# STREAMLINING POST-APPROVAL CHANGES
## Industry Insights on ICH Q14

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Simplified approaches that enable changes to analytical procedures over their lifecycle are needed to allow continual improvements and adaptations due to technological obsolescence and other challenges. This article reflects on the positive impact that the recent ICH Q14 guidance can have on facilitating these changes. Five examples are provided that are based on scenarios in which analytical procedure changes were required and show what these would look like in a future state where recent guidance is fully implemented. The examples illustrate the potential of ICH Q14 concepts to facilitate post-approval changes to analytical procedures, ultimately benefiting patients through improved assurance of product quality and regulatory efficiency.

## INTRODUCTION

The recently finalized ICH Q14 guideline outlines science- and risk-based approaches for developing and maintaining analytical procedures [1]. It also provides guidance on the change management of these procedures, using principles described in ICH Q12, which was finalized by ICH in late 2019 to facilitate post-approval changes for pharmaceutical products but has faced limited implementation due to the lack of regulatory harmonization and acceptance [2].

The analytical procedures in today's Quality Control (QC) lab, some of which were developed two or more decades ago, generally lag behind the advances in the field of instrumentation, sample preparation tools, and data processing. This is primarily because changing analytical procedures is expensive, time-consuming, and can pose challenges in implementation while maintaining regulatory compliance, given the variety of expectations from regulatory authorities and the complexity of global supply chains [3]. In a recent article authors from one major pharmaceutical company note that out of 6,000 changes for different commercial products, 55% were categorized as regulatory-relevant; these changes necessitated the submission of almost 90,000 variations to different countries. Of these, 43% (approximately 38,700) were related to analytical procedures [4].

To ensure that analytical procedures remain fit for purpose, they must accommodate product and process changes while incorporating the advances in analytical technology, instrumentation, and scientific knowledge that occur over time. Furthermore, as the molecular complexity of drugs increases, we anticipate the evaluation of their critical quality attributes (CQAs) to utilize more complex analytical procedures and instrumentation that are even more likely to require changes during the lifecycle of the drug. The ICH Q14 guideline emphasizes the need for continual improvement of analytical procedures, from smaller modifications to the complete replacement of outdated methods with new technologies. Changes in performance characteristics or additional information on analytical attributes to be tested may necessitate the revision of the Analytical Target Profile (ATP) or the adoption of a new procedure.

A frequent scenario in modern QC labs involves upgrading to state-of-the-art instrumentation and/or techniques to replace an obsolete one, which often requires a time-consuming and complex specification update because existing specification criteria are no longer appropriate for the newer, more sensitive methods. The shared goal of sponsors and regulators is to ensure that the updated analytical procedures continue to provide accurate, precise, and specific measurements of quality attributes.

## ICH Q14 CHANGE MANAGEMENT

As described in ICH Q14, the change management process for analytical procedures involves several key steps to systematically assess and implement modifications.

1. A risk assessment is conducted to evaluate the significance of the proposed change. Factors such as the complexity of the test, the extent of the modification, and the relevance of the analytical procedure to product quality are considered to classify the change as high-, medium-, or low-risk (after risk mitigation, if appropriate). Product and process knowledge should be reviewed along with prior knowledge on the analytical technology to understand potential impact on the performance of the modified analytical procedure. Representative samples should be available to enable bridging studies and build understanding of the revised analytical procedure and the analytical procedure control strategy.
2. Confirmation of analytical performance criteria according to the ATP ensures that the modified method remains fit for the intended use. Appropriate validation studies are conducted to finalize the new analytical procedure description, including parameters for system suitability and the analytical procedure control strategy if needed.
3. Bridging studies are designed to assess the new procedure against the existing one.
4. The impact of the change on regulatory reporting requirements is assessed, determining whether a notification or prior approval regulatory submission is required; reporting requirements might be lower if tools such as established conditions (ECs) or post-approval change management protocols (PACMPs) have been agreed upon in advance with the regulatory authorities.
5. Finally, the change can be implemented after the regulatory actions have been completed for each region, which can take years if multiple regions require prior approval for the change. Varying regulatory expectations for bridging study design and data for submissions can lead to complex and expensive need to segregate inventory or duplicate testing, ultimately increasing costs for patients and the risk of stockouts.

Thus, harmonization of global regulatory requirements is crucial for streamlining the analytical procedure change process and ensuring consistency in regulatory expectations across regions.

Harmonization benefits everyone by ensuring a robust drug supply, preventing shortages, enabling greener approaches in the QC lab, incorporating improved analytical technologies for product control, and improving overall regulatory efficiency by removing the burden of reviewing low-risk changes from regulators so they can focus their efforts on higher-risk changes. By not embracing and implementing Q14 concepts, QC labs may continue to use outdated analytical procedures that lack the ability to keep up with state-of-the-art technologies.

## PRACTICAL APPLICATION OF ICH Q12 CONCEPTS

Building on the examples provided in the Annex to Q14, we provide additional examples to illustrate the practical application of concepts introduced in ICH Q12 and described in more detail in ICH Q14, such as ECs and PACMPs, that have the potential to greatly facilitate post-approval changes to analytical procedures. These examples include:

1. A demonstration of how the description of enhanced development can justify established conditions with the potential to make changes in the analytical procedure parameters and end-point detection technology for monitoring dissolution of a solid oral dosage product,
2. A proactive example where it is known at the time of registration that an analytical procedure change will be required, so a PACMP could be utilized for implementing a new analytical procedure for the determination of assay for a solid oral dosage product,
3. An example of navigating a required change in an analytical procedure due to discontinuation of a key component for executing a test for carbohydrate analysis for a biologic product,
4. An example of responding to an instrumentation/technology change for charge variant measurements in biologic products, including sub-examples of differences in result impact, and
5. An example of continual improvement where the robustness of the platform analytical procedure for protein concentration determination is enhanced to ensure reliable execution.

