From Data to Decision: Leveraging Advanced Analytics for Enhanced Quality Control and Regulatory Compliance

CASSS CMC Strategy Forum Europe, 23-26 June, 2026

Dr. Christof Finkler, F. Hoffmann – La Roche AG

11 March 2026

ICH Q14 Tools and Principles

ATP
Prospective summary of performance characteristics and criteria that defines the intended purpose and performance requirements of the measurement

Knowledge and Risk Management
ICH Q14 promotes the use of QRM tools to identify, prioritize and assess analytical procedure parameters that could impact performance.

Evaluation of Parameter Ranges and Robustness Studies
Is providing the scientific knowledge needed to ensure analytical procedure meets the expected performance criteria during normal use. Can lead to the establishment of PARs or MODR

Analytical Procedure Control Strategy
Is a planned, science- and risk-based set of controls designed to ensure that the analytical procedure is fit for its intended purpose during routine use and throughout its entire life-cycle

Platform Analytical Procedures
Once a platform analytical procedure is established, the concept allows data from prior validations or development studies to be leveraged across multiple products

Multivariate Analytical Procedures and Real Time Release Testing
ICH Q14 includes specific considerations for the development of multivariate analytical procedures and for Analytical Procedures for Real Time Release Testing (RTRT)

Established Conditions (ECs) for Analytical Procedures
In line with ICH Q12, the enhanced approach can lead to a more appropriate, reduced set of ECs, which focuses on analytical procedure performance

Submission Chapter
Is establishing a structured framework for documenting scientific knowledge and risk justification especially for the enhanced approach and multivariate analytical procedures and procedures used for RTRT

Case Study - Determination of Polysorbate in A-mAB

Determination of Polysorbate 80 in A-mAb

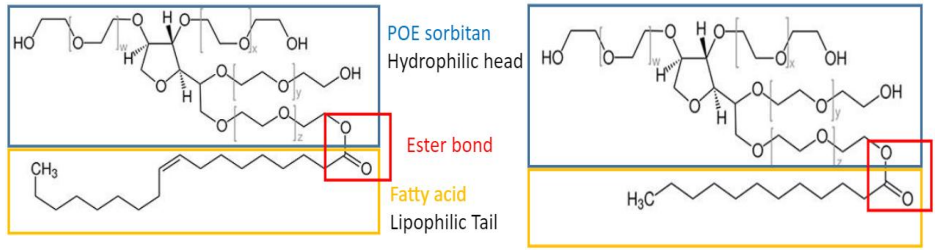
- Polysorbate 80 (PS 80) is a widely used surfactant to stabilise proteins against interfacial stresss in biotechnological products

- Surfactant content is a CQA and is monitored during formulation development, IPC, DS/DP release and stability testing

- Target concentration of PS 80 in A-mAB is 0.6 mg/mL with specification acceptance critria of target concentration +/- 50%

Commonly used surfactants for biologics

Polysorbate 20 (PS20) Polysorbate 80 (PS80)



- Mixed mode HPLC (RP/AIEX with evaporative light scattering detection (ELSD)) is the current standard technology for determination of PS 80 in protein formulations
  - HPLC-ELSD (robust, broad linear range, precision range of 1-7% RSD, intermediate: 3-7%, time intensive multi- point calibration)

Determination of Polysorbate 80 in A-mAb

Target concentration of PS 80 in A-mAB is 0.6 mg/mL with specification acceptance critria of target concentration +/- 50%

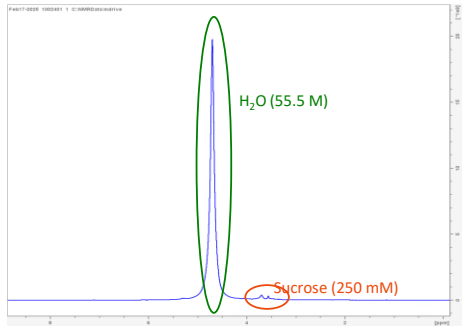
Intended Purpose: **Determination of polysorbate 80 content in A-mAb drug substance and drug product for release and stability testing**		
Link to CQA : **The analytical procedure should allow the determination of polysorbate 80 in the presence of the A-mAb and other formulation components. The analytical procedure should support the specification limits of A-mAb.**		
Performance Characteristic	**Acceptance criteria**	**Rationale**
Accuracy	Mean recovery of polysorbate 80 for samples at each level covering the range of the reportable result are within 80 and 120%. 90% confidence interval of mean recovery of all levels are within 80-120%.	Selected performance characteristics ensure that the intended analytical procedure delivers the quality of the reportable result.
Precision	Repeatability: Max. RSD of polysorbate 80 at all levels is ≤ 15%. Upper limit of 95% confidence interval of variance of all required levels (expressed as % RSD) is ≤ 15%. Intermediate precision: Max. RSD of polysorbate 80 at all levels is ≤ 15%. Upper limit of 95% confidence interval of variance of all required levels (expressed as % RSD) is ≤ 15%.	
Specificity	No interference from the presence of A-mAb and other formulation components when quantifying polysorbate 80 Confirmation that the analytical procedure is stability-indicating.	Confirmation of the capability to quantify polysorbate 80 in the presence of the components expected to be present. To ensure that potential changes in the amount of polysorbate 80 over shelf life can be detected.
Reportable Range	The quantitation of polysorbate 80 is proportional across the range from 0.3 mg/ml to 0.9 mg/ml Polysorbate 80.	Target concentration of polysorbate 80 in A-mAb is 0.6 mg/ml. The range needs to cover the assumed specification limit of polysorbate 80

