An Industry Perspective on Established Conditions in the Analytical Control System

Christof Finkler, F. Hoffmann-La Roche
Control System Development

INPUT: Process Parameter

CPPs

OUTPUT: Quality Attribute

CQAs

Acceptance Criteria

Overall Control Strategy

GMP - Procedural Controls

GMP - Environmental Controls

Control of Process Parameters (CPPs & Non-CPP)

Control of Materials

Attribute Testing Strategy
Specified CQAs
Monitored CQAs
Control System Development

INPUT:
- Process Parameter
  - CPPs

OUTPUT:
- Quality Attribute
  - CQAs

Acceptance Ranges

Control System Development

Overall Control Strategy

GMP - Procedural Controls
GMP - Environmental Controls

Control of Process Parameters (CPPs & Non-CPP)
Control of Materials

Attribute Testing Strategy
Specified CQAs
Monitoring CQAs

\[ \sigma = (\sigma(\text{process}) + \sigma(\text{analytical method})) \]
Applying QbD Principles to Analytical Methods

- Target Product Profile
- Risk Assessment
- Critical Quality Attributes
- Design Space
- Control Strategy
- Continued Process Verification

- Analytical Target Profile
- Risk Assessment
- Critical Method Attributes
- Method Operable Design Region
- Control Strategy
- Continued Method Verification
The Analytical Lifecycle

CQA

ATP

Method Design Scouting Evaluation

Method Development

Method Validation

Method Performance Control Strategy

Transfer to Commercial

Method Monitoring Continual Improvement

Method Development Strategy

Establishment of MODR and Method Control Strategy

Risk Assessment

Knowledge Management
What does analytical QbD stand for?

- Good Method Design
- Good Method Understanding
- Good Method Risk Control
- Good Operational Flexibility
- Good Change Control

Method Development Report

- Analytical Target Profile (ATP)
  Method performance criteria

Risk Mapping

- Method Control Strategy:
  - Risk based SST
  - Parameter Ranges

Multivariate statistical Analysis

Knowledge Management
Expectations of an analytical method

- Robustness
- State-of-The-Art
- Precision & Accuracy
- Speed
- Low Operational Costs
- Compliance
- Operator Safety
Analytical Target Profile

- **Intended Purpose**
  - Identity, Purity, Assay, Potency
  - CQAs: glycosylation, size variants, charge variants, oxidation, etc.

- **Performance**
  - Accuracy, precision, LOQ, Specificity etc. ICH Q2

- **Target**
  - IEC, CIEF, iCIEF, CZE, SEC, CE-SDS etc.

- **Technology**
  - Column, flow rate, Gradient, ampholyte etc.

- **Method Parameters**
Factors influencing ATP Generation

- Statistical requirements for measurement result
- Critical Quality Attribute requirements of Product (Specifications)
- Toxicological Considerations / Qualification
- Regulatory requirements, e.g.
  - ICH Guidelines
  - Pharmacopoeias
  - EMA Guidelines
- Measurement Context, e.g.
  - Type of test
  - Operating environment
# ATP Charge Heterogeneity

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intended Purpose CQA</strong></td>
<td>DS/DP IPC, release and stability</td>
</tr>
<tr>
<td></td>
<td>Determination of the acidic and basic variants of the native molecule</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>Separation of Acidic Region and Basic Region from Main Peak</td>
</tr>
<tr>
<td></td>
<td>No significant interference from stressed and non-stressed reagent blank and other matrix components</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>QL&lt; 0.5 area %</td>
</tr>
<tr>
<td><strong>Linearity</strong></td>
<td>Main Peak: $r \geq 0.99$</td>
</tr>
<tr>
<td></td>
<td>Determination of Product/Process Related Substances/Impurities: $r \geq 0.98$</td>
</tr>
<tr>
<td><strong>Accuracy</strong></td>
<td>Main Peak: 94-106 % of assumed true value (area%)</td>
</tr>
<tr>
<td><strong>Precision of reportable result</strong></td>
<td>Main Peak: $\leq 6%$ RSD (consider extent of Main Peak)</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>Main Peak: at least 80%-120% of nominal protein concentration</td>
</tr>
<tr>
<td></td>
<td>Other components: QL- 120% of upper spec limit</td>
</tr>
<tr>
<td><strong>Operating conditions and Environment</strong></td>
<td>Reagents from established vendor and equipment from preferred vendors used in QC network</td>
</tr>
<tr>
<td></td>
<td>The test procedure must be stable for at least 48 h of consecutive analyses</td>
</tr>
<tr>
<td></td>
<td>Short sample to sample run time</td>
</tr>
<tr>
<td></td>
<td>Consistent quality and supply of consumable</td>
</tr>
<tr>
<td></td>
<td>The method should work without harmful ingredients</td>
</tr>
</tbody>
</table>
Advantages of the ATP concept

- Facilitation of technology selection
- Facilitation of assessment of alternative methods and technologies
- Enabling balance between cost/safety
- Facilitation of analytical method change control
- ATPs can be retrospectively defined for already existing methods to anticipate future changes
- ATPs is a tool for evaluating advances in analytical technologies and adopting improvements
Enhanced Method Development
**Method Design Operational Region (MODR)**

**Case Study: Ion Exchange HPLC**

[Diagram showing various factors and their relationships.]

