Case Study #2 –

Q12 Unpublished Analytical Case Study: Reflection on Risk-based Approach

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Q12 Unpublished Analytical Case Study: Reflection on Risk-based Approach

- **Making-of the Analytical case study (2018-2019)**
  - Thought process
  - Unpublished example

- **Published Q12 case study for analytical procedures (Nov. 2019)**

Making of the Analytical case study

Q12: Evolution of EC for analytical procedures

ICH Q12 step 2b (2017):

3.2.3.2. Identification of ECs for analytical procedures

[…] The extent of ECs could vary based on the method complexity, development and control approaches.

- Where the relationship between method parameters and method performance **has not been fully studied** at the time of submission, ECs **will incorporate the details of operational parameters including system suitabilit**y.
- When there is **an increased understanding** of the relationship between method parameters and method performance defined by a systematic development approach including robustness studies, **ECs are focused on method-specific performance criteria** (e.g., specificity, accuracy, precision) rather than a detailed description of the analytical procedure.

[…]

ICH Q12 step 4 (2020):

3.2.3.2. Identification of ECs for analytical procedures

[…] The extent of ECs and their reporting categories could vary based on the degree of the understanding of the relationship between method parameters and method performance, the method complexity, and control strategy. A justification to support the identification of ECs and corresponding reporting categories for changes to ECs based on risk management should be provided.

Different approaches can be used to identify ECs for analytical procedures, for example as analytical technology and development approaches advance; these approaches include, but are not limited to the following:

- When **more limited development studies** have been conducted this **may result in a narrow operating window** to ensure method performance. In such cases **ECs may be more extensive with fixed and/or tight conditions.**
- **Enhanced understanding** can lead to **a wider operating window** that ensures method performance, where **ECs can be reduced and focused on method performance** (e.g., method parameters acceptable ranges rather than set points, performance criteria).

[…]

Making of the Analytical case study

Thought process

Analytical case study should illustrate what EC could look like if following minimal development approach

Method must at least comply to pharmacopeial monograph

Example should differentiate EC for minimal vs enhanced analytical development

At the minimum methods should be validated in accordance to Q2

Capillary electrophoresis used in somatropin EP monograph selected

What is enhanced analytical development?

Making of the Analytical case study

Thought process

Quality attribute measured as the sum of pre-peak (mixture of undefined fragments)

	Traditional approach	Enhanced approach
Product knowledge (e.g. CQA assessment, degradation profile, impurity profile, potential contaminant, interaction with container…)	+/_	+++
Method knowledge (e.g. signal characterization, stability indicating properties, performance, method validation parameter)	+/_	+++

Characterisation studies identified low molecular weight species that are considered CQA; confirmed by orthogonal methods

Traditionally developed and validated in accordance to ICH Q2

Method development using risk management approaches, multivariate analysis of inputs and outputs; Validation in accordance to a verification protocol that will be periodically excecuted or when changes are introduced

Unpublished draft

2 approaches:
Parameter ("traditional")
vs *Enhanced*

CQA and Technology = EC

Method description	Acceptable ranges and reporting categories (White boxes are ECs and **grey ones are not-ECs**.)	
	Parameter Based Approach	**Enhanced Approach**
Critical Quality Attribute	Sum of Pre-peaks	Low molecular weight species
Technology	Capillary Electrophoresis **(PA)**	Capillary Electrophoresis **(NM)**
Critical Instrument / Material / Reagent	- Capillary system manufacturer X, type Y - UV Detection 280 nm - Capillary, uncoated-fused silica / Capillary ID and length - Buffer composition - SDS gel buffer - labelling dye **(NM)**	-Capillary system manufacturer X, type Y - LIF Detection 488 nm / 560 nm - Capillary, uncoated-fused silica / Capillary ID and length - Buffer composition - SDS gel buffer - labelling dye
Conditions	- Inject voltage - Injection duration - Separation Voltage - Separation duration - Capillary temperature - Autosampler Temperature **(NL)**	- Inject voltage - Injection duration - Separation Voltage - Separation duration - Capillary temperature - Autosampler Temperature - Labeling reaction conditions
System suitability	- Interference - Repeatability - Tailing factor - Resolution factor **(NL)**	- Interference - Repeatability - Tailing factor - Resolution factor
Validation / Performance verification protocol (or scheme?)	Method validation results: Range 0.2 %-5.0% Accuracy: 90-110% Precision: SD ≤0.5% Repeatability: RSD≤20% Linearity: r2≥0.80. Sensitivity: QL≤0.2%	Performance verification protocol that can include (non exhaustive list) - Acceptance criteria aligned with the performance claim Range 0.05 %-3.0% Accuracy: 95-105% Precision: SD ≤0.3% Repeatability: RSD≤20% Linearity: r2 ≥0.99. Sensitivity: QL≤0.05% - Study design (e.g. number and type of samples…) - Stability indicating properties - Characterization of signals including use of orthogonal methods **(NM)**