Benchtop ^{1}H NMR as alternative technology

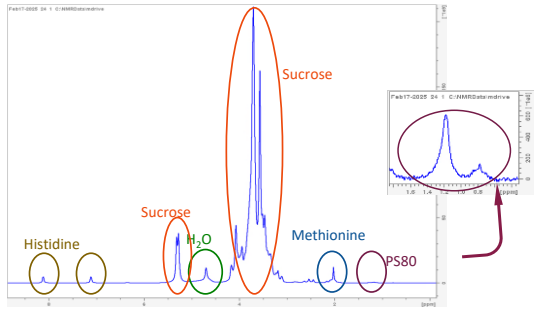
- NMR spectroscopy is commonly used in the pharma environment
  - limited use in GMP environments (complexity and costs)
- Benchtop NMR instruments
  - Much lower capital invest and maintenance costs compared to high field NMR
  - Fit on a lab bench
  - Can also be used as at-line technology

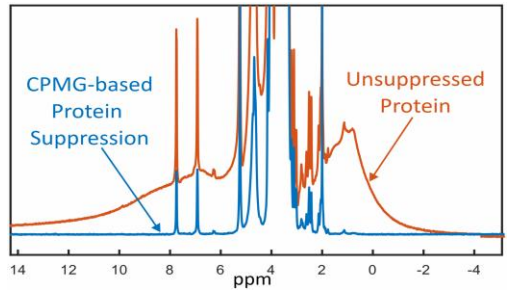
- Simple sample preparation - no dilution steps, no deuterated solvent needed
  - External lock system with ^{19}F reference material to prevent signal shifts

- Biologics are challenging matrices:
  - Aqueous solutions → Solvent suppression needed
  - Macromolecules at high concentrations (up to 200 mg/ml)
    - ➢ Strong broad signals overlapping with analytes' signals
    - ➢ Relaxation filters to suppress protein signals



Solvent suppression: removes water signal

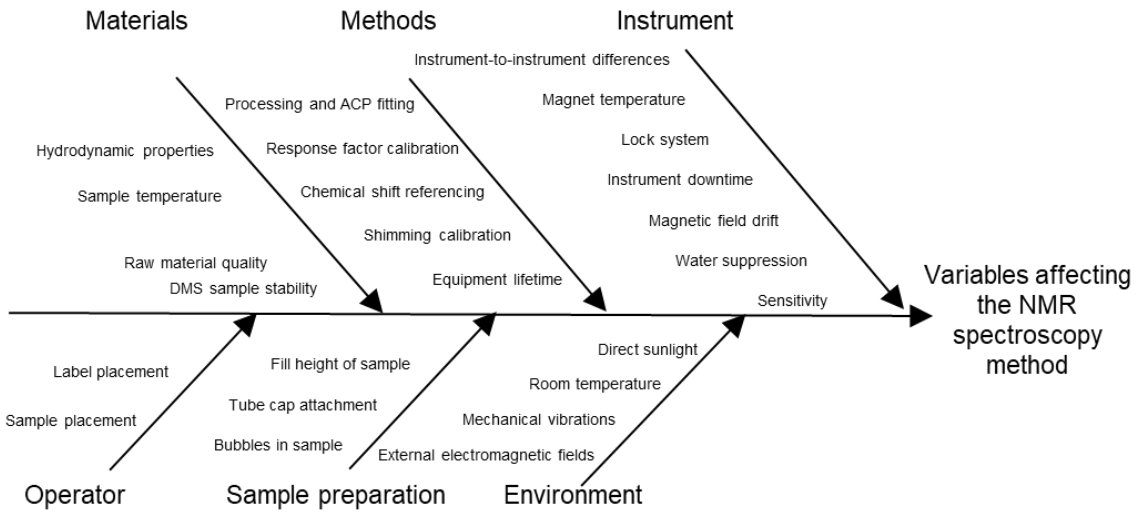




Protein suppression: removes Mab signals to yield a clear baseline

Skidmore K, Hewitt D and Kao YH. Biotechnol. Prog. 2012 *28* (6), 1526-33 and Lynch CC, Khirich G, and Lee RT Anal. Chem. 2024 *96* (17), 6746-6755