The following examples demonstrate a diversity of analytical procedure changes, encompassing different modalities and scenarios, from simple to complex.

## EXAMPLES OF IMPLEMENTATION

### EXAMPLE 1

#### Change in Endpoint Detection Technology for Dissolution Testing of a Solid Oral Dosage Form

This example is a description of an actual interaction between an applicant and a health authority. The applicant provided enhanced understanding of a dissolution procedure to justify their risk-based approach for the proposal of ECs and reporting categories. Through discussion with the health authority, the ECs were accepted, and the outcome is found below.

Dissolution procedures consist of an involved sample preparation (the dissolution step) followed by an "analytical finish," or end analysis step, which incorporates sample handling and an analytical procedure used to determine the amount of drug substance dissolved during the dissolution step [5]. The parameters of a dissolution step (e.g., dissolution apparatus, media, agitation rate) are often critical to the performance of this routine control test for drug products to assure consistent product quality. Dissolution is typically considered a CQA for solid oral dosage products because failure to meet this CQA may impact in vivo performance [6]. When applying the concepts described in ICH Q14, Figure 2, "A risk-based approach for identification of ECs and reporting categories for associated changes in the enhanced approach," the parameters of the dissolution step are likely ECs with a prior approval reporting category because they are selected to ensure robustness, reproducibility, and discriminatory capability.

Commonly, spectrophotometric determination and HPLC are the analytical techniques used to analyze the dissolved drug substance in a dissolution procedure. Changes in the technology or parameters of the end analysis that do not impact the capability

of the procedure to meet its required performance criteria could be made through an enhanced understanding of the product and analytical principles. Therefore, adherence to an ATP could allow for parameters of the end analysis to be ECs with a lower reporting category or managed within a sponsor's Pharmaceutical Quality System (PQS).

Table 1 provides a list of the ECs for the dissolution procedure of an immediate release formulation. These ECs and reporting categories were proposed to a regulatory authority, and the agreed-upon reporting categories were described in a Product Lifecycle Management (PLCM) document. As recommended above, the parameters associated with the dissolution step were found to be ECs with a prior approval reporting category. The parameters were justified through robustness data and demonstration of potential discrimination for variant formulations that included high granule size and over-coated granules. Because performance criteria were not established for changes to the dissolution step parameters, the risk of any change was high, and therefore, a prior approval reporting category was proposed.

Performance characteristics and criteria are in place for the end analysis (Table 1). While not described as an ATP at the time of submission (prior to the approval of ICH Q14), the performance characteristics, along with a statement of intended purpose, would comprise an ATP based on the definition in ICH Q14. The risk associated with changes to analytical procedure parameters in the end analysis was reduced by the defined performance criteria. Therefore, a lower reporting category was proposed for these parameters. The selection of HPLC as the analytical technique and the associated procedure parameters were determined based on prior knowledge of the drug substance properties (including UV profile), impurity and degradation profile (including acceptance criteria of impurities in drug substance and drug product), and properties of the excipients.

Two examples of end analysis parameters that were agreed to as ECs are described below, along with potential changes to the ECs that may occur during the lifecycle of the product and procedure. If these changes were to be made post-approval, the applicant, now the marketing authorization holder, would need to perform a risk assessment to evaluate the potential impact on the performance characteristics and the link to the CQA, complete necessary development, execute bridging studies used to demonstrate adherence to the performance characteristics, which can include validation of the performance characteristics affected by the change.

- **Chromatography Column C18 (USP L1):** A change in this EC to another column outside C18 (USP L1) may be needed due to column availability or performance. The risk for this potential change was assessed to be medium due to knowledge of the product. The levels of drug impurities and potential degradation products would not interfere with accurate quantitation of the active component, so a rapid method can be utilized without the need for a complicated separation. From the risk assessment, the existence of performance characteristics and prior knowledge would facilitate the design of a bridging study and thus enable the reporting category to be reduced to 'notification low' with regulatory agreement.
- **Detection Method Principle—Chromatography:** A quality control laboratory preferred UV spectroscopy over chromatography to allow for a greener technique and fully automated dissolution. In the risk assessment, this potential change was proposed as a medium risk. The risk for this change in technique was not considered high due to: a) an understanding that levels of drug impurities and potential degradation products would not interfere with accurate quantitation of the active component, and b) the detection wavelength was a separate EC and would be maintained or evaluated with a change in technique. As described above for the column change, performance characteristics and prior knowledge that would permit the design of an appropriate bridging study exist, therefore the risk level was reduced, and the reporting category was agreed to as 'notification low'.

## EXAMPLE 2

### Utilizing PACMP for Implementing a New Analytical Procedure for Determination of Assay for a Solid Oral Dosage Product

Rapid development of drugs for areas of unmet medical need [7] leaves little time to define the analytical control strategy and ensure the robustness of analytical procedures following the finalization of the product control strategy. In these cases, the analytical procedures provided in the commercial filing may need to be updated shortly after approval of the marketing application to ensure robust analytical procedures are in place for the lifetime of the drug.

