Post-Approval Flexibility in Analytical Methods

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Disclaimer: The opinions expressed are my own and not necessarily those of the HPRA or EMA
Health Products Regulatory Authority (HPRA)

➢ Licensing human and animal medicines
➢ Approving clinical trials
➢ GMP, GCP & GDP inspections
➢ Medical device regulation
➢ Pharmacovigilance
➢ Medicines advertising
➢ Scientific animal protection
➢ Unlicensed medicines/exempt products
➢ Scientific advice & innovation support
➢ Regulation of tissues, cells, and organs for transplantation
➢ Cosmetics
How is post-approval flexibility interpreted?

From making “small” changes to a method without prior approval

To

Changing any aspect of a registered method without prior approval

To

Changing to a different method without prior approval
Industry goal

To have the flexibility to manage appropriate changes within the pharmaceutical quality system and to expect reasonable implementation timelines for global changes

Regulator’s goal

To facilitate reasonable flexibility, supported by appropriate data, while limiting inappropriate changes to analytical testing
## Current guidance

**ICH Harmonised Tripartite Guideline**

**Validation of Analytical Procedures: Text and Methodology**

Q2(R1)

<table>
<thead>
<tr>
<th>Type of analytical procedure</th>
<th>Identification</th>
<th>Testing for Impurities</th>
<th>Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>characteristics</td>
<td></td>
<td>quantit. limit</td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Precision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Repeatability</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>- Intern Precision</td>
<td>-</td>
<td>+ (1)</td>
<td>+</td>
</tr>
<tr>
<td>Specificity (2)</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Detection Limit</td>
<td>-</td>
<td>- (3)</td>
<td>-</td>
</tr>
<tr>
<td>Quantitation Limit</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Linearity</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Range</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

... 25 years old
The future ....

TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT

Q12

Draft version
Endorsed on 16 November 2017
Currently under public consultation

Final Concept Paper
ICH Q14: Analytical Procedure Development and Revision of Q2(R1) Analytical Validation
dated 14 November 2018

Endorsed by the Management Committee on 15 November 2018
ICH Q12 – implications for analytical methods
**ICH Q12 – lifecycle management**

The aim is to facilitate the management of post-approval CMC changes in a more predictable and efficient manner across the product lifecycle.

- **Prior-approval**: Certain changes are considered to have sufficient risk to require regulatory approval prior to implementation.

- **Notification**: Certain moderate- to low-risk changes are judged to not require prior approval and generally require less information to support the change.

This aligns with the principles of the EU variations regulation.

**Established Conditions (ECs)**

- Legally binding information considered necessary to assure product quality. As a consequence, any change to ECs would necessitate a submission to the regulatory authority.

- Regulatory submissions would contain a combination of ECs and supportive information.

- The details of ECs and the associated reporting category will depend on application of knowledge from product and process understanding to manage the risks to product quality.
Approaches to identifying ECs

Parameter based approach
- Development provides a limited understanding of the relationship between inputs and quality attributes.
- Will include a large number of inputs (e.g. process parameters) and outputs (IPCs)

Enhanced approach
- Increased understanding of interaction between inputs and quality attributes.
- Identification of ECs that are focused on the most important inputs and outputs.

Performance based approach
- ECs primarily focused on control of unit operation outputs rather than process inputs.
- Manufacturing steps with in-line continuous monitoring (e.g., NIR).
Is the process parameter either a CPP or a KPP?

Yes

It is an EC²

Reporting categories for changes to EC

What is the level of potential risk associated with the proposed change, taking into consideration the Control Strategy?

High

Prior Approval

Moderate to low

Notification

It is not an EC²

Not Reported
Established Conditions for Analytical Procedures (ICH Q12)

ECs related to analytical procedures should include elements which assure performance of the procedure. 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 suitability.

Where there is increased understanding of the relationship between method parameters and method performance, ECs are focused on method-specific performance criteria (e.g., specificity, accuracy, precision) rather than a detailed description of the analytical procedure.
The high-level description of the original method and the revised method should be the same (e.g., chromatography with spectroscopic detection).

Validation results should demonstrate that the revised method is equivalent to or better than the original method.