Unpublished draft

Method description	Acceptable ranges and reporting categories (White boxes are ECs and grey ones are not-ECs.)	
	Parameter Based Approach	**Enhanced Approach**
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Method description:

- EC includes *critical instrument, material, reagent, conditions and system suitability*
- Changes reported in accordance with regional requirements *(based on EU variation classification)*

Validation studies:
Supportive information

Technology change facilitated by:

- *Performance verification protocol*
- *Enhanced product knowledge and CQA understanding*
- *Enhanced method knowledge*

Performance verification protocol = EC

- Performed periodically or when change is introduced
- Can include additional requirements to enable site transfer or technology change

Making of the Analytical case study
Include or not include ?

- Q12 example allude to concepts were not yet defined in Q14 (e.g. verification protocol, MODR)

- Consider: i) no publishing analytical case study in Q12 or ii) published later when concepts settled.

Benefit of including in Q12	Challenges of including in Q12
- Requested during consultation - Illustrate how EC could be applied - Leverage other regulatory concepts (e.g. site transfer) which may not be in the scope of Q14	- May contradict or may not be fully aligned with future Q14 - Limited terminology can be used as they are not defined yet - Additional concepts may be drafted in the future and could benefit the example
Benefit of including in Q14	**Challenges of including in Q14**
- Good link/coordination between EWGs - Ensure alignment with Q14 concepts	- Need to ensure consistent Q12 concepts - Delayed publication by several years

Making of the Analytical case study

Include or not include ?

Option	Example	Impact
1	Describe Traditional + Enhanced approach	- Risk of misalignment with Q2R + Q14 - Illustrate how EC can be applied
2	Describe Enhanced approach	- Risk of misalignment with Q14 - Illustrate how EC can be applied but no differentiation between enhanced and traditional
3	No example	- No conflict with upcoming Q2R/Q14 - Step 1 text already provides possibility of using EC for analytics - Less clarity on how EC can be applied - May be considered in Q14
4	Other options?	

Describe minimal approach and align with WHO reporting (published case study)

Annex IC: Identification of Established Conditions for Analytical Procedures

- The following is an example to illustrate how ECs could be **presented** for an analytical procedure, acceptance criteria, and testing facility, along with their suggested reporting categories.
- This example considers an analytical procedure (capillary electrophoresis) for a biological drug substance (non-glycosylated recombinant protein) referred to as *Illustropin*, using a **minimal development approach validated in accordance to ICH Q2.**
- To better illustrate the example, the change categories, conditions, and **data requirements are according to the WHO Guidelines** on procedures for changes to approved biotherapeutic products. The actual reporting categories and data requirements may differ for a particular product and by region.

Published case study

	All information listed are ECs	Reporting (as example referring to WHO)
Method	Measurement of Purity: Determination of charged variants of active substance by capillary electrophoresis (Non-reduced) and corrected relative area %.	**NM** *Conditions: None* *Supporting Data:1-5*
Test solutions	Illustropin Reference Standard: Concentration of test solutions and reference standards: 1 mg/ml Illustropin in water	**NL** *Conditions 1-4* *Supporting Data:1, 4, 5*
Equipment	Suitable Capillary Electrophoresis system and Suitable spectrophotometric detector. Capillary: Material: uncoated fused silica capillary diameter Ø = 50 µm. Size: effective length = at least 70 cm	
Condition	**- Chemicals (Pharmacopoeial quality):** Separation buffer (CZE): 13.2 g/l solution of ammonium phosphate adjusted to pH 6.0 with phosphoric acid filtered; Rinsing Agents: 1M sodium Hydroxide, water, 0.1M sodium Hydroxide- **- Instrument parameters:** Detection: 200 nm (UV); Electric Field Strength: 217 V/cm; Temperature: 30 °C **- Sample Analysis:** Injection test solution (a) and the reference solution; injection for at least 3 s then CZE buffer injection for 1 s. Separation: Separation buffer at both ends of the capillary; Sample storage at 4 °C during analysis. **- System conditioning:** Preconditioning: At least 20 min 1M Sodium Hydroxide; At least 10 min water; At least 20 min separation buffer Between-run rinsing: 0.1M Sodium hydroxide at least 2 min; Separation buffer at least 6 min	**NL** *Conditions 1-4* *Supporting Data:1, 4, 5*
System suitability	Specificity: the electropherogram obtained is similar to the electropherogram of Illustropin supplied with Illustropin reference; 2 peaks (I1, I2) eluting prior to the principal peak and at least 2 peaks (I3, I4) eluting after the principal peak are clearly visible.	**NL** *Conditions 1-4* *Supporting Data:1, 4, 5*
Acceptance Criteria	Deamidated forms: maximum 5.0 per cent; Any other impurity: for each impurity, maximum 2.0 per cent; Total: maximum 10.0 per cent.	Widening: **NM** *Conditions: None* *Supporting Data:1, 5, 6* Narrowing: **NL** *Conditions: 2, 7* *Supporting Data:1*
Site transfer	Published case study	**NM** *Conditions None* *Supporting Data: 7 & 8* **NL** *Conditions 4-6* *Supporting Data: 7 & 8*