As defined in ICH Q12, a PACMP is a viable pathway to facilitate anticipated changes via predetermined approaches that may reduce the burden on regulatory authorities and Marketing Authorization Application (MAA) holders. It involes submitting a protocol to the regulatory authority describing the proposed change, rationale, proposed studies, acceptance criteria, and the proposed reporting category. Once approved, the studies are conducted and, if the results meet the acceptance criteria, the information is submitted to the regulatory authority per the protocol's reporting category. Depending on the category, regulatory approval may be required before implemention.

As a demonstration of this approach, the following example is presented. A small molecule, solid oral drug candidate was clinically successful in reducing solid cancer tumors in an area of unmet medical need. This molecule was discovered and developed by a small biotechnology company with limited resources and was then acquired by a major pharmaceutical company less than a year before MAA submission.

The experience with the analytical procedure for assay of the active pharmaceutical ingredient (API) in the drug product was reviewed to assess the robustness of the procedure, and it was determined that the procedure had significant robustness issues. These included peak elution order shifts, peak shape erosion, and

Table 1: ECs of a dissolution procedure for an immediate-release drug product formulation.

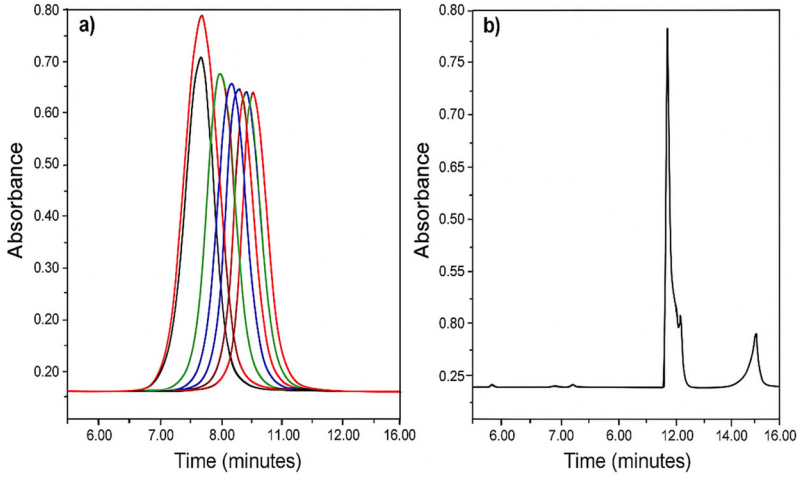
| CTD Section | Established Condition | | Proposed Change Reporting Category |
|---|---|---|---|
| 3.2.P.5.2 | **Dissolution Step:** | | Prior Approval |
| | Apparatus: USP Apparatus I (baskets) | | |
| | Dissolution Medium: 50 mM sodium acetate, pH 5.0, de-aerated | | |
| | Volume: 900 mL | | |
| | Temperature: 37.0 ± 0.5 °C | | |
| | Agitation Rate: 50 rpm | | |
| 3.2.P.5.2<br><br>Dissolution Rate Test | Performance Characteristics for End Analysis:<br><br>Accuracy: Mean recovery of active ingredient is 97-103%<br><br>Precision: Overall %RSD of all accuracy values ≤ 2%<br><br>Specificity: Interference ≤2.0 % after compensated by blank<br><br>Reportable Range: Minimum 50% of the lowest strength to 125% of the highest strength | | Prior Approval |
| | Detection Method Principle: Chromatography | Change of end analysis principle from chromatography to UV spectroscopy | Notification Low |
| | | Change of end analysis principle from chromatography to any technique other than UV spectroscopy | Prior Approval |
| | Technology- Specific Analytical Procedure Attributes:<br><br>Specificity, system precision, linearity, filter suitability, solution stability, range, and robustness<br>Tighten (Non-Reportable) | | Notification Low |
| | Wavelength: 322 nm | | Notification Moderate |
| | System Suitability Test:<br>Injection Precision ≤ 1.5% RSD for active component<br>Peak Asymmetry ≤ 3.0 USP tailing for active component | | Notification Low |
| | Chromatography Column: C18 (USP L1)<br>(i.e., a change to a different reversed phase column outside of USP L1) | | Notification Low |
| | Mobile Phase: (80/20, v/v) Buffer Solution/Acetonitrile<br><br>Buffer Solution: 0.15% phosphoric acid and 0.1% of ammonium hydroxide in water, pH 2.5 ± 0.2 | | |

short column lifetime (see Figure 1). A detailed risk assessment was conducted that identified analytical procedure risk as an item to be addressed post submission.

To ensure the quality of the measurement in the interim, additional controls were put in place to confirm method performance. These controls consisted of enhanced system suitability requirements to confirm peak elution order (using impurity marker solutions) and peak shape, and an enhanced column wash program to improve overall robustness and column lifetime. Furthermore, a shorter assay method was desired by the commercial QC laboratory to reduce overall analysis time, reduce solvent consumption, and enhance laboratory efficiency, as the assay is employed frequently during batch analysis and stability for determination of multiple CQAs (i.e., identity, assay, uniformity of dosage units, and dissolution endpoint determination).

As noted above, by including a PACMP in the initial MAA, the sponsor can obtain agreement with regulators on what information is required for a change and the reporting requirements, resulting in more efficient implementation of CMC changes while reducing regulatory burden. This hypothetical example outlines the details ideally included in a PACMP, submitted as part of the MAA, and approved by regulators.

**Figure 1:** Example challenges with the analytical procedure robustness. a) Overlay of chromatograms demonstrating retention time shifting and band broadening that could occur during a typical analysis (7-hour run of 40 injections), b) Example chromatogram demonstrating peak splitting that could occur as a column begins to fail.




