EFPIA position paper on ICH Q6 A/B revision

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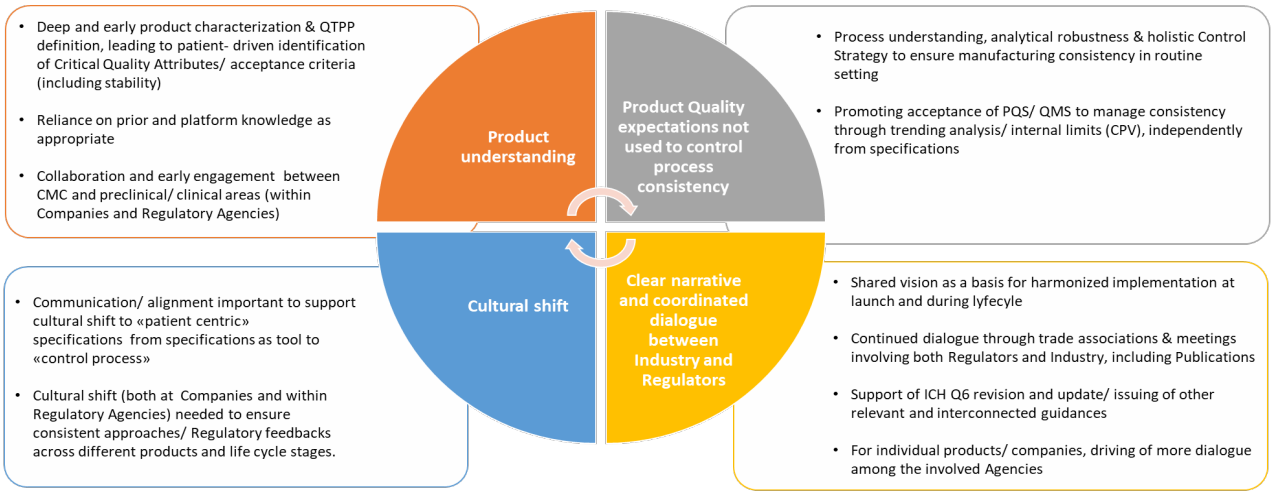
Contents

Graphical Abstract

How to define Specifications addressing patient needs, access, and global harmonization



Introduction

According to ICH Q6, specifications are "*a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described.*"[1][2]The primary goal of a specification is to ensure patients receive a safe and effective product. As such, specifications represent a crucial element of each Marketing Authorization Application.

Dialogue between Regulatory Agencies and Industry on the principles for setting specifications has been ongoing for several years (e.g.,[3] [4]), with recent emphasis on accelerated access scenarios [5] and patient-centric (or clinically relevant) specifications [6]Together, these are summarised in the reflections shown in the Executive Summary. The COVID19 pandemic has further highlighted the necessity to consolidate strategies for setting specifications, without compromising product quality, safety, or efficacy, when development timelines are extremely short. A fruitful outcome of the ongoing dialogue can be seen in the recent EMA Toolbox guidance on early access [7], which includes considerations on specification setting strategies for accelerated development scenarios of medicinal products for unmet medical need.

Collectively, these discussions underline the need for an update of the ICH Q6A and Q6B Guidelines, which were first issued in 1999. Concurrently, ICH Quality Discussion Group (QDG) proposed in 2021 that revision of the ICH Q6A and Q6B Guidelines is of the highest priority for ICH [8], and EWG activities are expected to start soon.

Learnings resulting from more than 20 years of implementation highlight the necessity to consolidate core principles of patient- centric specifications, include new product modalities, foster harmonization across different regions, align the expectations for specification setting to more recent ICH Guidelines, clarify guidance on use of pharmacopoeias, integrate contemporary science/ risk- based approaches, and enable accelerated development and lifecycle management.

In this context, EFPIA has identified the following issues with guidance in the current versions of ICH Q6A and B.

- Attributes required in specifications may go beyond those which are critical to safety and efficacy e.g., the ICHQ8 Critical Quality Attributes (CQAs).
- Limits are primarily defined based on statistical assessment of available manufacturing batch data (often tightened as more lots become available). Such approaches, however, do not necessarily reflect clinically relevant safety and efficacy considerations or scientific understanding of true process capability when operated at the limits of input material specifications and the defined process ranges.
- There is no clear mention of the use of ICHQ8-11 (QbD) principles to develop the specification as part of a holistic control strategy.

