ICH Q2 / Q14

From good to great
CASSS CMC Summer Forum
Dr. Oliver Grosche
The importance of analytical procedures (AP)

- Our materials, processes and products are all characterized by analytical procedures
- The property / quality of a material appears only as good as perceived through the analytical procedure
### How big is the elephant? An estimation...

<table>
<thead>
<tr>
<th>Category</th>
<th>Procedures</th>
<th>Materials/Excipients</th>
<th>GMP Steps/Strengths</th>
<th>Total Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting and raw materials:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Procedures x 5 Materials</td>
<td></td>
<td></td>
<td></td>
<td>20 Procedures</td>
</tr>
<tr>
<td><strong>In process controls (API):</strong></td>
<td></td>
<td></td>
<td></td>
<td>10 Procedures</td>
</tr>
<tr>
<td>2 Procedures x 5 Materials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>API Precursors:</strong></td>
<td></td>
<td></td>
<td></td>
<td>20 Procedures</td>
</tr>
<tr>
<td>4 Procedures x 5 GMP Steps</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>API:</strong></td>
<td></td>
<td></td>
<td></td>
<td>10 Procedures</td>
</tr>
<tr>
<td>10 Procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Excipients:</strong></td>
<td></td>
<td></td>
<td></td>
<td>25 Procedures</td>
</tr>
<tr>
<td>5 Procedures x 5 Excipients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>In process controls (Drug product):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Procedures x 5 Materials</td>
<td></td>
<td></td>
<td></td>
<td>15 Procedures</td>
</tr>
<tr>
<td><strong>Drug Product:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Procedures x 2 Strengths</td>
<td></td>
<td></td>
<td></td>
<td>12 Procedures</td>
</tr>
<tr>
<td><strong>Sum</strong></td>
<td></td>
<td></td>
<td></td>
<td>112 Procedures</td>
</tr>
</tbody>
</table>

1 Manufacturing Process but easily > 100 Analytical Procedures!
ICH Q2 – A good guideline ...

- Step 2 in 1993 and 1995
- Q2R1 with minimal changes in 2005
- 2021 and still a good guideline!

### Document History

<table>
<thead>
<tr>
<th>First Codification</th>
<th>History</th>
<th>Date</th>
<th>New Codification</th>
</tr>
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<tbody>
<tr>
<td>Q2(R1)</td>
<td></td>
<td></td>
<td>November 2005</td>
</tr>
</tbody>
</table>

### Parent Guideline: Text on Validation of Analytical Procedures

<table>
<thead>
<tr>
<th>Q2</th>
<th>Approval by the Steering Committee under Step 2 and release for public consultation.</th>
<th>26 October 1993</th>
<th>Q2</th>
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<tbody>
<tr>
<td>Q2A</td>
<td>Approval by the Steering Committee under Step 4 and recommendation for adoption to the three ICH regulatory bodies.</td>
<td>27 October 1994</td>
<td>Q2</td>
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</table>

### Guideline on Validation of Analytical Procedures: Methodology developed to complement the Parent Guideline

<table>
<thead>
<tr>
<th>Q2B</th>
<th>Approval by the Steering Committee under Step 2 and release for public consultation.</th>
<th>29 November 1995</th>
<th>in Q2(R1)</th>
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<tr>
<td>Q2B</td>
<td>Approval by the Steering Committee under Step 4 and recommendation for adoption to the three ICH regulatory bodies.</td>
<td>6 November 1996</td>
<td>in Q2(R1)</td>
</tr>
</tbody>
</table>

### Current Step 4 version

| Q2A and Q2B | The parent guideline is now renamed Q2(R1) as the guideline Q2B on methodology has been incorporated to the parent guideline. The new title is "Validation of Analytical Procedures: Text and Methodology". | November 2005 | Q2(R1) |
Then in 1995...

HPLC with Diode-Array detection was a Luxury!

Now...

Mobile phones

Analytical Technology

Hyphenated techniques like HPLC-MS are standard

4%

BLA approvals for new biological drugs*

25% (in 2020)

... and new vaccines too!

Why change?