An ATP, outlined in Table 2, is defined and included in the PACMP. The approach detailed in Q14 is used to identify ECs for the revised procedure, and a risk assessment is conducted to categorize changes to ECs into high-, medium-, or low-risk levels. Each risk category is then associated with a specific reporting category for changes, whereby the high-risk category necessitates prior approval, and the low-risk category translates to minor notifications, such as inclusion in an annual report, as demonstrated in Table 3.

The PACMP would also include detailed studies proposed to identify the revised analytical procedure conditions. It is assumed in this scenario that the MAA holder employed enhanced approaches to develop the new analytical procedure. The PACMP would include a detailed description of experiments aimed at thoroughly understanding the chromatographic operating-space, including the generation of samples representative of process impurities and degradation products in addition to samples for screening. The steps undertaken to select analytical procedure conditions that are robust against typical sources of variability are also delineated.

The PACMP would also include a commitment to validate the new analytical procedure to meet the expectations outlined in ICH Q2(R2). The final step in fulfilling PACMP requirements would involve the execution of a bridging exercise. This hypothetical scenario involves a comparative analysis of multiple samples that represent the variability of the manufacturing process against predefined acceptance criteria.

The experimental design of this study is listed in Table 4, and the summary of results from the execution of this study is listed in Table 5. Since the acceptance criteria were met, the proposed reporting category for the method change would be designated as 'notification low' and the regulatory submission would be made accordingly.

This example shows how a PACMP and ECs with elements of ICH Q14 may be leveraged to proactively implement anticipated changes to analytical procedures. These approaches are valuable for both the MAA holder and regulatory authorities as they reduce the burden on each organization and the time required for implementation of these value-added changes. Broader application of these ideas will enable analytical procedure robustness and result in enhanced supply chain integrity, which ultimately serves patients.

## EXAMPLE 3

### Retrospective Case: Managing Carbohydrate Analysis Before ICH Q12/Q14

A retrospective example is presented for a change management scenario for an analytical procedure which was approved before adoption of ICH Q12 and Q14. The procedure was Fluorophore-Assisted Carbohydrate Electrophoresis (FACE) gel analysis of N-linked carbohydrates for a protein therapeutic registered in multiple jurisdictions. The procedure involved enzymatic release of carbohydrates, fluorescent labeling, and resolution and quantitation by gel electrophoresis. The pre-cast FACE gels used for analysis were sourced from a single supplier who announced limited supply and potential discontinuation of the product, necessitating the company to promptly identify backup options.

The ATP for the procedure is listed in Table 6. It takes into consideration the performance needed to ensure sufficient process control and quality of this attribute.

In response to the supply challenge, a chromatography-based fluorescence-labeling oligosaccharide profiling method was developed using anthranilic acid (AA) labeling with HPLC separation. This technology represented an industry standard with improved sensitivity and precision, as well as enabling faster development through in-line oligosaccharide identification by mass spectrometry [6]. The development included comprehensive identification and mapping of all oligosaccharide species between the FACE and chromatography-based methods (see Figure 2).

Table 2: ATP for assay of solid oral dosage form.

| | |
|---|---|
| **Intended Purpose** | |
| Quantification of the API in drug product for release and stability | |
| **Link to CQA (Assay)** | |
| Analytical procedure should quantitate API in drug product to verify the CQA of assay values between 90.0-110.0% | |
| **Characteristics of the Reportable Results (performance characteristics)** | |
| Characteristic | Acceptance Criteria |
| Accuracy | Recovery between 98.0% to 102.0% at three levels 80%, 100%, and 120% of nominal concentration; %RSD ≤ 2.0% at each level |
| Precision | %RSD for intermediate precision samples ≤ 2.0% for each analyst<br>%RSD for intermediate precision samples ≤ 3.0% for both analysts combined |
| Specificity | Method is capable of separating impurities (process impurities and degradation products) from API. Any interference from placebo components is < 0.5% of the nominal concentration of the API. |
| Reportable Range | High level: 70 — 130% of nominal |

Table 3: Evaluated risk, proposed established conditions, and proposed reporting categories.

| Established Condition | Overall Risk Category | Reporting Category | Justification/Rationale |
|---|---|---|---|
| ATP | High | Prior Approval (PA) | If widening the ATP is necessary, it will be reported as PA. |
| Technology: HPLC | Low | Notification Low | ATP must be met, defined bridging strategy must be met using representative materials. |
| System suitability tests (SST)<br>SST 1: system precision<br>SST 2: blank interference<br>SST 3: resolution<br>SST 4: peak symmetry | Low | Notification Low | SST were established based on a risk assessment and considering compendial expectations.<br>A change to SST should ensure similar control of the factors listed. |

Table 4: Experimental design that could be leveraged in a bridging study between existing and proposed analytical procedures.

| Setup | Day | Analyst | HPLC | Batch Number |
|---|---|---|---|---|
| 1 | 1 | A | 1 | 1, 2 |
| 2 | | B | 2 | 3, 4 |
| 3 | 2 | A | 2 | 3, 4 |
| 4 | | B | 1 | 1, 2 |
| 5 | 3 | A | 1 | 3, 4 |
| 6 | | B | 2 | 1, 2 |

Table 5: Summary results from execution of bridging study between existing and proposed analytical procedures.

| Method | Mean % Label Claim |
|---|---|
| Current method | 99.9 |
| Proposed method | 100.3 |
| **Absolute Difference** | 0.4 |
| **Acceptance Criteria** | NMT 1.4 |
| **Result** | Pass |

The new procedure was demonstrated to meet the ATP requirements through validation studies. Extensive bridging studies were conducted between the FACE gel- and chromatography-based methods. Statistical correlation was demonstrated across large-scale batches, as well as with carbohydrate-remodeled samples engineered at small-scale, which provided a robust dataset for comparison. These bridging studies established the correlation between the two methods.

