QbD and CE:
Some practical points for attention

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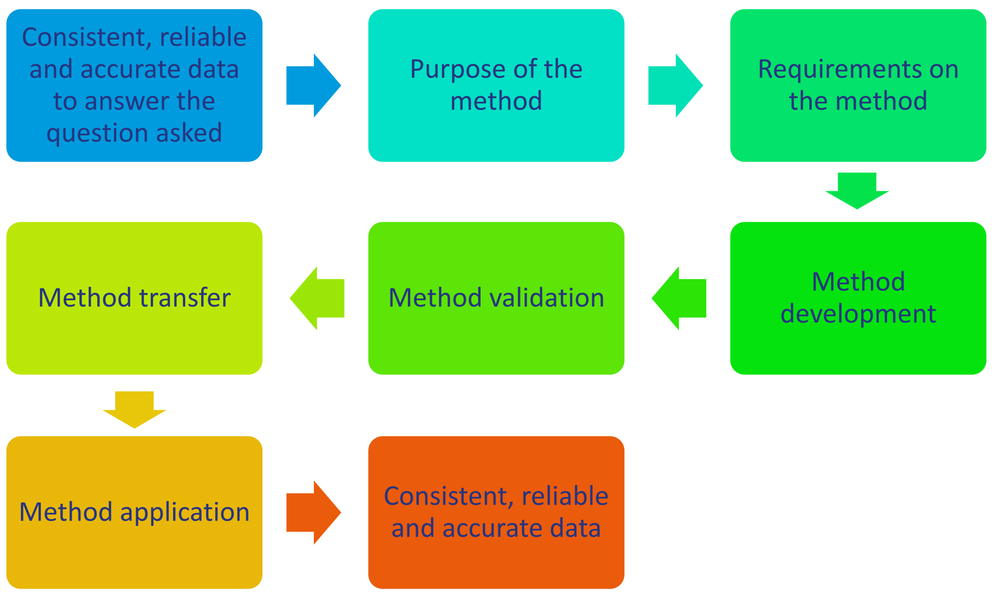
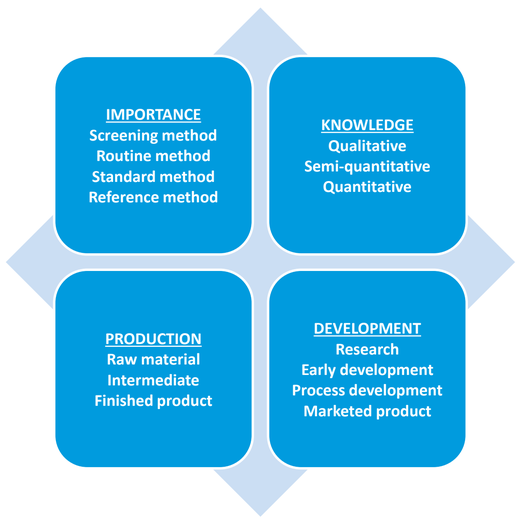
Introduction

Quality by Design means a scientific, risk-based, holistic and proactive approach. It has been successfully applied for some years within the pharmaceutical industry for formulation development and there is an increasing interest to apply QbD for analytical method development. ICH Q8 reads: “The degree of regulatory flexibility is predicated on the level of scientific knowledge provided.” and “... quality cannot be tested into products, i.e. quality should be built in by design.” This is just as valid for analytical methods.

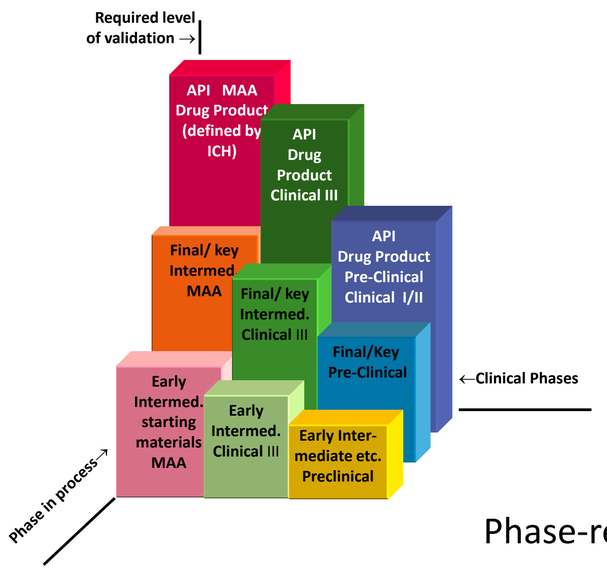
Fit for Purpose



Fit-for-purpose method development: why are we going to determine what?