From risk to robustness - enabling Benchtop NMR for QC release



Extract from Risk Assessment

	Factor	Failure Mode and Risk	Detection Controls	Prevention Controls	Risk
Materials	Raw material quality	Impurities (i.e. EtOH) in raw materials used for DS/DP production might lead to incorrect quantitation by overlapping signals with analytes	Defined raw material quality. Establish change Control with suppliers	The ACP fitting tool can successfully detect and quantify polysorbate in the presence of ethanol at relevant levels	Medium
	NMR tube quality. Hydrodynamic properties of sample. Sample temperature. DMS sample stability				Low
Method	Processing and fitting; Response factor calculation; Chemical shift referencing; Shimming calibration; Equipment lifetime				Low
Instrument	Instrument-to-instrument differences	Differences in hardware, calibration, and inherent variability in permanent magnet strength can lead to slight variations in the overall magnetic field strength and instrument-specific pulse power/length impacting quantitation	During method development, excipients will be quantified on the same samples using different instruments	Standardized procedures across instruments, including a one-time, instrument-specific calibration of pulse length and power during initial setup	High
	Magnet temperature; Lock system, Sensitivity, Instrument downtime, Magnetic field drift; Water suppression				Low
Operator - to - operator differences	Label placement	The sample is not fully inserted into the magnet. Distorted line shape, inconsistent signal integral and quantitation	Visual inspection of tubes prior to analysis	Operator training to Ensure labels are placed consistently and according to defined procedures	Medium
	Sample Placement	Distorted line shape, inconsistent signal integral and concentration determination	Visual inspection of tubes prior to sample submission as outlined in test procedure	Procedural control as outlined in test procedure	Low
Environment	Direct sunlight	Variation in the equipment field strength and performance (lock and shim system) due to elevated temperatures	Regular temperature monitoring of the lab environment. SST and Functional tests.	Ensure that the laboratory area for the instrument is shielded from direct sunlight.	Medium
	Mechanical vibrations	Signal distortion, noise and vibration side peaks	vibrations manifest as random distortions at the base of larger resonance lines. If the vibration source is persistent, it will be detected during the IQ or during the annual OQ / PM	Instrument must be placed on a stable bench or table and no other equipment which produces vibrations should be placed on the same table. Instrument placement part of IQ	Medium
	External electromagnetic fields	Interference with NMR signal, modulations of high-magnitude resonance lines. Symmetrical ghost peaks	Visual inspection of fitted NMR peaks in the reports and regular equipment maintenance are conducted.	Instruments must be placed in a location with no proximity to other equipment that produces electromagnetic fields or large moving metallic structures	Medium
	Room temperature	Variation in the equipment field strength and performance	Regular temperature monitoring of the lab environment. SST and Functional tests.	Maintain a controlled temperature environment	Low
Sample preparation	Fill height of sample; Tube cap attachment; Bubbles in sample				Low

Structured method development approach using elements of the enhanced approach described in ICH Q14

- Systematic identification of risk variables using Ishikawa diagram
- Failure mode effect analysis
- Risk ranking

From risk to robustness - enabling Benchtop NMR for QC release

Design of robustness studies

- Moderate and High Risk addressed through targeted development studies to define **Parameter Ranges**

Identified Risk	Experimental Mitigation	Robustness Outcome
Consumable Variability	**Tube Lot Qualification**	Confirmed tube quality as the highest variability contributor (0.47% RSD).
Sample Geometry	**Fill Height Assessment**	Established a reliable range of sample volume.
Matrix Specificity	**Response Factor Calibration**	Established locked factors to account for different response of analytes in mAb formulations.
Network Transfer	**External Referencing**	Preserves quantitative ratios across instruments by scaling signal intensity with field strength and instrument sensitivity.

- Additional robustness testing will be performed as part of method validation. Sample incubation time, Instrument influence: intermediate precision.

Detectability: Variables like direct sunlight or mechanical vibrations were assigned high detectability scores, allowing them to be mitigated via procedural and IQ controls without extensive experimental testing.

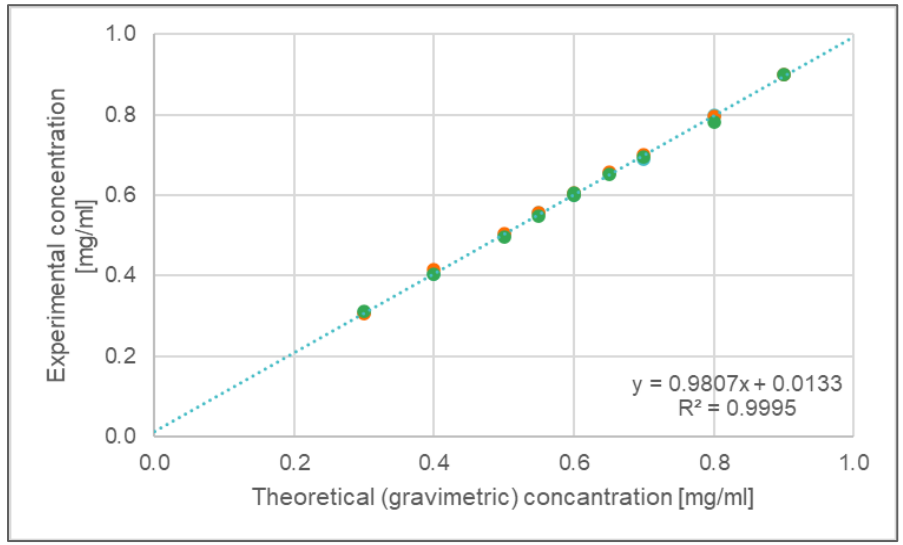
Analysis, data processing and evaluation:

- Peak recognition, peak fitting and automatic integration to eliminates user-to-user variability
- Quantitation using response factors determined once during method development per product and stored in instrument database
- External quantification
  - The method is transferable between instruments
  - Reference standard (we chose DMS in water, sealed NMR tube)
    - Stable for months at RT
- Method is automated from acquisition to reporting

Analytical performance

Analytical performance from prevalidation studies on Linearity, Accuracy, Precision of PS80 content in the formulation including mAb

Concentration from preparation [mg/ml]	Experimental concentration from triplicates [mg/ml]	Recovery [%]	%RSD from triplicates
0.30	0.309	103.0	1.29
0.40	0.407	101.8	1.63
0.50	0.501	100.1	0.83
0.55	0.554	100.7	0.96
0.60	0.602	100.4	0.38
0.65	0.654	100.7	0.54
0.70	0.695	99.3	0.72
0.80	0.791	98.9	1.15
0.90	0.900	100.0	0.13
Target for excipients		80.0 – 120.0%	15%