Under the regulatory framework at the time, the sponsor submitted prior-approval applications to multiple regulatory authorities to implement the method change and adjust acceptance criteria. This process required significant resources and time before implementation could occur across all markets.

In retrospect, this example provides an opportunity to consider how ICH Q12 and Q14 principles could have facilitated a more efficient change management process.

The following considerations might have been made, taking into consideration the risk assessment described in ICH Q14's Figure 2:

1. The method performance characteristics and acceptance criteria would be considered ECs.

Table 6: ATP for analysis of N-linked carbohydrates.

| **Intended Purpose** | |
|---|---|
| Relative quantitation of main N-linked carbohydrate species in product Drug Substance A. | |
| **Link to CQA** | |
| The main carbohydrate species is important for receptor binding and potency of the therapeutic. | |
| **Characteristics of the Reportable Results (performance characteristics)** | |
| Characteristic | Acceptance Criteria |
| Precision | RSD of the main N-linked carbohydrate species percentage < 5% as measured by intermediate precision studies. |
| Specificity | Method is capable of resolving main carbohydrate species from the remaining species. Specificity demonstrated by identification of carbohydrate species using orthogonal procedure (off-line or in-line mass spectrometry) |
| Linearity and Range | Linearity of response demonstrated across the specification range for the main carbohydrate species, $R^2 \geq 0.98$. |
| Accuracy | Leveraged by demonstration of precision, specificity, and linearity. Practical consideration for demonstrating any statistical offsets through appropriately powered bridging studies. |

2. The risk associated with the change to the procedure would initially be considered high based upon impact of oligosaccharide structure on clinical efficacy.
   a) Enhanced product knowledge of the relationship between carbohydrate structure (the CQA measured by the method) and potency was presented in the dossier, with the correlation confirmed using carbohydrate-remodeled samples for both methods. This knowledge included an understanding of the relationship between potency and carbohydrate structure, and the detectability of potency changes by the *in vitro* potency method on release.
   b) Enhanced understanding of the method was presented in line with ICH Q14 principles. Identities of carbohydrate structures were mapped between the methods. Robust method control was demonstrated with an enhanced understanding of separation mechanism, including column-to-column ruggedness, which improved the risk profile of single-vendor sourcing, as encountered with FACE gels. Based on the product and method understanding, the risk associated with the changes would be considered medium.
3. The extensive, successful bridging studies (n = 44 batches), successful method validation, and strong statistical correlation between the methods lowered the overall risk level for the change. This demonstrated sufficient understanding of the procedure bias and precision to confirm adherence to specifications. Taken together, these considerations may have supported a case for 'notification moderate' (with prior agreement from the regulatory agencies), rather than the prior approval path that was followed.
4. The superior performance of the new method compared to the filed FACE method, and adherence to the ATP further supported the change.

This retrospective example reinforces the utility of how ICH Q12 and Q14 principles provide a framework for a risk-based approach to change management. The extensive method bridging, thorough understanding of the analytical targets and product, and superior performance of the new method all are successful risk reduction approaches and highlight how this change should have been readily implementable under a more streamlined regulatory pathway.

Under the current environment with Q12, a PACMP containing the ATP could be proactively submitted to multiple jurisdictions which could drive agreed-upon lowered reporting categories and simultaneous implementation. This retrospective analysis highlights the value of the ICH Q12 and Q14 guidelines in facilitating science- and risk-based approaches to pharmaceutical change management, ultimately supporting continual improvement and innovation in analytical methods while maintaining product quality.

## EXAMPLE 4

### Instrumentation/Technology Change – Charge Variant Measurements in Two Biologics

The enhanced approach described in ICH Q14 provides a workflow to allow flexibility in instrument choice with reduced regulatory impact, including for commercial products. Here, we use the measurement of charge variants in biologics drug products as an example of where this flexibility may be beneficial.

The charge profiles of biologic products are indicative of product manufacturing consistency and product stability over time under different conditions. They may also be used to directly or indirectly to monitor specific product CQAs upon release and stability testing. Imaged capillary isoelectric focusing (icIEF) is an electrophoretic technique that uses differences in isoelectric point (pI) to separate and monitor charge variants. In addition to ion exchange chromatography (IEX), icIEF is widely used across industredilry as a release and stability assay for biologic drug substances and drug products.

Recently, the vendor of the commercially available and widely used icIEF iCE3 instrumentation announced discontinuation of support for the iCE3 due to the release of the updated icIEF Maurice model. The differences between the systems are primarily related to the ease of use and not the mechanism of separation/detection, though the newer model does also allow an alternative

detection mode (native fluorescence) with higher sensitivity than the traditional UV detection [8].