Immediate notification (no prior approval).

Test results obtained using the original method and revised method should be equivalent.

SSTs should be established for the revised method.

* Out of scope – test method based on a biological/immunological/immunochemical principle or a method using a biological reagent (e.g., bioassay, binding assay, ELISA, testing for viral adventitious agents).
Purpose and scope ICH Q14

- Currently analytical validation results are presented alone at a point in time
- ICH Q14 proposes that **analytical procedure development** can be presented in the dossier
- Inclusion of development work for analytical methods complements ICH Q8 and Q11.

Facilitate applicants to present a **scientific basis** for flexible regulatory approaches to post-approval analytical procedure changes

Harmonise the scientific approaches of analytical procedure development

Provide the principles relating to the description of analytical procedure development process

Improve regulatory communication between industry and regulators

Facilitate more efficient, sound scientific and risk-based approval

Simplify post-approval change management of analytical procedures
ICH Q14: Areas for harmonisation

Key elements and terminology

QbD

Concept of enhanced approaches for analytical procedures

Risked-based change management

Analytical procedure development in CTD format

Performance criteria
Embracing these approaches requires a change in thinking

**Old thinking**
Analytical method validation occurs at a point in time

**New thinking**
Analytical method validation is a **process** with its own lifecycle

- Like any process, understanding the source of variability allows for more reliable data
- Processes are not static but evolve over time. This requires lifecycle management and ongoing verification
- Applying an **enhanced approach** for analytical procedures can de-risk post-approval method changes
Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission.
Analytical target profile (ATP)
Analytical target profile (ATP)

There are many definitions......

➢ ATP is a statement that defines the method’s purpose which is used to drive method selection, design, and development activities.

➢ The ATP describes the purpose and scope of the method along with a set of performance criteria including: the parameters to be measured; the critical method attributes of the reportable results; their specifications and quality levels.

➢ The ATP explicitly states the intended performance, capability and use of the analytical procedure for ensuring patient safety, manufacturing consistency and efficacy of the product through appropriate monitoring of product critical quality attributes.

➢ The ATP defines method performance requirements, and should incorporate a joint criterion for accuracy and precision in order to define method acceptability in terms of the uncertainty of results generated by the method.

1. EFPIA/PhRMA definition
Analogous to the quality target product profile (QTPP) from ICH Q8

- Recognises that the knowledge base for analytical methods is greater than what is usually presented in the method validation section
- The ATP can be used to assess the suitability of a method through the lifecycle of a product
- Also introduces a measurement of uncertainty and an estimation of confidence in the reportable result
- Focuses on the properties of a method which impact quality decisions rather than method descriptions*
- The ATP should be consistently met throughout the lifecycle of the product, SSTs can support this

USP definition of ATP

The ATP states the required quality of the reportable value produced by an analytical procedure in terms of the **target measurement uncertainty** (TMU)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectivity</td>
<td>Sample preparation</td>
</tr>
<tr>
<td>Linearity</td>
<td>Weighing</td>
</tr>
<tr>
<td>Extraction efficiency</td>
<td>Instrument</td>
</tr>
<tr>
<td>Filter recovery</td>
<td>Integration</td>
</tr>
<tr>
<td>Detector wavelength</td>
<td>Background noise</td>
</tr>
<tr>
<td>Solution stability</td>
<td>Replicate strategy</td>
</tr>
<tr>
<td>Analyte solubility</td>
<td>Analyst</td>
</tr>
</tbody>
</table>

**TMU**

- The maximum uncertainty that can be associated with a reportable result while still remaining fit for its intended purpose.
- TMU is a consolidation of the uncertainty from all sources
- Statistical analysis included to quantify the uncertainty (currently not reported)

The procedure must be able to quantify [analyte] in the [description of test article] in the presence of [x, y, z] with the following requirements for the reportable values:

Accuracy = 100% ± D% and Precision ≤ E%.
Or
The reportable values fall within a TMU of ±C%
Some of the possible benefits to the ATP approach

1. Can be used as the basis to select the appropriate analytical technique
2. Can provide assurance that the method is fit for the intended purpose
3. May lead to improved understanding of the sources of variability
4. Used to support continuous improvement and change control
5. When used in conjunction with QbD approaches it should result in fewer method related OOS results and reduce the risk of issues during method transfer
6. Can provides assurance that analytical measurements are made to within a specified level of uncertainty throughout the lifetime of the method
7. May (?) allow for future regulatory flexibility
What are the Agencies’ views with respect to the use of analytical target profile (ATP) for analytical methods?