Intermediate precision in model formulation with mAb:
1.6 % RSD

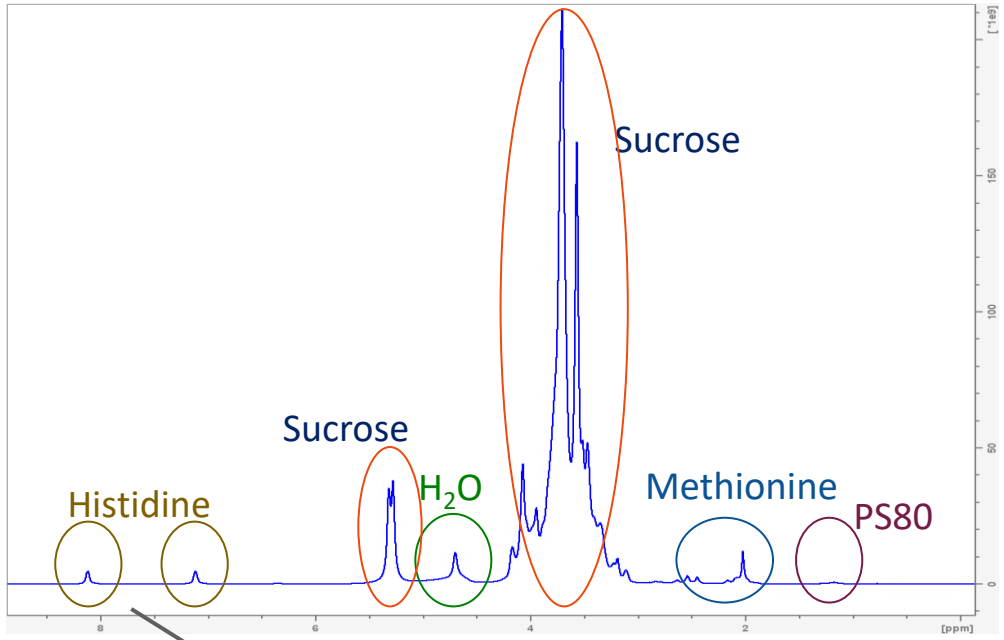
Test	Instrument	NMR tube	Day	PS80 content [mg/ml]
1	A	a	1	0.501
2	A	b	1	0.494
3	A	a	2	0.508
4	B	b	1	0.495
5	B	a	2	0.503
6	B	b	2	0.486

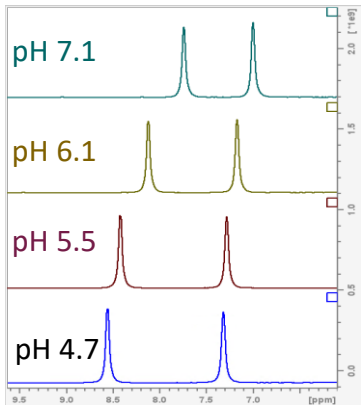
Robustness

- No major factors affecting the method precision were found so far that can not be mitigated
- Influence of analyst is negligible
  - Simple sample preparation
  - Automated analysis
- External standard method: NMR tube quality is a key factor
  - Chosen tube type adds about **0.47% RSD** (from 2 Lots, 40 tubes tested)

NMR as Multi Attribute Method

Simultaneous quantification of other excipients and pH?





Analyte	Recovery [%] Average	%RSD
Sucrose	**100.3**	**1.5**
Histidine	**100.7**	**2.0**
Methionine	**101.7**	**1.5**
Polysorbate 80	**100.9**	**1.3**

15 Sample
x 3 replicate tubes
x 3 replicate spectra

135 tests

From risk to robustness - enabling Benchtop NMR for QC release

Simplified Method with Superior Precision

- No sample preparation (fill-into-tube-and measure), direct measurement in a complex matrix.
- **fully automated end-to-end workflow** from acquisition to reporting
  => low Operator-to-operator variability
- Single-Point Calibration: Simplified, robust quantitation with a sealed standard. Supports method transfer.
- Sample suitability assessment against internal spectra library
- Highly precise: Reached an intermediate precision of **< 2% RSD** in A-mAb matrix
- Up to an 80% reduction in analysis and hands-on time
- Sustainable: No solvents or cryogens required

Outlook

- Use as multi-attribute method: simultaneous quantification of multiple excipients e.g.: sucrose, histidine, and methionine in a single run
- Explore the use as platform analytical procedure for quantitation of PS80 and PS20
- In process control: reduced analysis time (up to 80%) can be a game-changer for in-process control