• Evolution of new analytical technologies and multivariate analysis
• ICH Q8-Q10 guidelines were created
• Methodology for analytical procedures development has evolved in the same direction (analytical QbD, enhanced approaches)
• Increased importance of biopharmaceuticals and related analytical procedures
• More widespread use of design of experiments and CMC statistical tools
• New harmonized principles on post-approval changes in ICH Q12
A day in the lab with Maria*... (*Maria is a fictional character)
Maria’s supervisor asked her to establish thermogravimetry as alternative technique to water (Karl-Fischer) and demonstrate that both procedures can be used to determine the water in the API.

How to cross-validate and compare procedures if they are so different in technology?
From Validation Characteristics ...  

<table>
<thead>
<tr>
<th>Validation Characteristic</th>
<th>Karl-Fischer Titration</th>
<th>Thermogravimetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>Absolute measurement, amounts titrant used is proportional to amounts of water by principle</td>
<td>Secondary procedure comparison (with KF titration)</td>
</tr>
<tr>
<td>Precision</td>
<td>Repetitive analysis of sample preparations</td>
<td>Repetitive analysis of sample preparations</td>
</tr>
<tr>
<td>Specificity</td>
<td>Specific for water, some side reactions may occur with other components</td>
<td>Not specific for water only, other volatile components may also be detected</td>
</tr>
<tr>
<td>Linearity</td>
<td>Titration levels of water</td>
<td>By principle (weighing) linear, why need to demonstrate?</td>
</tr>
<tr>
<td>Range</td>
<td>Better at lower water levels</td>
<td>Better at higher water levels</td>
</tr>
</tbody>
</table>

- Validation experiments may look very different depending on the technical principles used
- Not all ICHQ2 characteristics make sense to be experimentally verified
### Performance Characteristics

<table>
<thead>
<tr>
<th>Intended Purpose:</th>
<th>Determination of water content in API (Specification NMT 2.0 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Performance Characteristic</strong></td>
<td><strong>Criteria</strong></td>
</tr>
<tr>
<td>Accuracy...</td>
<td>Max 10% rel. bias from theoretical water content ... over the range of at least 0.2-2.4 % of specified water level</td>
</tr>
<tr>
<td>Precision...</td>
<td>max. 5 % RSD for n=6 samples</td>
</tr>
<tr>
<td>Specificity...</td>
<td>No interference by other components resulting in a bias of greater than 10% rel.</td>
</tr>
</tbody>
</table>

- Driven by product requirements
- Technology independent
- Focus on the required performance of the analytical procedure
- Defines the suitability for its intended purpose
- Common denominator
From good to great when

• Performance characteristics drive the validation methodology
• Performance characteristics drive the bridging strategies
• Analytical procedure performance is defined based on product needs and knowledge
Next challenge of the day – Maria’s discussion with QA

Maria has developed a new UPLC procedure for a new oncology product. She has created a comprehensive dataset to understand the procedure’s performance. She has therefore proposed to include relevant development data into her validation dataset rather than repeating the experiments again for the validation. QA fears a compliance issue and insists on recreating data once a validation protocol has been signed off.

*Is validation a checkbox exercise?*

*How to reduce experimental efforts, unnecessary costs and accelerate drug availability?*
Key Elements of Quality by Design (QbD) for Analytical Procedures

Product and Analytical Knowledge

ATP
Intended Purpose & Performance Characteristics/Criteria

Selection of Technology and AP

AP parameters

AP attributes

Systematic AP development/design

Risk analysis (e.g. Fishbone, FMEA)

Parameter Mapping/Clarity of instructions

Robustness testing/Experimental design (DoE)

Statistical multivariant data analysis

Method validation

Critical AP parameters

Critical AP attributes

Method Operable Design Range

AP Control strategy incl. Risk based SST

Input

Tools

Output

Not all elements may exist or are meaningful to be used!
From good to great when

- Pre-existing knowledge can be used
- Development data can be used in lieu of validation data
- Individual enhanced tools and elements (including MODR) are used only when meaningful
- Supportive information from an analytical development can be submitted
- A new eCTD module in ICH M4Q is in place
A call came in from a partner laboratory. The lab wants to increase the costs per analysis as the SST for enantiomer resolution fails after approx. 200 runs. The laboratory has worked on proposals for adjustments to maintain column performance for longer... but that would require the change of the parameters of the analytical procedure.