- The answer automatically sets the requirements on e.g. the precision, accuracy and range needed for the application.
- Awareness of the requirements leads to conscious choices during development in order to fulfil all these requirements.
- Method validation proves in a pre-defined set of procedures and specifications that the method indeed fulfils the requirements.



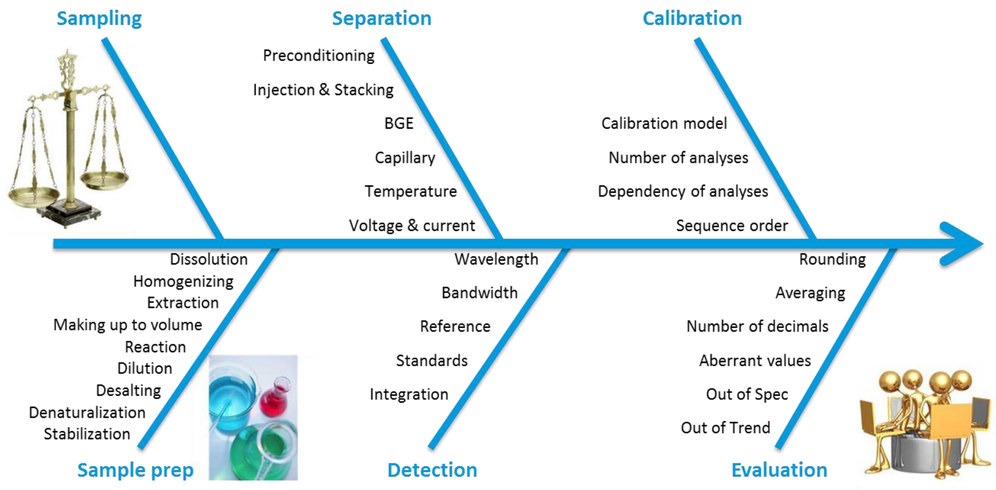
Phase-related approach

Method limitations

QbD includes a risk management and quality control strategy

- In-depth knowledge of the analytical method and its critical aspects gives understanding about the experimental conditions under which the method will perform according to the requirements (design space).

Method limitations - all steps contribute to the method uncertainty:



The fishbone diagram is a useful QbD risk assessment tool

- Identify and organize potential critical method attributes
  - The head represents a critical method attribute
  - The bones represent potential critical method parameters that could influence the critical method attribute

FMEA (Failure Mode Effect Analysis)

- Potential critical parameters can be graded to find those parameters that should be evaluated for robustness and/or System Suitability Testing.

Variable	Current Value	Deviation of variable or parameter from its current value or potential failure	Potential Cause	Probability	Potential Impact on Output Quality	Impact	Current Detection Mode or Control Mechanism	Detect ability	Follow-up Action / Mitigation Strategy Responsibility
				P		I		D	P · I · D

Method precision limitation: sample prep

- Pipettes and volumetric glassware - weighing is more precise than pipetting
- Mixing is difficult, especially viscous liquids in small volumes. Use round-bottomed tubes. Vortexing alone does not mix very well, combine with inverting the tubes. Use “master mixes”
- Check filtration steps
- Check reaction steps
- SDS denaturisation pH, time and temperature should be optimized