Case Study – Identity Testing by Lys-C Peptide Mapping with MS detection

Problem Statement

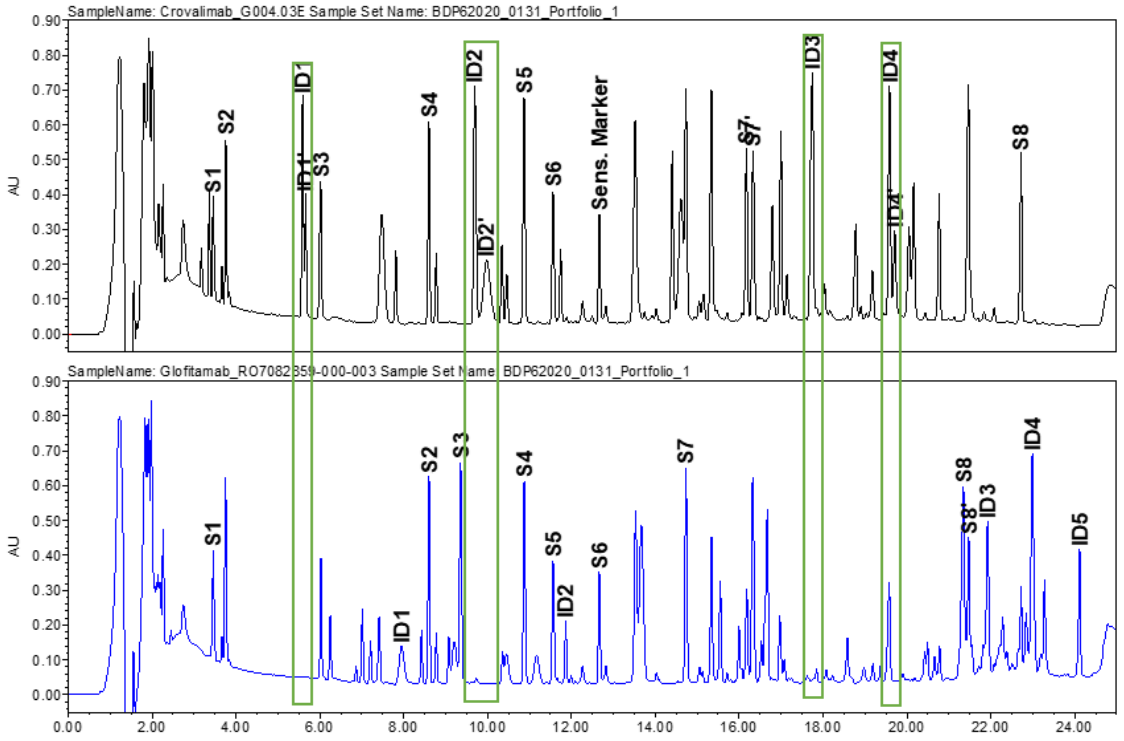
- Multiple identity tests used across Roche's network to ensure identity for protein based products
- Increasing portfolio puts pressure (risk of loosing specificity) on identity tests for the respective products at individual sites
- Maintaining a large number of different identity tests used across Roche's products (protein-based) creates a burden on testing sites
- Most of legacy identity tests rely on analyst's evaluation to confirm identity of the product in scope

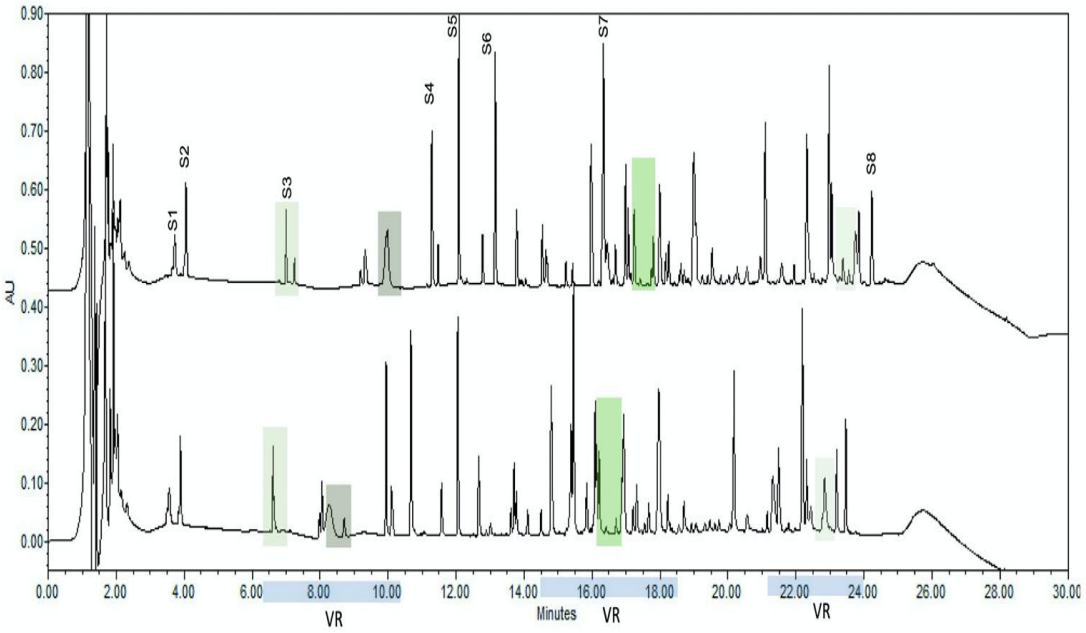
➡ Development of **one** state of the art and future proof identity test

Starting Point – Lys-C Peptide Mapping with UV Detection

UV Method based **on visual chromatogram comparison**:

- Presence of **product specific ID peaks for determination of identity**
- Example chromatogram **fixed in the procedure for SST and evaluation of generic peaks**





DRAWBACKS:

- **UV peak variability** such as retention time shifts, differences in resolution (splitted peaks/ co-elution) etc. by using different analytical conditions (column lot, aging, apparatus…):
- Requires **thorough training** to prepare analysts for consistent evaluation
- Proper profile comparison **only possible with data from the same analysis sequence → impact specificity demonstration during validation**
- **HA requests for additional quantitative parameters**

Lys-C Peptide Map with Mass Detection for the Determination of Identity

01

Analyst performs **sample preparation,** runs the injection scheme and analysis according to the **platform analytical procedure**

5.4 Suggested injection protocol

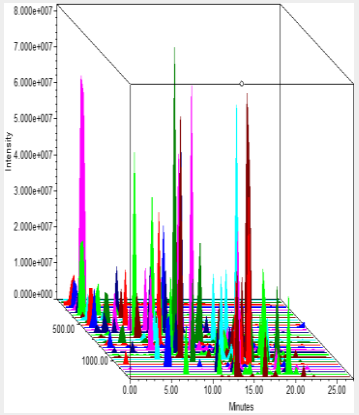
Equilibrate the column with initial conditions until a stable baseline is obtained.
Example of an analysis sequence:

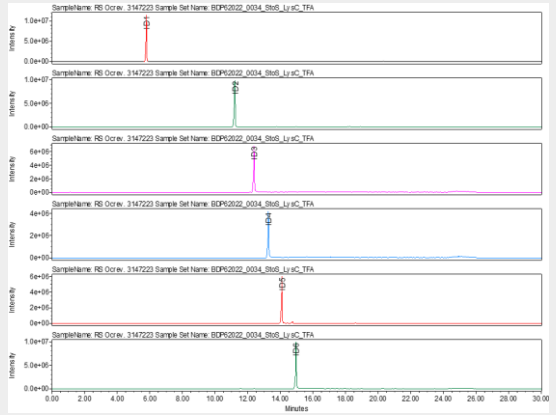
Nr.	Solution	Gradient	Injection volume (µL)
1	Blank	A	30
2	Washing solution	Wash	50
3	Standard solution	A	30
4	Washing solution	Wash	50
5	Sample solution 1	A	30
6	Washing solution	Wash	50
7	Sample solution 2	A	30
8	Washing solution	Wash	50
...	Sample solution ...	A	30
	Washing solution	Wash	50
...	Sample solution 6	A	30
	Washing solution	Wash	50
...	Standard solution	A	30

02

Data Analysis of extracted Ion Chromatograms (XIC) and 2D MS Spectra:

- SST performed on Reference Standard or Generic Control injections
- Confirmation of Identity performed on sample injections based on detection of a product specific ID peptide list





03

Data Reporting

- Locked automated report including automatized SST evaluation and Pass/Fail evaluation for sample ID
- Electronic signature

Peak Results

	Peak Name	Result Id	Retention Time (min)	Target Mass 1 (Da)	Calculated Mass 1 (Da)	Mass 1 Error (Da)	Mass 1 (Pass/Fail)	Target Mass 2 (Da)	Calculated Mass 2 (Da)	Mass 2 Error (Da)	Mass 2 (Pass/Fail)
1	ID1	29954	5.939	592.157	592.11	0.05	Pass			0.00	Pass
2	ID2	29956	17.111	1047.354	1047.39	-0.03	Pass			0.00	Pass
3	ID3	29950	19.610	1144.527	1144.54	-0.01	Pass			0.00	Pass
4	ID4	29952	20.550	1225.859	1225.83	0.03	Pass			0.00	Pass

Peak Results

	Sample Name	Peak Name	Result Id	Retention Time (min)	Mass 1 (Pass/Fail)	Mass 2 (Pass/Fail)	Final Result	Processing Method
1	Atezolizumab/602044	ID1	29954	5.939	Pass	Pass	PASS	Atezolizumab_HClass_QDa
2	Atezolizumab/602044	ID2	29956	17.111	Pass	Pass	PASS	Atezolizumab_HClass_QDa
3	Atezolizumab/602044	ID3	29950	19.610	Pass	Pass	PASS	Atezolizumab_HClass_QDa
4	Atezolizumab/602044	ID4	29952	20.550	Pass	Pass	PASS	Atezolizumab_HClass_QDa

Sign Offs

S. Leibe et al, MABS 2026, VOL 18, NO. 12643964

VS

Analytical Integrity:

The 4-Pillar SST Control Strategy

RETENTION TIME (RT)

< 3.0 min

Origin

Leverages legacy UV method knowledge. Expected RTs averaged from low-pressure (QSM) and high-pressure (BSM) pump validations.

Absorbs standard lab variations (column aging, instrument drift) while strictly preventing peak misalignment.

MASS ERROR

≤ 0.6 Da

Origin

Calibrated against theoretical mass calculations and robust QDa detector hardware capabilities.

Distinguishes closely related molecular weights to ensure absolute accuracy in peptide identification.

INTEGRATION THRESHOLD

≥ 150,000

units

Origin

Derived from method validation limits (empirically verified down to 137,059 intensity units).

Differentiates true signal from baseline noise, eliminating the risk of false positives from artifacts.

EXPECTED INTENSITY

≥ 0.2%

(Relative to base peak)

Origin

Established via processing algorithms and observed empirical data.

Verifies the relative abundance of secondary charge states and filters out weak or spurious ion signals.