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[1] ICH Q6A Guideline: Specifications: Test Procedures and acceptance criteria for new Drug Substances and New Drug Products: chemical substances
[2] ICH Q6B Guideline: Specifications: Test procedures and acceptance criteria for biotechnological/ biological products
[3] EMA/CHMP/BWP/30584/2012, Report on the expert workshop on setting specifications for biotech products, European Medicines Agency, London, 9 September 2011f
[4] EMA/CHMP/BWP/187162/2018, Meeting Report: Joint BWP/QWP workshop with stakeholders in relation to prior knowledge and its use in regulatory applications
[5] EMA/CHMP/BWP/812924/2018, Meeting Report: Workshop with stakeholders on support to quality development in early access approaches (i.e., PRIME, Breakthrough Therapies)
[6] IABS Conference on Global Harmonized Specifications: current state and future opportunities, Basel, January 10-12 2023, https://globally-harmonized-specifications-basel-2023.iabs.org/ (including discussion and case studies on the four topics reported in the Executive Summary)
[7] EMA/CHMP/BWP/QWP/IWG/694114/2019, Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorisation applications targeting an unmet medical need
[8] https://database.ich.org/sites/default/files/ICH_QDG_Recommendation_2021_1012.pdf

- Q8-11 tools such as prior knowledge from similar products and processes and Quality Risk Management are not mentioned in the guidance.

This document reports EFPIA recommendations for ICH Q6A and Q6B key improvements and additions, to address emerging medical needs and fully embrace progress in science, technology, and CMC strategies. Principles and proposals reported in this document are applicable to different pharmaceutical modalities (including, for instance, small molecules, biotherapeutics (like mAbs/ Antibody- Drug conjugates) ATMPs, vaccines, drug/ device combinations), and are based on multidisciplinary and extensive experience of EFPIA member companies. Development elements needed for justification of specifications are covered, along with marketing application and lifecycle management considerations.

1. Patient- centric strategies

A patient-centric specification (PCS) is a set of CQAs and acceptance ranges to which product quality attributes should conform for the product to be safe and effective when used as labeled. Justifications for acceptance ranges focus on risk/knowledge-based assessment of the impact to patient and improve access to medicines through reliable, robust supply chains.[9,10] Patient-centric specifications may also be referred to as clinically relevant specifications (CRS) and Patient Centric Quality Standards (PCQS) in the literature.[11] In 2012, FDA suggested "*CRS are those specifications that take into consideration the clinical impact of variations in the critical quality attributes (CQA) and process parameters assuring a consistent safety and efficacy profile*" .[12]

Within a patient centric paradigm, the role of the specification is assuring patient safety and product efficacy. Consistency is assured through direct process controls (input material controls, process parameter controls, in-process controls, etc.) and ongoing process verification within an appropriate quality management system to meet cGMP requirements.

It is recognized that ICH Q6A already incorporates patient centric principles in that it describes setting a specification in consideration of the overall product control strategy and focusing on characteristics that ensure the safety and efficacy of drug substance and drug product (1.2 & 1.3). ICH Q6A also recognizes that at the time of filing only limited batch data may be available and that the focus should therefore be on safety and efficacy (2.5- and 3.2.2-part d). Furthermore, the existing guidance highlights that data from all relevant development experience should be considered when setting a specification limit and appropriate manufacturing and analytical variability included (3.1.2 paragraph 1 & 4). Such principles are equally applicable to all product types, including biological products currently in scope of only ICHQ6B.

While these core principles align well with patient-centric approaches, they are subsequently undermined within the guidance itself by principles that put primacy on actual results over 'theoretic considerations', which could be interpreted as risk/knowledge-based approaches (3.1.2 paragraph 2). In addition, and as an example, decision tree #1 and 'section 3.2.2 part a' directs the applicant to establish acceptance criteria in consideration of a statistical analysis of the batch data available at time of filing. Although the guidance itself

[9] Ruesch MN, Benetti L, Berkay E, Cirelli DJ, Frantz N, Gastens MH, Kelley WP, Kretsinger J, Lewis M, Novick S, Rellahan B, Pack L, Stroop CJM, Subashi A, Yin P, Zeng M, Stult Js, Strategies for Setting Patient-Centric Commercial Specifications for Biotherapeutic Products, Journal of Pharmaceutical Sciences, 110(2), 771-784 (2021)
[10] Bercu, J., Berlam, S.C., Berridge, J. et al. Establishing Patient Centric Specifications for Drug Substance and Drug Product Impurities. J Pharm Innov 14, 76–89 (2019).
[11] Daniel Peng, PhD Joel Bercu, PhD Ann K. Subashi Lawrence X. Yu, PhD ISPE PQLI Patient Centric Specification Working Group, Patient- centric specifications: regulatory & pharma industry progress, Pharmaceutical Engineering, September/ October 2019
[12] https://fda.report/media/85355/Establishing-Clinically-Relevant-Drug-Product-Specifications--FDA-Perspective--Sandra-Suarez-Sharp--Ph.D.--October-16--2012--AAPS-Annual-Meeting.pdf