	All information listed are ECs	Reporting (as example referring to WHO)
Method	Measurement of Purity: Determination of charged variants of active substance by capillary electrophoresis (Non-reduced) and corrected relative area %.	NM *Conditions: None* *Supporting Data:1-5*
Test solutions	Illustropin Reference Standard: Concentration of test solutions and reference standards: 1 mg/ml Illustropin in water	NL *Conditions 1-4* *Supporting Data:1, 4, 5*
Equipment	Suitable Capillary Electrophoresis system and Suitable spectrophotometric detector. Capillary: Material: uncoated fused silica capillary diameter Ø = 50 µm. Size: effective length = at least 70 cm	
Condition	**- Chemicals (Pharmacopoeial quality):** Separation buffer (CZE): 13.2 g/l solution of ammonium phosphate adjusted to pH 6.0 with phosphoric acid filtered; Rinsing Agents: 1M sodium Hydroxide, water, 0.1M sodium Hydroxide- **- Instrument parameters** ure: 30 °C **- Sample Analysis:** Injecti en CZE buffer injection for 1 s. Separatio during analysis. **- System conditioning:** Preconditioning: At least 2 paration buffer Between-run rinsing: 0.1M	NL *Conditions 1-4* *Supporting Data:1, 4, 5*
System suitability	Specificity: the electrophe d with Illustropin reference; 2 pea eluting after the principal peak are clea	NL *Conditions 1-4* *Supporting Data:1, 4, 5*
Acceptance Criteria	Deamidated forms: maximum 5.0 per cent; Any other impurity: for each impurity, maximum 2.0 per cent; Total: maximum 10.0 per cent.	Widening: NM *Conditions: None* *Supporting Data:1, 5, 6* Narrowing: NL *Conditions: 2, 7* *Supporting Data:1*
Site transfer	Published case study	NM *Conditions None* *Supporting Data: 7 & 8* NL *Conditions 4-6* *Supporting Data: 7 & 8*

Reporting in accordance to

WHO Guidelines on procedures and data requirements for changes to approved biotherapeutic products,

Technical Report Series, No. 1011, 2018

	All information listed are ECs	Reporting (as example referring to WHO)
Method	Measurement …esis (Non-reduced) and	NM *Conditions: None* *Supporting Data:1-5*
Test solutions	Illustropin Re Concentratio	NL *Conditions 1-4* *Supporting Data:1, 4, 5*
Equipment	Suitable Capi Capillary: M Size: effectiv	
Condition	**- Chemicals** adjusted to pl …sphate …sodium Hydroxide- **- Instrument** …30 °C **- Sample An** …CZE buffer injection for …ring analysis. **- System con** Preconditioni …tion buffer Between-run	NL *Conditions 1-4* *Supporting Data:1, 4, 5*
System suitability	Specificity: the electropherogram obtained is similar to the electropherogram of Illustropin supplied with Illustropin reference; 2 peaks (I1, I2) eluting prior to the principal peak and at least 2 peaks (I3, I4) eluting after the principal peak are clearly visible.	NL *Conditions 1-4* *Supporting Data:1, 4, 5*
Acceptance Criteria	Deamidated forms: maximum 5.0 per cent; Any other impurity: for each impurity, maximum 2.0 per cent; Total: maximum 10.0 per cent.	Widening: NM *Conditions: None* *Supporting Data:1, 5, 6* Narrowing: NL *Conditions: 2, 7* *Supporting Data:1*
Site transfer	Published case study	NM *Conditions None* *Supporting Data: 7 & 8* NL *Conditions 4-6* *Supporting Data: 7 & 8*