- **IEC MAB**
- **Running Conditions**
- **Sample prep.**
- **Storage of diluted sample**
  - **final conc.**
  - **Diluent**
- **Storage temperature**
  - **Duration: Min. 1d**
- **Digestion**
  - **Temperature**
  - **Duration**
  - **Concentration**
  - **Use-by-period**
  - **Lot-to-lot variability**
  - **Vendor**
  - **Waterbath/Thermomix**
- **Integration**
- **Injection protocol**
- **Buffer Substance**
- **pH**
- **Buffer Conc.**
- **Use-by-period: 2w BRT**

**Polymer part:**

- **Dissolved polymer**
- **Solution pH**
- **Solution concentration**
- **Solution type**
- **Solution temperature**
- **Solution viscosity**
- **Solvent type**
- **Solvent temperature**
- **Solvent viscosity**
- **Solvent purity**
- **Impurities**

**Quality:**

- **purity**
- **impurities**
- **endotoxins**
- **pyrogen content**
- **sensitivity**
- **stability**

**Controlled Parameters:**

- **Variable factors**
  - **parameters which are fixed and can be controlled**
  - **parameters which cannot be controlled**
  - **parameters which may change and can be controlled**

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**Legend:**

- **C**
- **N**
- **X**
Method Design Operational Region (MODR)

Case Study: Ion Exchange HPLC

Responses
- % Area of Main Peak, Acidic Species & Basic Species
- Resolution, ...

<table>
<thead>
<tr>
<th>Factor</th>
<th>Lower Edge</th>
<th>Center Point</th>
<th>Upper Edge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buffer conc.</td>
<td>15</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Salt conc.</td>
<td>180</td>
<td>200</td>
<td>220</td>
</tr>
<tr>
<td>Column Tp.</td>
<td>32</td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td>Flow rate</td>
<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>pH</td>
<td>7.4</td>
<td>7.5</td>
<td>7.6</td>
</tr>
<tr>
<td>Column</td>
<td>Two different lots each: MAAbPac SCX-10 &amp; YMC BioPro SP-F</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[mM ACES]  
[mM NaCl]  
[°C]  
[ml/min]
No model for Area% of Main Peak, Acidic & Basic Region ➔ Desired Outcome, parameters are not influenced by changing method parameters
Method Design Operational Region (MODR)

Case Study: Ion Exchange HPLC

No model for Area% of Main Peak, Acidic & Basic Region ➔ Desired Outcome, parameters are not influenced by changing method parameters

MODR well within the white working space

Method Control Strategy
- Parameter ranges, SST’s, method monitoring etc.
ESTABLISHED CONDITIONS

CASE STUDY: CONTROL OF ANTIBODY FRAGMENTS
Size variants of Monoclonal Antibodies

- Aggregation
- Hinge cleavage
- Side chain specific cleavage (e.g. Gly-Gly, Pro-Ser, Asp-Gly etc.)
- Disulfide cleavage
- Thioether bond formation
- Half antibodies (IgG4)
- Ragged cleavage sites

- Antibody fragments are also referred to as low-molecular-weight species (LMWS)
- Different technologies and analytical methods are capable to control fragmentation e.g. SDS PAGE, CE-SDS, SE-HPLC
Case study - control of fragments

- Antibody fragments (Fab, Fab/c, light chain, heavy chain, and others) are identified for this case study as Critical Quality Attributes (CQA).