(3.2.1, part d) highlights that the applicant is unlikely to have sufficient batch data to apply decision tree #1 at time of filing, this has inadvertently become the default approach in establishing specification limits.[10]

ICH Q6B also incorporates some principles that are consistent with a patient- centric approaches. For example, ICH Q6B acknowledges heterogeneity is inherent to biological products and that if a consistent pattern of product heterogeneity is demonstrated, an evaluation of the activity, safety and efficacy of individual forms may not be necessary. ICH Q6B also allows manufacturing capability to be leveraged in some situations to justify not including specifications for some process-related impurities when control or removal to acceptable levels is demonstrated by suitable studies, and for some testing to be performed as an in-process test rather than a specification. ICH Q6B also allows for science-based justification for which tests to include on the specification. However, the document states that specification acceptance criteria should be linked to analytical procedures and based on data obtained from lots used in pre-clinical and clinical studies, and those used to demonstrate manufacturing consistency.

Revision of ICH Q6 to incorporate patient- centric principles, based on control of CQAs, is consistent with strategies currently outlined in ICH Q8 (R2)[13], stating that "Adoption of the principles in [the] guideline can support the justification of alternative approaches to the setting of specification attributes and acceptance criteria as described in Q6A and Q6B." ICH Q8 (R2) goes further to indicate that, if appropriately supported by enhanced process and/or product knowledge, product specifications can be based on desired product performance rather than batch data (Appendix 1). Revision of ICH Q6 to incorporate patient- centric principles would align concepts for creation of a control strategy as envisioned in ICH Q8 (R2) with those for establishment of specifications, particularly the concept of Drug Product and Drug Substance CQAs, as well as how these are linked to input materials attributes, process parameters etc, as the basis for the specification, in the context of control strategy.

The focus of a patient-centric revision to ICH Q6 will address these internal inconsistencies by further strengthening the statements around risk/knowledge-based approaches (aligning to ICH Q8-10) and re-focus on the primacy of drug substance/product safety and efficacy considerations. In addition, the revision could clarify and expand how different pharmaceutical development approaches (e.g., minimal vs. enhanced/QbD) impact the ability to develop an integrated control strategy including the establishment of patient-centric specifications and the inclusion of prior/platform knowledge into the considerations of establishing specifications.

Clarification of patient-centric terminology should be addressed throughout the guidance, for example better defining the meaning of 'clinically acceptable' (3.3.2-part a). From a patient-centric perspective, a clinically acceptable range is one in which an attribute may vary without having a clinically meaningful impact on the safety and efficacy that was established in the clinical trials. A clinically meaningful impact is grounded on holistic CQA assessment and acceptance criteria considering overall quality of a product. For instance, as part of this exercise, potential impact on safety and efficacy should be assessed in the context of the overall control strategy, and justified by thorough understanding of molecular attributes, clinical relevance, reliance on nonclinical (in vitro/in vivo) models, and use of prior knowledge (e.g., on safety of some impurities, to be used across different products)."

Coherently, a review/ potential extension of the decision trees or the consolidation into a single high-level decision tree should also be considered. A high-level decision tree could illustrate the types of information (eg, clinical experience, prior knowledge, established standards/guidance) that can be used to assess attribute impact on safety and efficacy, and considerations for how this information is used to establish a

[13] ICH Q8(R2) Guideline: Pharmaceutical Development

patient centric control strategy. Additional illustrative information outlining inputs into a patient- centric specification is reported in the literature (e.g., [14])

In case of patient-centric approach for specifications definition, tightening of specification acceptance criteria solely based on process capability/historical data (e.g., as post- approval commitment) does not fit with setting quality expectations based on product safety and efficacy. Thus, such restrictions would become unnecessary under the patient- centric paradigm.

The next sections will provide more detail on patient- centric elements, their interplay with holistic control strategy, and their relevance for identification of relevant quality attributes to be tested, appropriate acceptance criteria, analytical strategy, and ultimately integrating all relevant information in the quality target product profile (QTPP).