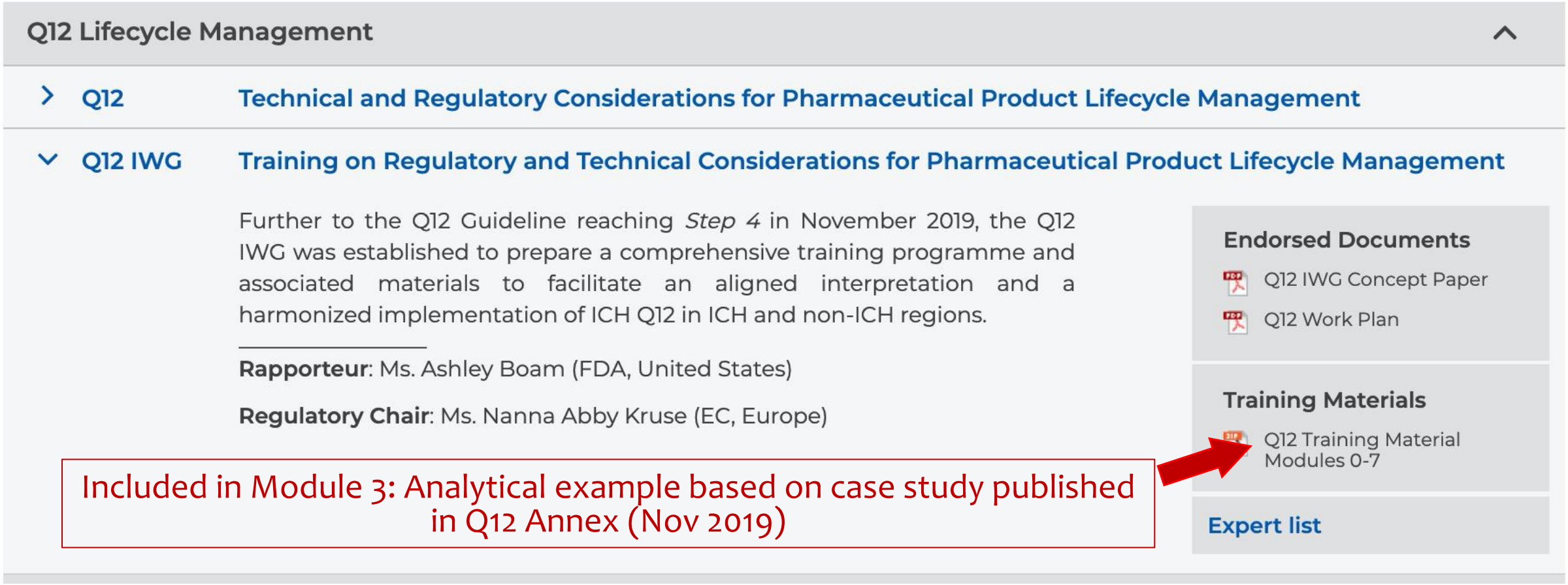
- **conditions to be fulfilled** for a given change to be classified as moderate or minor
- if any of the conditions outlined for a given change are not fulfilled, the change is assessed and if appropriate the **next higher reporting category** may be used
- for example, if any conditions recommended for a low quality change are not fulfilled, the change is may be considered to be a moderate quality change;

Conditions and supporting data

(e.g., change in SST Conditions 1-4 Supporting Data:1, 4, 5)

Conditions that must be met: in order to implement the change at the corresponding reporting category
1. There is no change in the limits/acceptance criteria outside the approved limits for the approved assays used at release/ stability. 2. The method of analysis is the same and is based on the same analytical technique or principle (for example, change in column length or temperature, but not a different type of column or method) and no new impurities are detected 3. The modified analytical procedure maintains or improves performance parameters of the method 4. The change does not concern potency-testing 5. No changes made to the test method 6. The transfer is within a facility approved in the current marketing authorization for performance of other tests 7. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity, change in total impurity limits)
Supporting Data (Documentation to be submitted)
1. Updated drug substance specifications. 2. Copies or summaries of analytical procedures if new analytical procedures are used. 3. Validation/qualification results if new analytical procedures are used. 4. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent. 5. Justification for the proposed drug substance specification (for example, tests, acceptance criteria or analytical procedures). 6. Documented evidence that consistency of quality is maintained. 7. Information demonstrating technology transfer qualification for the non-pharmacopoeial assay or verification for the pharmacopoeial assay. 8. Evidence that the new company/facility is GMP-compliant.

ICH Q12 training material – Module 3



Included in Module 3: Analytical example based on case study published in Q12 Annex (Nov 2019)

https://www.ich.org/page/quality-guidelines#12