Establishment of Platform Analytical Procedure

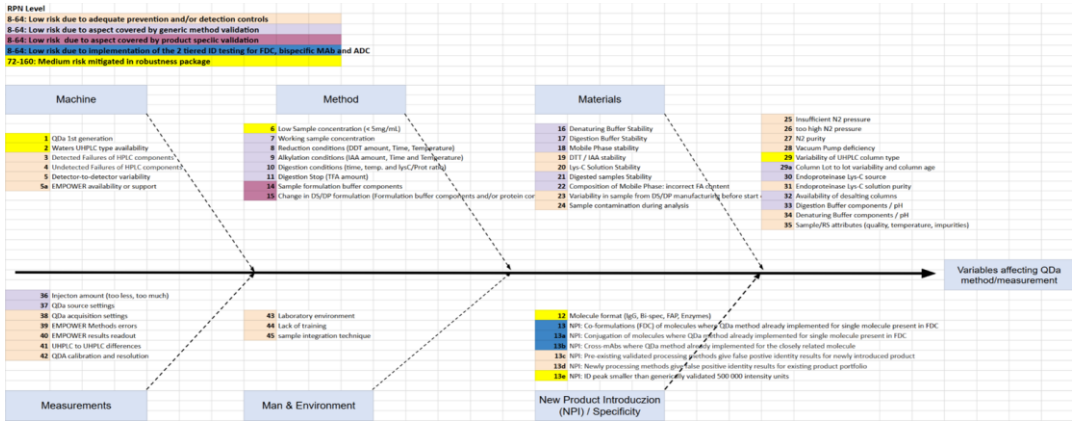
Product independent

Sample Preparation
Chromatography
Mass Spec Analysis
Automated Data Evaluation

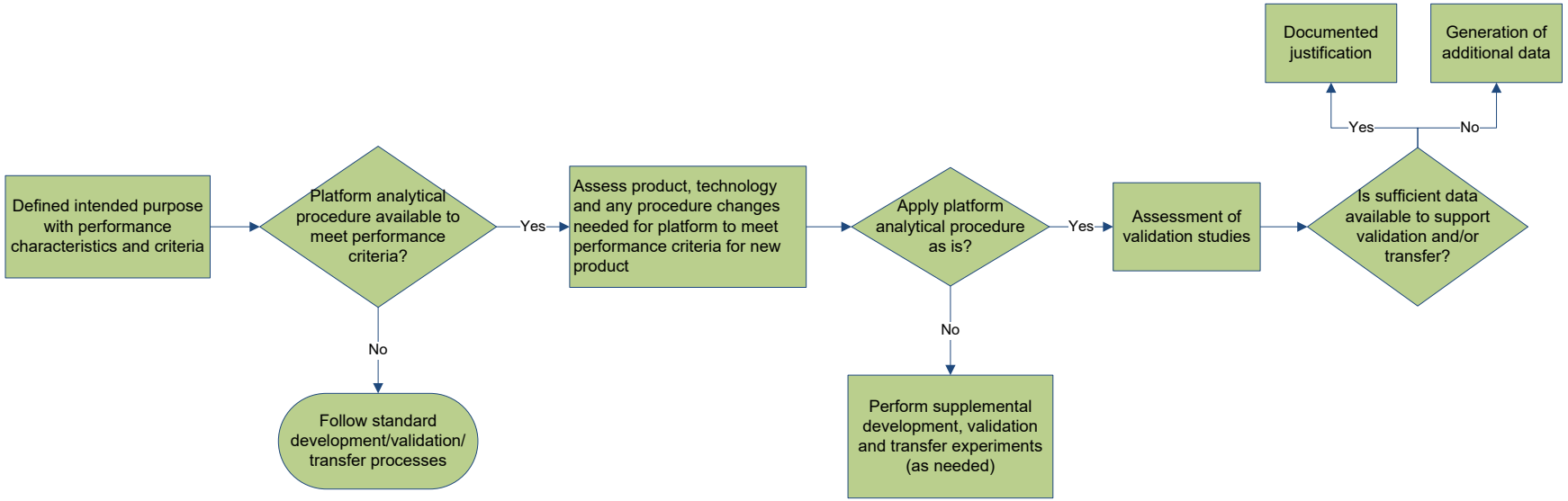
Product specific

List of product specific ID Markers
Product Specific Mass Extraction

- **Platform analytical procedure was established leveraging data from validation and robustness studies of 11 different products**
- **Additional robustness studies where performed based formal risk assessment**
  - **Stability of Solutions, e.g.:**
    Reagents - Digested Samples - Mobile Phases
  - **Sample Preparation, e.g.:**
    Denaturation cond.- Red./Alk. cond. - Enzymatic reaction (...)
  - **Chromatographic Settings, e.g.:**
    Column temp. - Flow rate - Influence of LC System (...)
  - **MS-Detector Settings, e.g.:**
    Cone Voltage - Probe Temp. - Cap. Voltage
  - **Verification of Integration Threshold**



Extension of the Platform Analytical Procedure to a new Product



Validation of specificity for new product

ICH Q2(R2) / Q14 Training Module 7

Identification of list of ID-markers

- **Selection of candidate ID peptide list (after in silico digestion)**
- **Experimental ID peptide list performance verificaton against predefined criteria**
- **Definition of expected retention time window for each ID peptide using differnt types of UPLC's**
- **Sequence confirmation of ID peptides by high resolution MS**