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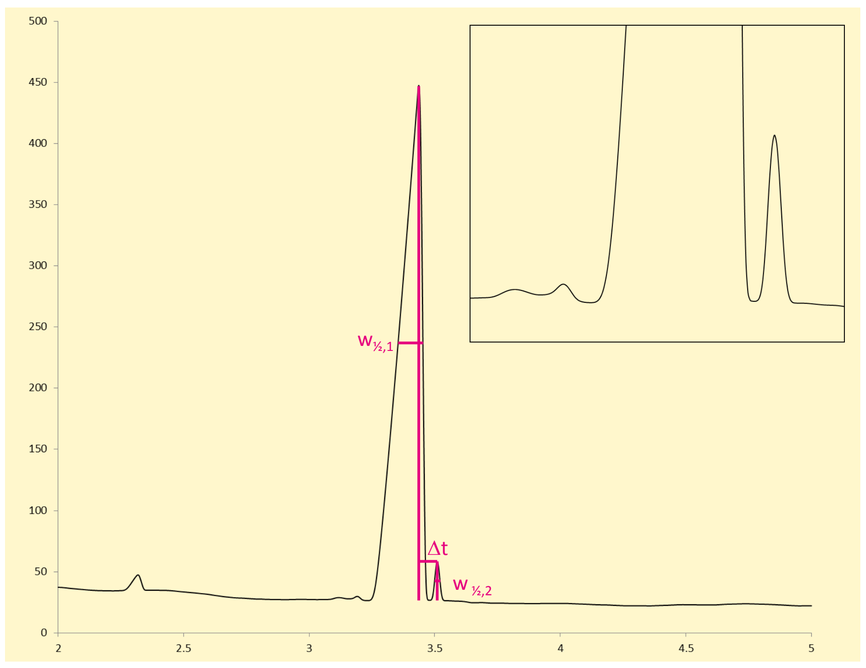
Separation Sciences

Method requirements

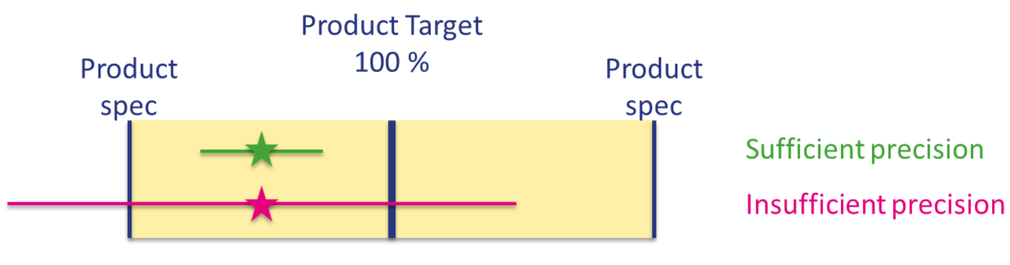
Resolution



If the difference in migration times of the main peak and its impurity is less than the peak-width-at-half-the-peak-height of the main peak, the calculated resolution (here $R_s = 0.7$) is less than the theoretical baseline resolution defined as $R_s = 1.5$ for Gaussian peaks.

- The common resolution determination assumes that peaks are Gaussian shaped and of similar height.
- In CE it is not uncommon that peaks are asymmetrically triangular shaped because of electromigration dispersion (EMD).
- The apex of an EMD peak, taken as the migration time, is not in the middle of the analyte zone
- Typically very low calculated resolution numbers can still give baseline separation.

Precision



The analytical precision required depends on the method purpose. For example, if the method is an assay for a product with specification of target 100 % ± 5 %, the precision of the method (incl. sample prep) has to be better than 1.9 % RSD.

Unambigueous method description

- **Precise BGE recipes!**
  - How?
    Good example:
    Prepare a solution of 100 mM phosphoric acid and 88 mM TRIS. Check the pH, which should be pH 3.0 ± 0.1

    Bad example:
    0.1 M phosphate buffer adjusted to pH 3.0 with TRIS

  - Why?
    - Constant ionic strength gives better reproducibility
    - Influence on EOF and electrophoretic mobility
    - Unambiguous recipe is easier to repeat
    - Many buffers outside calibration range of pH-meter
    - Preparation order unclear: when is the pH checked?
    - Many vague descriptions in literature, e.g.:
      - The concentration of what is indicated?
      - Borate buffer – from borax or from boric acid?
      - Phosphate buffer – What kind of cations?

- **Add a typical current profile**
  This is a tool for system suitability checking as well as an opportunity for controlling of aberrant results.

- **Precise rinsing descriptions**
  - A proper method description includes all procedures for conditioning
    - New capillary, pre-sequence, between injections, post-sequence
    - Storage of the capillary
  - Between-run rinsing should be as simple as possible, preferably only with electrophoresis solution. Add on if needed. Extreme rinsing with e.g. NaOH or HCl can introduce hysteresis effects.

- **Critical method attributes**
  - Any knowledge on critical method parameters or preparation steps and examples of successful and unsuccessful runs should be included in the method documentation.
  - If integration can be critical, also add examples of integrated electropherograms.