• In general, an analytical process profile can be acceptable as a qualifier of the expected method performance by analogy to the QTPP as defined in ICH Q8 (R2).

• However, the Agencies would not consider analytical methods that have different principles (e.g., HPLC to NIR) equivalent solely on the basis of conformance with the ATP.

• An applicant should not switch between these two types of methods without appropriate regulatory submission and approval.
Questions which may be relevant for future discussions

• The regulatory purpose of the ATP and what it should contain remains to be agreed
• What level of detail should be in the ATP e.g. should the studies which support precision estimates be stated?
• How would the ATP be used in lifecycle management?
• If two (or more) methods can be demonstrated to achieve the same ATP, could they be used interchangeably?
• Should they have the same scientific basis? For example should the principle of separation be the same or would changes between different modes of separation (e.g. reversed phase to normal phase liquid chromatography) be acceptable?
• Would changes to potency assays be acceptable e.g. cell based assay to ELISA?
Analytical method QbD and design space
Quality by design (QbD) for analytical methods

- ICH Q8 concepts can be adapted for analytical methods
- Use of risk-based approaches.
- Greater level of understanding of a method’s performance
- Use of design of experiment (DoE) approaches rather than one-factor – at-time robustness studies
- Investment in method development may result in a reduction in out-of-trend and out-of-specification results due to the increased robustness
Risk assessment

Should include all relevant parameters for the method, some examples include:

<table>
<thead>
<tr>
<th>HPLC</th>
<th>Cell based assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow rate</td>
<td>Cell number</td>
</tr>
<tr>
<td>Injection volume</td>
<td>Cell passage</td>
</tr>
<tr>
<td>Temperature</td>
<td>Growth medium</td>
</tr>
<tr>
<td>Load</td>
<td>Sample concentration</td>
</tr>
<tr>
<td>Operator</td>
<td>Reagent concentration</td>
</tr>
<tr>
<td>Instrument</td>
<td>Incubation time</td>
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<tr>
<td>Column</td>
<td>Assay reagent volume</td>
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<tr>
<td>Mobile phase</td>
<td>Analysis instrument</td>
</tr>
<tr>
<td>Run time</td>
<td>Analysis settings</td>
</tr>
<tr>
<td></td>
<td>Number of replicates</td>
</tr>
</tbody>
</table>

Including such parameters in DoEs allows ranges to be set which provides confidence that the analytical procedure will generate results that meet the ATP.
Design Space/Method Operable Design Region (MODR)

- MODR for an analytical method is equivalent to a design space for a manufacturing process.
- Like a design space, analytical method input parameter ranges are studied by multivariate DoEs which define a region of control.
- Examines the impact of changes to input parameters on method performance and improves on current approaches to robustness studies.
- If the analytical method is run away from registered set points, but within the MODR, then no regulatory action is required.
- When an analytical method is run within the MODR, it should meet the requirements of the ATP.
- A demonstration of greater understanding of method performance could facilitate regulatory flexibility; similar concept to how greater process knowledge allows for some flexibility in the manufacturing process.
What are the Agencies’ expectations in regulatory submissions for Method Operational Design Ranges (MODR)?

Data to support an MODR could include:

a) appropriately chosen experimental protocols to support the proposed operating ranges/conditions; and

b) demonstration of statistical confidence throughout the MODR.