- Case study on lifecycle management of capillary electrophoresis sodium dodecyl sulfate (CE-SDS) under non-reducing conditions:
  - Scenario 3: current state, method changes follow existing regulatory pathways (e.g. regulatory submission)
  - Scenario 2: method changes within a given technology will be performed in accordance to Post Approval Change Management Protocols (PACMP)
  - Scenario 1:
    - enhanced method development
    - changes across technologies (e.g. chromatography, mass spectrometry, ...) will be performed in accordance to preapproved protocols (PACMP).
Case study for established conditions

• Method description and validation will be submitted in all scenarios
  – Different options define the extent of information that will be part of EC
  – EC scenario 1: method capability / performance commitment
  – EC scenario 2: capability performance commitment for a specified technology
  – EC scenario 3: method description (including operating conditions)

• Method changes:
  – Amount of information will be the same for all 3 options at the time of implementation
  – Difference in sequence and timing (i.e. pre or post approval)
    ▪ Frontloading of lifecycle relevant information for option 1 and 2
    ▪ Use of protocols without approval prior implementation for option 1 and 2

• Specifications and acceptance criteria are established conditions in all scenarios
## Overview to the typical knowledge expected for each EC options

<table>
<thead>
<tr>
<th></th>
<th>Scenario 3</th>
<th>Scenario 2</th>
<th>Scenario 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scenario 3</strong></td>
<td><strong>“enhanced knowledge”</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Scenario 2</strong></td>
<td><strong>“intermediate knowledge”</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Scenario 1</strong></td>
<td><strong>“traditional knowledge”</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Product knowledge</strong></td>
<td>+++</td>
<td>++</td>
<td>+/−</td>
</tr>
<tr>
<td>(e.g. CQA assessment,</td>
<td></td>
<td></td>
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<tr>
<td>degradation profile,</td>
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<tr>
<td>impurity profile,</td>
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<tr>
<td>potential contaminant,</td>
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<td></td>
<td></td>
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<tr>
<td>interaction with</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>container…)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Method knowledge</strong></td>
<td>+++</td>
<td>++</td>
<td>+/−</td>
</tr>
<tr>
<td>(e.g. signal</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>characterization,</td>
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<td></td>
<td></td>
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<tr>
<td>stability indicating</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>properties, performance,</td>
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<td></td>
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<tr>
<td>method validation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parameter)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Scenario 3: Traditional - Single Method

- CE-SDS was traditionally developed and validated.

- *Established conditions would include used instrument (CE-SDS system), operating conditions, and critical materials/reagents/buffers (e.g. fluorophore).*

- Any change to these conditions will follow existing regulatory pathways (e.g. regulatory submission). Method performance has to be demonstrated by revalidation that would be submitted.
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Changes requiring Pre-Approval:
- use of an alternative instrument or a new technology (e.g. change from CE-SDS to Chip electrophorese)
- Implementing alternative critical materials/reagents/buffers
- Changes of ECs
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- Changes of ECs

Changes within PQS:
- Use of alternative vendors/supplier for non-critical materials/reagents/buffers
- Change in operating conditions that are non-EC
Comparison Capillary Electrophoresis with Chip Electrophoresis

CE-SDS (non-reduced)

MCE-SDS (non-reduced)
## Comparison Capillary Electrophoresis with Chip Electrophoresis

<table>
<thead>
<tr>
<th>Sample (nr)</th>
<th>CE-SDS</th>
<th></th>
<th>MCE-SDS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LMW forms</td>
<td>main peak</td>
<td>HMW forms</td>
<td>LMW forms</td>
</tr>
<tr>
<td>Ref. Standard</td>
<td>5.0</td>
<td>94.5</td>
<td>0.5</td>
<td>4.6</td>
</tr>
<tr>
<td>4 weeks, 5 °C</td>
<td>5.2</td>
<td>94.2</td>
<td>0.6</td>
<td>4.7</td>
</tr>
<tr>
<td>4 weeks, 40 °C</td>
<td>11.3</td>
<td>87.8</td>
<td>0.8</td>
<td>10.2</td>
</tr>
</tbody>
</table>

- **CE-SDS** and **MCE-SDS** represent different techniques for analyzing protein samples.
- The results show differences in the percentages of LMW (low molecular weight), main peak, and HMW (high molecular weight) forms between the two methods.
- The table illustrates the changes in sample composition over different storage conditions (5°C and 40°C for 4 weeks).

### Graphical Representation

- The bar chart compares the percentage distribution of LMW, main peak, and HMW forms for CE and MCE methods under 5°C and 40°C conditions.
- The chart visually represents the data from the table, highlighting the impact of temperature on sample composition.
Scenario 2: Performance Based - One Technology

- Method performance characteristics and criteria are defined in an analytical target profile (ATP) that is dependent of technology (method type)
- Risk assessment principles guide development CE-SDS and validation
- Method parameter ranges based on uni- and multivariate studies
- **Established conditions: the claimed performance of the method, Separation principle (electrophoresis), commitment to reestablish MODR for new method, a predefined assay comparability protocol that would enable to make changes to the CE procedure, performance verification program**
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Changes requiring Pre-Approval:
- use of an alternative technology
  (e.g. change from CE-SDS to HPLC)
- Changes of EC’s
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Changes requiring Pre-Approval:
- use of an alternative technology (e.g. change from CE-SDS to HPLC)
- Changes of EC’s

Changes within PQS*:
- Change in operating conditions
- Change in instrument type e.g. CE vs MCE
- Use of alternative vendors/supplier for materials/reagents/buffers

* pre-approved PACMP available
Scenario 1: Performance Based

- Performance characteristics and criteria are defined in an analytical target profile (ATP) technology independent

- A systematic science and risk based development approach.