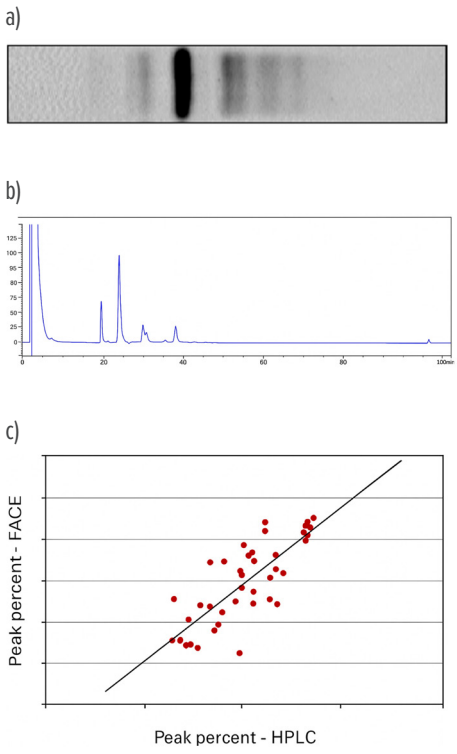
While the vendor of these two instruments has authored technical notes establishing comparability [8], at least one recent paper [9] has highlighted differences between iCE3 and Maurice instrumentation for a biologics drug product, indicating that bridging still needs to be demonstrated on a case-by-case basis and could result in additional changes to the analytical procedure conditions (such as, master mix (ampholytes, standards, etc.) composition, digestions or conditions for sialylated or other non-traditional molecules, or minor changes in instrument parameters). For several molecules the instruments are equivalent, with no changes to conditions, and the two instruments can be used interchangeably [8, 10]. However, in some cases, the instruments result in different profiles that require evaluation of product release and/or stability specifications (see Figure 3). Changes to specifications are by default high risk requiring prior approval per ICH Q12.

Table 7 indicates the instrument parameters used for the side-by-side iCE3 and Maurice analysis of two biologics, Product A and Product B. Parameters were kept as similar as possible for the comparison, with one minor change in autosampler temperature for Product A due to stability observations over long runs, and cartridge and sample injection load changes for both products as required to accommodate the model change.

The left side of Figure 3 illustrates a biologics program, Product A, with no significant impact to profile or results from the change in instrument model from iCE3 to Maurice. Figure 3c shows overlays of Product A with no stress (0x) and 2x light stress on both iCE3 and Maurice. While minor changes, such as improved peak resolution in Maurice, are observed, the profiles are overall comparable. Furthermore, the box plot in Figure 3a shows that the reportable results are not impacted by the change, as the % area differences between the two models hovers around zero for the Acidic, Main, and Basic species. For programs similar to Product A, where there is no significant impact on the profile or reportable results, or differences fall within the variability of the method, comparability between the iCE3 and Maurice should be documented through either development and/or bridging studies. No formal change needs to be reported to the agency; the change should instead be documented and managed through the internal PQS.

The right side of Figure 3 shows another biologics program, Product B, that did have observed differences in the profiles between the iCE3 and Maurice instruments, leading to changes in reported results (see Figure 3d). The transition to the Maurice causes shifts in % area of Main and Basic species, evident in both the control sample (0x stress) and more apparent in the 2x light stress samples. While the overall species observed are similar between the two models, relative amounts of the different species differ as indicated by the % area differences shown in the box plot in Figure 3b. Specifically, the average % Basic species was observed to have an ~5% increase, on average, for Maurice as compared to iCE3 with a concurrent ~5% decrease in Main. Acidic species were similar between the two models. Shifts in profile similar to that observed for Biologics

**Figure 2: Profile comparison of (a) FACE gel analysis, (b) AA-Labeling/HPLC analysis, (c) combined correlation analysis of HPLC vs. FACE results across small- and large-scale lots (n = 44).**




Product B can result in changes to the specification, in which case prior approval would be required prior to implementing the change consistent with ICH Q14 recommendations. Additional details on the potential risk and reporting categories are summarized in Table 8.

## EXAMPLE 5

### Continual Improvement of a Platform Analytical Procedure for Protein Concentration Determination

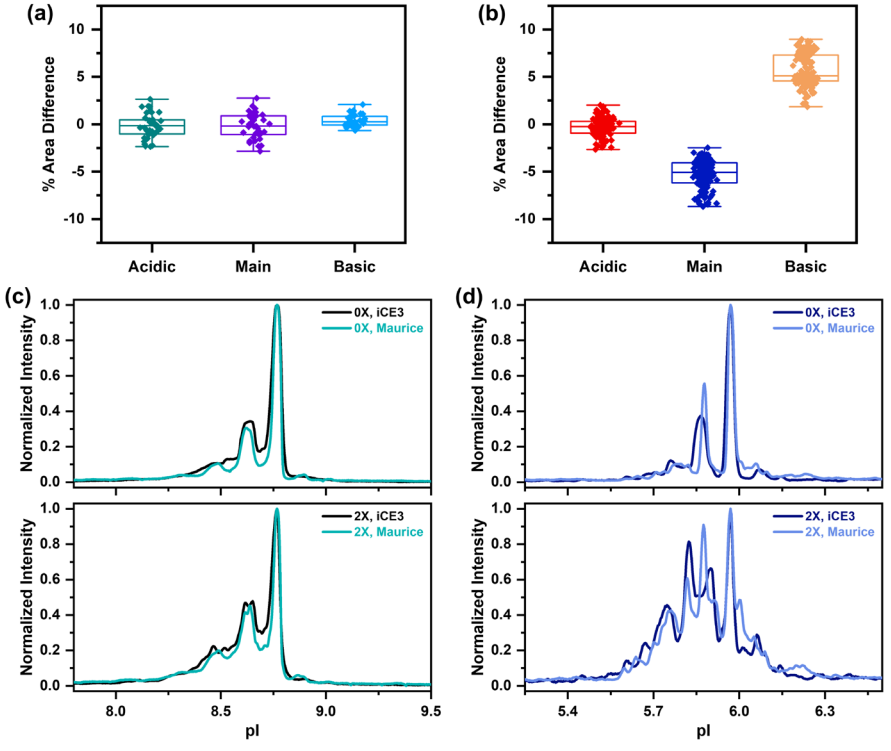
The CTech™ SoloVPE® has become a standard industry approach for measurement of protein concentration [11]. Through a variable pathlength approach, the SoloVPE® instrument enables UV/Vis measurements of varying solution concentrations without need for manual sample dilutions prior to analysis [12]. SoloVPE® is deployed in QC laboratories as well as in manufacturing plants directly due to ease of execution and minimal manual steps, allowing for real-time in-process testing and at-line measurement. Furthermore, the elimination of manual sample dilution steps presents an improvement in protein concentration result accuracy and precision relative to traditional fixed-path length UV/Vis analysis.