Issues for further reflection include the assessment of validation requirements as identified in ICH Q2(R1) throughout the MODR and confirmation of system suitability across all areas of the MODR.
Analytical method design space case study

mAb luciferase-based potency bioassay

Design of experiments (DoE) - fractional factorial design with 32-factor combinations

<table>
<thead>
<tr>
<th>Factor</th>
<th>Unit</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-culture time</td>
<td>day</td>
<td>1, 2 and 3</td>
</tr>
<tr>
<td>Cell number</td>
<td>cells x10⁵ /well</td>
<td>6, 8, 10</td>
</tr>
<tr>
<td>Assay incubation time</td>
<td>hours</td>
<td>4.5, 6, 7.5</td>
</tr>
<tr>
<td>Substrate incubation time</td>
<td>min</td>
<td>10, 35, 60</td>
</tr>
<tr>
<td>Substrate volume</td>
<td>µl</td>
<td>25, 50, 75</td>
</tr>
</tbody>
</table>

- Potency results for all runs were within 80 – 120%
- Response surface model included two-factor interactions and quadratic terms
- No statistically significant interactions found

Superior approach to robustness studies
Analytical method lifecycle
Analytical lifecycle

Design

Development

Validation

Ongoing/continued verification
STAGE 1
Procedure Design, Development & Understanding

Analytical Target Profile (ATP)

Target Measurement Uncertainty (TMU)

Analytical Control Strategy

STAGE 2
Procedure Qualification
- Qualification & Calibration of Instruments & Validation of Systems
- Procedure Performance Qualification (PPQ)

Continual Improvement

Operational Release

STAGE 3
Procedure Performance Verification
- Trend analysis
- Quality Review
- Deviation Management
- Change Control

Continual Improvement
Analytical method control strategy

• Set of controls that ensure the ATP is always met
• Recognises that an analytical method can be viewed as a process
• Consistent output within the predefined target performance range
• Based on ICH Q8 – Q11 concepts
Analytical method control strategy

Control strategy
- Reagents
- Standards
- Buffers
- Columns

Sample preparation
- Operators
- Instrument error

Variability

Measurement

Accuracy

Precision

Inputs

Outputs
ATP

- Selection of appropriate method
- Risk assessment
- Understanding of inputs → outputs/ MODR
- Continuous improvement
- Lifecycle management
Prior knowledge and analytical methods
Prior Knowledge

Prior knowledge is almost never discussed for analytical methods in regulatory submissions and may be an untapped resource

• Could it be used to justify SSTs?
• Could it be used to support a change to an analytical method by showing a similar change had no impact on testing of related products?
• Is there useful data to be analysed and collated in the thousands of analytical runs for platform products?
• Can big data & AI be used to identify and quantify sources of variability from the same analytical technique across multiple products?
• Could models be built to facilitate greater flexibility in analytical methods based on Prior Knowledge?
Platform control space for analytical methods

- The new molecule has comparable characteristics to those used to establish the platform, *(next-in-class-molecule)*.
  => It falls into the established *Platform Design & Control Space*.

- The validity of the Platform / Prior Knowledge will be demonstrated by a molecule specific risk assessment combining the QTTP, the Platform risk assessment & molecule developability data.
Current issues ... relevant while we wait for the implementation of ICH Q14
Using “method variability” as a justification for wide specifications or an unexpected result

Very common scenario

➢ “The specifications are acceptable given the known 20% variability for this method”
➢ However .. intermediate precision turns out to be <5%!
➢ When using “variability” as a justification, it is important to justify where the variability comes from

Sample variability can sometimes be inferred from other sources e.g. potency assay stability data where no clear trends are observed
Changes to analytical methods without prior approval

• Dossiers commonly state the equipment or reagents etc. can be changed for “equivalent” ones as long as the SST requirements are fulfilled

• Often there is no discussion of what “equivalent” means

• Also the SSTs are never justified in submissions

• For this type of approach to be considered, strong justification is generally required and should cover relevant points, such as:
  – The applicant’s understanding of “equivalent” should be clearly stated
  – The studies to be conducted and statistical analysis used to ensure equivalent method performance should be stated
  – It should be justified that the SSTs would be sufficient to detect any changes
The future

- ICH Q12 and ICH Q14 will continue to develop
- Greater flexibility in post approval analytical method changes
- Greater understanding of method performance through experimental/DoE studies
- More frequent use of analytical design spaces
- Challenges in validating advanced analytical methods e.g. multi-attribute methods
- Crystal ball gazing .... AI controlled manufacturing process linked to real time testing and big data analytics used to develop analytical methods
Questions?