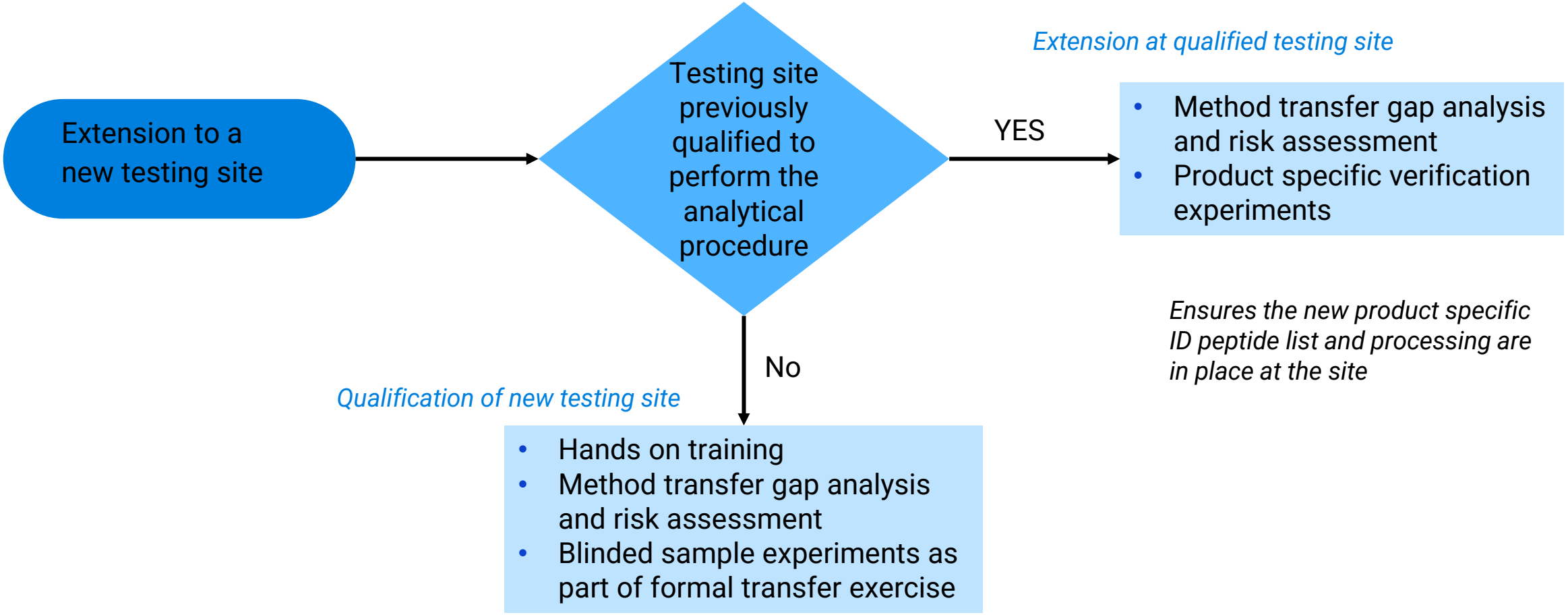
Extension to a new Product – Partial Revalidation

Validation Characteristic	Study Design	Acceptance Criterion
Specificity		
Absence of interference from blank and formulation buffer solutions	Product specific formulation buffer and blank solution are evaluated to demonstrate that the identification of the product is not impacted by components of the product buffer and sample preparation	For the formulation buffer and the blank solutions, the identity of the validated product is negative identity (or has failing results)
Identity of the validated product	Product representative sample[a] is evaluated for positive identity	For the product representative sample, positive identity of the validated product is confirmed (or has passing results)
Evaluation of method's ability to distinguish the new product from the MAH's bio-pharmaceutical marketed products	Spectra from the MAH's marketed biopharmaceutical products are processed using the new product's specific ID peptide list[b] and corresponding acceptance criteria to demonstrate negative identity, confirming method specificity.	Negative identity (or failing) results for all tested MAH bio-pharmaceutical marketed products

[a] A sample with the same composition (e.g., reference standard).

[b] This evaluation can utilize spectra stored in a dedicated project folder in the MAH's chromatography data system or newly generated spectra from a validation experiment.

Extension of the Platform Analytical Procedure to Additional Sites



Project Benefits - Technical

Harmonization from 15+ methods to 1 platform analytical procedure= compliance, efficiency, simplification, and innovation

Compliance: Automated user independent quantitative data evaluation for specificity

Efficiency: Platform procedure development/validation/and transfer process results in less work and shorter analytical tranfer lead times. Less time needed for extention to new products

Simplification: QC operations and process for method training, equipment/systems maintenance, and record review with automated reporting of results

Innovation: Establishes state of the art method is QC and paves way for future MAM implementation and CQA monitoring via mass spectrometry

Conclusion

- **ICH Q14** offers a science- and risk-based framework that accelerates the adoption of advanced analytical technologies
- Using **risk management tools** systematically mitigates variables to ensure method robustness
- Defining an **Analytical Target Profile (ATP)** allows laboratories to prospectively set performance requirements for new measurement technologies.
- The concept of **platform analytical procedures** enables organizations to reduce efforts for analytical procedure devolvement and use (prior) validation data across multiple products
- Ultimately, applying these structured concepts fosters innovation, simplifies quality control operations, and speeds up analytical procedure transfers across networks.

Acknowledgement

- Andrea Lomoschitz and the Benchtop NMR team
- Sebastien Leibe and Sebastien Violini and the Platform Identity Team
- Alexander Buettner
- ….

Doing now what patients need next