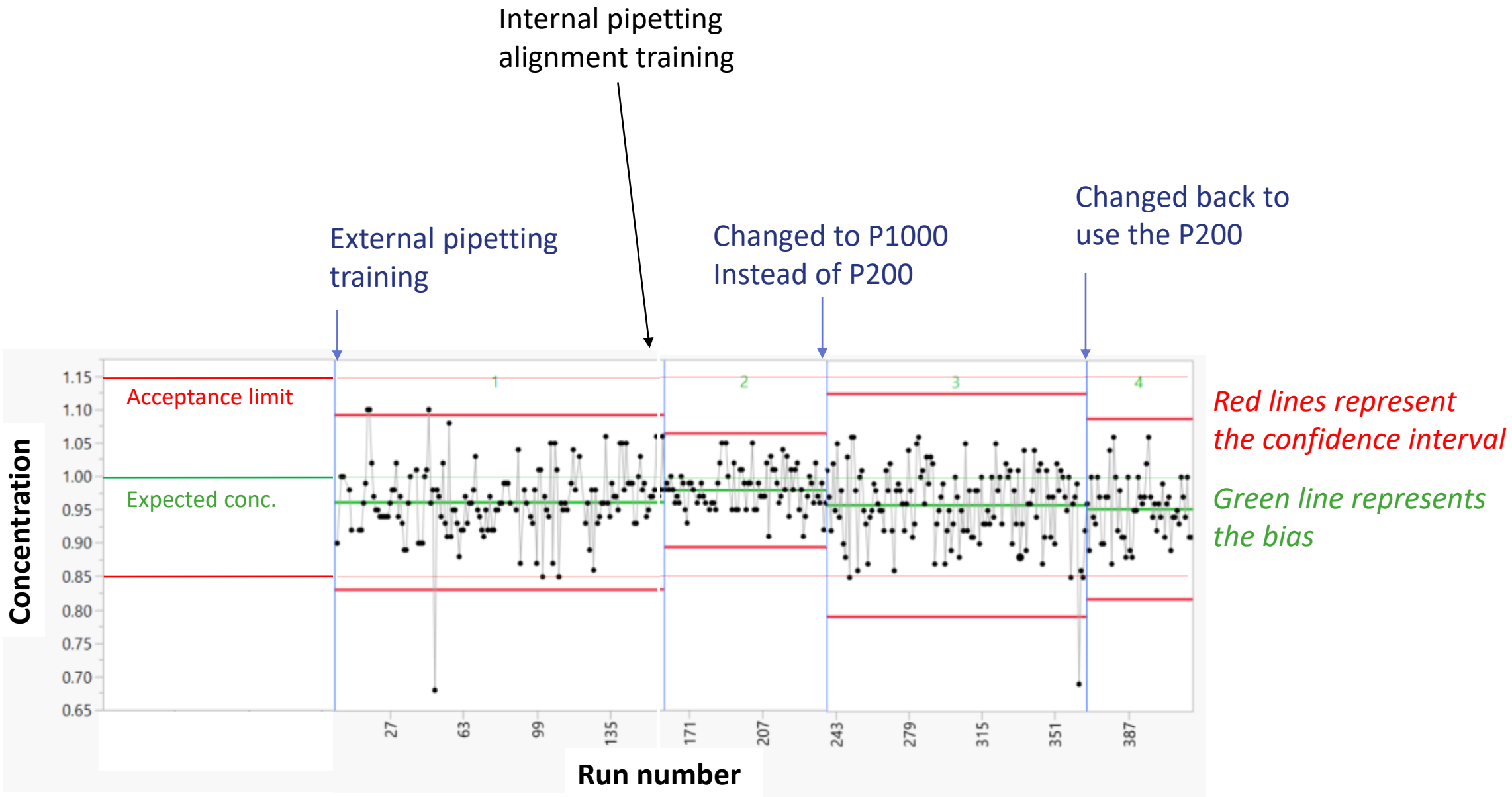


- Method validation ICHQ2
  - Snapshot if treated as exercise-to-pass
  - Instead, focus on prospective view on future use
- Validation by user, not by developer



- Method life cycle management
  - Verification that the method keeps performing according to the ATP
  - Trending

Why trending can be important

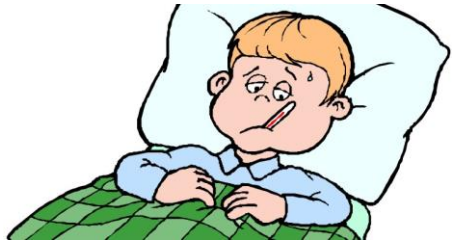


Red lines represent the confidence interval

Green line represents the bias

Method Life Cycle Management

- Lessons learned
  - Troubleshooting and issue logging
  - Learn and improve
- Critical material changes
- Adaptions: method is never finished…
  - Method scope change
    - Methods started in Early Phase will change scope throughout the lifecycle of the project, e.g. :
      - Requirements on the product might change with the clinical phase
      - Formulations are adapted
  - Re-evaluate the ATP and take it from there



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Available

Reliable

R&D, GMP, QC

Science

Knowledge sharing

Traceability

Fit-for-purpose

Fit

Define purpose

E.g. assay, purity, potency, stability

Specifications

Method requirements

AQbD

- AQbD does not replace profound knowledge of the technique and applications
- AQbD is not an aim in itself! (Neither is analytical chemistry…)
- AQbD is a mindset & toolbox
  - To help in the process of understanding, controlling, and documenting the method
- A good AQbD method development flow gives:
  - Fit-for-purpose
    - Only develop method if there is a clear request
    - Alignment/handshake on purpose with requestor and end-user
  - Structure
    - Alignment within AD, everyone the same approach
    - Knowledge is captured, re-usable and shareable, reasons for decisions are documented
  - Control
    - Sources of variation are understood
    - CMPs are known and under control through mitigations
    - Less troubleshooting and re-analysis

AQbD

Quality is isn’t a checkbox exercise,

Acknowledgement vaccine examples

Dr Lars Geurink Dr Ewoud van Tricht Dr Luuk van Oosten

Janssen Vaccines Leiden

Janssen Infectious Diseases & Vaccines

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Thesis **Lars Geurink**

Analytical Quality by Design Method Development for Vaccine Characterization

http://uu.diva-portal.org/smash/get/diva2:1698746/FULLTEXT01.pdf

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SEPARATION SCIENCES

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