Are the adjustments worth the effort for changing the procedure.

Shall we just accept the additional financial burden of replacing columns often instead?
Adjustment of analytical procedures to increase performance

- The column costs are 20kUSD/year
- The cost of changing the procedure internationally is 250 k in registration fees and internal costs for preparation

→ Maria decides not to change and accepts the additional costs and work with buying frequently new columns, contributing to the product costs

Source: C. Chevreau, Elanco Animal Health, with permission
From good to great when

- Minor adjustments increasing the analytical procedure performance or reliability should be
  - Easy
  - Immediate
  - Within the Company’s PQS
Maria is attending the presentation of the company’s summer intern. The student has successfully developed a new uHPLC procedure which can monitor the degradation products of 5 different marketed products with the same analytical procedure. He also achieves a better resolution of individual degradation products. Applying the procedure would save more than 30% of resources by pooling stability samples of multiple products in one analysis. Additionally, the organic solvent waste was reduced by 50%.

What would it take to change the analytical procedures for all the products. How and when could that harmonized status be reached?
Dimension 1: Change Procedure

Triggers:
- Increased knowledge & Innovation
- Changes in Regulations & Compendia
- Health Authority Requests
Dimension 2: non-consistent change classification on a global level

<table>
<thead>
<tr>
<th>Example</th>
<th>US</th>
<th>Europe (centralized)</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change of Water determination (KF to Coulometric)</td>
<td>Minor</td>
<td>Type Ib</td>
<td>Notification</td>
</tr>
<tr>
<td>Replacement TLC by HPLC for (purity)</td>
<td>Moderate</td>
<td>Type Ib</td>
<td>Partial Change Application</td>
</tr>
<tr>
<td>Alternative analytical method: conventional HPLC and uHPLC</td>
<td>Minor</td>
<td>Type Ib</td>
<td>Partial Change Application</td>
</tr>
<tr>
<td>Change in a Biological Assay Technique</td>
<td>Major</td>
<td>Type II</td>
<td>Partial Change Application</td>
</tr>
</tbody>
</table>

Non-consistent classification of changes leads to different implementation timelines
Common understanding of AP change risk

Impact on product attribute tested + Extent of Change + Levels of control

Impact on product attribute tested:
- Extent of change:
  - AP Performance
  - Technology
  - AP Parameters
-xbd

Extent of Change:
- Different performance expectations
- New technology, same performance expectations
- New procedure same technology
- Adjustments

Levels of control:
- ATP
- Validation
- SST
- AP description

Change
Cycle times are likely to be 1-3 years and sum of licensing costs are high

- Full harmonization may be never reached
- Harmonized method
- Change of Method
- New
- Change Submission
- Different approval timelines
- Multiple license fees
- Next change coming in before completion of previous
- Parallel Testing required
- Implement -tion
- Change Approval
- Duplicate Testing / Regional SKU Routing
- Old
- New
From Good to great when

- Risk evaluation for AP changes is harmonized globally
- Additional control elements from the enhanced approach can be used to lower the risk category of change
- Changes can be implemented globally at the same time
Level of detail in Q2 and Q14 guidelines

- **Blind Compliance**
  - Application of full concepts for all APs
  - No additional operational flexibility

- **Waste**
  - Over-application of enhanced tools
  - Over-formalized approach

- **Optimal Benefit**
  - Application of enhanced concepts where meaningful
  - Sufficient detail level to ensure AP performance

- **Inexperienced application**
  - Neglecting of product safety context for analytical procedures
  - Wrong/unsafe use of operational flexibility
Conclusions – Q2 and Q14 will be great if...

- Analytical performance characteristics and criteria are used to their full potential
- Pre-existing knowledge can be used
- Relevant development data can be used in lieu of validation data
- Individual enhanced tools and elements can be used as meaningful
- Supportive information from an analytical development can be submitted → new eCTD module in ICH M4Q
- Risk evaluation for AP changes is harmonized globally
- Additional control elements can be used to lower the risk category of change
- Changes can be implemented globally at the same time
- Level of detail in Q2 / Q14 is appropriate to maximize benefits for safety, availability and cost of medicines
Thank you!

- Industry colleagues from Bio, Efpi, PhRMA, Elanco, Seagen
- ICH Q2/Q14 EWG