- Method parameter ranges and MODR based on uni and multivariate data

- *Established conditions: the claimed performance of the method (ATP), commitment to reestablish MODR for new method, a predefined assay comparability protocol that would enable to make changes to the CE procedure, performance verification program*
Scenario 1: Performance Based

- Performance characteristics and criteria are defined in an analytical target profile (ATP) technology independent
- A systematic science and risk based development approach.
- Method parameter ranges and MODR based on uni and multivariate data

**Established conditions:** the claimed performance of the method (ATP), commitment to reestablish MODR for new method, a predefined assay comparability protocol that would enable to make changes to the CE procedure, performance verification program

Changes requiring Pre-Approval:
- Changes of EC’s

Changes within PQS*:
- Change in operating conditions
- Change in instrument type
- Use of alternative vendors for critical materials/reagents/buffers
- Change of technologies (e.g. electrophoresis to HPLC)*

* pre-approved PACMP available
## EC for control of fragments

<table>
<thead>
<tr>
<th>Method Description</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP: capability to measure fragments</td>
<td>ATP and Technology: capability to measure fragments with CE</td>
<td>Detailed method description</td>
<td></td>
</tr>
</tbody>
</table>
| Development approach | - Method Operable Design Region  
- Risk analysis (e.g. structured method factor analysis) | Targeted development, dependent of risk assessment | Classical |
| Predefined assay comparability protocol** | - Acceptance criteria aligned with the claim  
- Study design (e.g. number and type of samples…)  
- Stability indicating property  
- Characterization of signals including use of orthogonal methods | - Acceptance criteria aligned with the claim  
- Study design (e.g. number and type of samples…)  
- Stability indicating property | Not applicable |
| Performance verification** | yes | yes | none |

** part of the Post Approval Change Management Protocol (PAMC)
## EC for control of fragments (2)

<table>
<thead>
<tr>
<th></th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technology</strong></td>
<td>None*</td>
<td>- Electrophoresis</td>
<td>- Capillary Electrophoresis</td>
</tr>
</tbody>
</table>
| **Instrument / Critical Material** | None*      | None*      | - Capillary system manufacturer X, type Y  
- Detection mode  
- Capillary |
| **Conditions** | None*      | None*      | Comprehensive description (e.g. Inject voltage, Injection duration, sample preparation, system operating conditions …) |
| **Buffers / Critical Reagents (EC)** | None*      | None*      | Comprehensive description (e.g. sodium bicarbonate, pH) |

* Information equivalent as the one presented in Scenario 3 would be presented in the filing as non-EC
Level of Risks

Risk:
- Wrong Pass fail decision for a measured attribute
- Use of a certain technology
- Deviation from operation parameters

HA Change control
Level of Risks

Risk

- Wrong Pass fail decision for a measured attribute
- Use of a certain technology
- Deviation from operation parameters

Scenario

<table>
<thead>
<tr>
<th>Scenario</th>
<th>3</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA Change control</td>
<td>HA Change control</td>
<td>HA Change control</td>
<td>HA Change control</td>
</tr>
</tbody>
</table>
Analytical Target Profile

- **Intended Purpose**
  - Accuracy, precision, LOQ, Specificity etc ICH Q2
  - Identity, Purity, Assay, Potency
    - CQAs: glycosylation, size variants, charge variants, oxidation, etc

- **Performance Target**
  - IEC, CIEF, iCIEF, CZE, SEC, CE-SDS etc

- **Technology**
  - Operational Flexibility
    - Column, flow rate, Gradient, ampholyte etc
  - Established Conditions Based on critical Method Parameters

- **Method Parameters**
  - Technology based Established Conditions

- **ATP**
  - Performene Based Established Condition
Conclusions

• Quality by design tools and lifecycle concepts can be applied to analytical methods

• The Analytical Target Profile is a key element of analytical QbD

• Application of QbD Elements leads to robust methods

• The extent of information that will be part of Established Conditions should be linked to the development approach

• Enhanced development concepts may lead to a reduction of ECs

• Post Approval Change Management Protocols should facilitate changes to analytical methods and technologies
Thank You

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Doing now what patients need next