In this case study, a sponsor maintains a single multisite platform analytical procedure for UV/Vis measurement of protein concentration that is used across > 25 commercial and > 30 clinical products, across stages of manufacture and QC testing, at five global manufacturing and testing facilities. Now supported by ICH Q14 and

Table 7: Instrument parameter comparison between iCE3 and Maurice for biologic Products A and B.

| Parameter | Product A | | Product B | |
|---|---|---|---|---|
| icIEF System | iCE3 | Maurice | iCE3 | Maurice |
| Cartridge | Fluorocarbon Coated icIEF Cartridge | Maurice icIEF Cartridge | Fluorocarbon Coated icIEF Cartridge | Maurice icIEF Cartridge |
| Focus Period | Focus Period 1: 1 min at 1500 V<br>Focus Period 2: 7 min at 3000 V | Focus Period 1: 1 min at 1500 V<br>Focus Period 2: 8 min at 3000 V | Focus Period 1: 1 min at 1500 V<br>Focus Period 2: 9 min at 3000 V | Focus Period 1: 1 min at 1500 V<br>Focus Period 2: 9 min at 3000 V |
| Autosampler Temperature | 10 °C | 4 °C | 10 °C | 10 °C |
| Sample Injection Load | Transfer Time Plateau + 40 s / 2000 mBar | 90 s | Transfer Time Plateau + 40 s / 2000 mBar | 55 s |

Figure 3: icIEF of biologic Product A and B measured using iCE3 and Maurice. The box plots of % area of Product (a) A and (b) B obtained by subtracting the % area of samples obtained using iCE3 from those using Maurice. The electropherograms of biologic Product (c) A and (d) B subjected to up to 2× light exposure where 1× corresponds to 200 watt hours/m2 of UV energy and 1.2 million lux hours of white light according to ICH Q1B guideline.




ICH Q2(R2), leveraging a platform analytical procedure allows for enhanced global consistency and a streamlined process for method qualification and transfer. However, the method's widespread use prompts complex regulatory reportability assessments whenever an improvement to the method is considered.

The SST for the platform procedure employs a proprietary chemical standard (CHEM013) from CTech in two tests: a 280 nm test and a 310 nm test. The purpose of the 280 nm test is to assess the capability of the SoloVPE® usolonit to take accurate and precise measurements using its automatic path length optimization algorithm at the wavelength at which proteins are measured. The purpose of the 310 nm test is to assess the operation of the SoloVPE® unit at the minimum path lengths within its range, thus representing analysis of a highly concentrated sample. This approach has successfully allowed for routine verification that the instruments are suitable for their intended analysis. However, it has also contributed to a high assay invalid rate, impacting the operational efficiency of test laboratories and manufacturing plants.

Assay invalids occurred when the 310 nm Fixed-M test failed to produce responses with sufficient linearity, due to low absorbance

Table 8: Evaluated risk, proposed established conditions, and proposed reporting categories.

| Established Condition | Overall Risk Category | Reporting Category | Justification/Rationale |
|---|---|---|---|
| Technology: Model update from iCE3 to Maurice with no significant impact to profile/ reported results. | Low | Not reported; managed through PQS. | No significant impact to profile/pI/reported results thoroughly demonstrated through bridging using representative materials.<br>ATP is therefore still fully met, and instruments can be used interchangeably assuming comparability established. |
| Technology: Model update from iCE3 to Maurice with impact to profile/reported results. | Dependent on the extent of change. | Notification. Prior approval could be required if changes are signif-icant (e.g., require specification update). | Impact of model change demonstrated through bridging using representative materials. Shifts in the profile with impact to %Acidics/Main/Basics reporting should be characterized, including potential impact to specifications and stability.<br>Charge variants are typically identified and characterized during isolation and characterization of impurities workflows prior to commercial filing. This infor-mation can be leveraged to determine overall risk of change and understand the impact of method performance on control of product CQAs. |

of the CHEM013 standard at 310 nm. To address this challenge an alternative SST was developed using a more concentrated standard (Patent Blue Standard Solution) and leveraging an alternative path length algorithm. This change has been demonstrated to improve the invalid rate and has additional benefits in requiring 50% less time for execution compared to the current SST, and lowering costs due to the need for less standard volume for each SST execution and a lower cost of the standard itself.

For these reasons a change to the analytical procedure was desired, and a regulatory reportability assessment was performed for all products that leverage the method in all regions where those products have been filed (see Table 9).

Considering that four products require approval prior to implementation, an agile strategy was developed to enable immediate implementation of the change for other products while maintaining continued use of a single multiproduct multisite platform method. Within the method, sub-procedures were defined with reference to an external form listing all products and their corresponding sub-procedure. The first sub-procedure leverages the legacy SST, and this procedure will continue to be used to test the four impacted products until the change is approved in regions that leverage AND. The second sub-procedure employs the new SST, which all other products will be able to leverage and benefit from as soon as the quality change control process is completed. Once the change has been approved for all products in all regions, the method procedure will be updated a second time to remove the legacy SST sub-procedure, and all products will then be tested following a single harmonized procedure from that point forward.

While this implementation strategy does grant some relief from the high assay invalid rate, it was recognized that yet another creative strategy will soon be needed for the evolution of the protein concentration method in response to recent news from CTech™ that they will retire the SoloVPE® instrument, ceasing support for it in 2031, and will transition to a new instrument model called the SoloVPE® PLUS system which has lower minimum path lengths, that potentially may trigger yet another SST update, or other analytical procedure modification.

Applying ICH Q12 and Q14 principles could have enabled a faster path to full global implementation of the change, which could have been considered low risk since it does not affect sample analysis or reported results. By sharing the risk assessment with regulatory authorities and securing prior agreement on a low reporting category for these established conditions, duplicate testing could have been avoided. The change could have been implemented through internal change control procedures with appropriate experimentation and documentation, followed by reporting. Alternatively, use of a PACMP covering the SST change for all products could have been an option. Had such a protocol been in place and approved by the various agencies, the new SST could have been immediately implemented for all products. This change did not affect the ATP for the method and was an operational improvement yet still prompted a requirement for approval prior to implementation in certain regions, underscoring the criticality of efforts to drive health authority alignment and innovation during commercial life cycles [4].

## CONCLUSION

From the examples presented above, it is evident that managing changes to analytical procedures is a complex and lengthy process. ICH Q14 offers a science- and risk-based framework that streamlines change management while ensuring product quality and regulatory compliance while fostering innovation. Therefore, it is essential to encourage sponsors to utilize and submit the regulatory tools described in ICH Q14 whenever implementation in individual markets has been realized. Furthermore, regulators are encouraged to harmonize change requirements with ICH Q12 so that the industry may fully harness the potential of the ICH Q14 framework. Ultimately, the success of this guidance depends on both adoption into industry practices and supportive regulatory oversight.

The examples demonstrate how an ATP (and other elements of the enhanced approach), ECs, and PACMPs can be leveraged to

**Table 9: Summary of regulatory activities required and timing to implement the system suitability test change for the SoloVPE® measurement of protein concentration.**

| Reporting Category | General Assessment | Expected Implementation |
|---|---|---|
| Not reportable to any regulatory agencies. | Method update does not need to be reported in clinical trial applications affected by this change, as this level of detail is typically not registered. | Immediately following change control completion including internal implementation activities. |
| Reportable with no product restriction. | Annual notification required for approved commercial products in the US and EU. | Immediately following change control completion including internal implementation activities. |
| Reportable with product restriction. Requires prior approval from a regulatory agency before product distribution. | Full SoloVPE method is described in RU, BY and KZ Analytical Normative Document (AND[1]) and therefore the change to the method requires prior approval in these countries. | Approximately 4-5 years from initiation of the change. |

The Analytical Normative Document (AND) is a product-specific registration document required by several markets, including Russia, Kazakhstan, Belarus, and Ukraine, for national licenses and for products registered with the Eurasian Economic Union (EAEU). The AND typically contains detailed information on specifications and analytical procedures. For most products in many regions, the change either does not need to be reported or can be reported post-implementation. However, for four commercial products registered in regions that utilize the AND, the change has been assessed as requiring prior approval. Unfortunately, other mandatory and planned activities (ongoing CMC variations) have affected the timing of filing this method change, resulting in an expected implementation timeline of no sooner than four to five years.

streamline the implementation of necessary changes to analytical procedures, ranging from minor modifications to complete technology updates. These tools allow for appropriate risk categorization and corresponding reporting requirements, reducing regulatory burden for low-risk changes while maintaining appropriate oversight for higher-risk modifications. Harmonization of global regulatory expectations for analytical procedure changes, as facilitated by ICH Q14/Q2(R2) and Q12 tools, is crucial for ensuring a robust drug supply and compliance by minimizing unnecessary duplicate testing using obsolete procedures while awaiting individual regulatory approvals.

By enabling QC laboratories to incorporate state-of-the-art technologies and greener approaches, these guidelines support continual improvement of analytical procedures. As demonstrated across diverse applications—from dissolution testing to complex carbohydrate analysis and charge variant measurements in biologics—this modernized approach to analytical procedure lifecycle management ultimately benefits patients through enhanced product understanding, improved quality control, and more efficient regulatory processes.

The authors recognize the need to further clarify ICH Q14 concepts and principles by providing additional examples. This article marks the beginning of this effort, and we invite readers to contribute more real-life examples to enhance understanding, application, and adoption of ICH Q14.

## Acknowledgements

The authors would like to acknowledge the ISPE Product Quality Lifecycle Implementation (PQLI) Analytical Methods Strategy technical team for its contributions to the subject matter discussed in this paper. The authors would also like to acknowledge Michael Brenner, John Prior, Manoj Menon, Qun Zhou, Cynthia Hammill, Wendy Yang, Scott Hartzell, Anjana Patel, David Mirakian, and Lauren Roschen.

For more information about ISPE's PQLI Initiative, visit ispe.org/initiatives/pqli

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