2. Specifications as part of a holistic Control Strategy

ICH Q10 defines the control strategy as "*A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control*." [15]

The control strategy should consider controls on input materials (attributes related to raw materials, drug substance and drug product input materials and components), in-process materials and intermediates and finished product specifications. Process controls can include in-process analytical controls, control of process parameters and equipment

The control strategy should integrate all elements necessary to adequately ensure the product efficacy and patient safety. For example, certain CQAs can be appropriately controlled upstream (e.g., in input materials or intermediates) and/or via parametric controls (e.g., process parameters, design space). For these instances, the CQAs do not require additional, redundant, testing in drug substance or product. The ability to control attribute(s) can be demonstrated with traditional approaches (e.g., consistent impurities clearance demonstrated during development and Process Performance Qualification) or with Real Time Release Testing/ advanced control strategies.

A science and risk- based approach should be used to develop the specification as part of the overall control strategy, covering both drug substance and drug product. The strategy may differ, based on product/molecular complexity and the level of process understanding. More traditional control through specifications may be needed where there is less product and process knowledge.

A control strategy employing testing at multiple points (e.g., in intermediates and the end product) may not be necessary where justified on the basis of process understanding.

Specification tests should be knowledge based and consider what needs to be controlled for the specific product (e.g., considering manufacture across process ranges and/or at the limits of input material attributes and process parameter ranges, as opposed to relying strictly on batch history). The drug substance/product specification is one part of a total control strategy and not all CQAs need to be included in the drug substance/product specification, as reported in ICH Q11.

[14] EMA/CHMP/BWP/187162/2018 Case Study 3: Prior knowledge in the Control Strategy for Biotechnology Products
[15] ICH Q10 Guideline: Pharmaceutical Quality Systems

The establishment of a holistic control strategy, showing the ability to control and monitor product quality through process and analytical elements, is key to build confidence on the ability to consistently manufacture commercial products, and to ensure appropriate selection of CQAs to be included in specifications.

3. Specification elements

3.1. Identification of quality attributes for specifications

Following ICH Q8 (R2) principles, specifications should be set considering the Quality Target Product Profile (QTPP) expectations, thus including those CQAs which need to be routinely monitored based on the control strategy. This section will provide an overview of the proposed principles to identify such attributes.

3.1.1. Specifications to support CQA monitoring and fulfill QTPP expectations

The QTPP, is defined by ICH Q8 [13] "*a prospective summary of the quality characteristics of a drug product that should be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product*". As per ICH Q8, the critical safety & efficacy elements of the QTPP should be justified within the regulatory file and the QTPP elements should be updated as knowledge of the requirements for attributes of the drug product develops, as appropriate, for example, for a new dosage form, patient population, indication, stability profile, etc. Whilst the manufacturing process or control strategy may evolve, this will not alter the QTPP.

A CQA is a "p*hysical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality [i.e., the QTPP]. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product*" (ICH Q8). "The *QTPP provides an understanding of what will ensure the quality, safety and efficacy of a specific product for the patient and is a starting point for identifying the CQAs*." (ICH Q8, Q9, Q10 Points to Consider).

To fully deliver the QTPP and develop an effective control strategy, CQAs must be identified, and potential clinical impact of their changes understood. Incomplete or inconsistent identification of CQAs may adversely impact the patient (for example uncontrolled impurities in small molecule APIs or product-related variants with reduced efficacy for vaccines or biopharmaceutical products).

A holistic scientific approach should be taken to the identification and assessment of potential CQAs. This should involve a risk-based justification as appropriate, e.g., considering impact on safety/ efficacy and associated level of uncertainty [16].

Attributes of the drug substance and drug product should be identified as critical based on risk, considering ICH Q8 -11[17] principles. For many drug products, the risk assessment to identify CQAs may be based on consideration of the dosage form and requirements of the QTPP, and through consideration of prior knowledge. For drug substance, CQAs should include those attributes (e.g., physico-chemical properties) which impact the drug product, as well as other attributes impacting efficacy and safety (e.g., potential impurities). Some illustrative examples could be included in the revised guidelines but should not be perceived as prescriptive for specifications setting, because the list of attributes in the specifications may depend on pharmaceutical modality and control strategy. Emphasis should be given to principles for selecting the attributes to be included in the specifications for release and shelf-life.

[16] Khan MA, Campa C (eds), Quality by Design - An Indispensable Approach to Accelerate Biopharmaceutical Product Development, Parenteral Drug Association, 2021
[17] ICH Q11 Guideline: Development and manufacture of drug substance

For complex biological products, it is generally more challenging to identify CQAs. Knowledge regarding mechanism of action and biological characterisation, such as studies evaluating structure-function relationships, can contribute to the assessment of criticality of product attributes.

Additional knowledge on attributes such as impurities and their structure-function relationship gained during lifecycle may change the designation of criticality.

3.1.2 Additional testing to support control strategy and process consistency

Non- critical quality attributes may be included in the analytical testing strategy, to gain and increase product and process understanding and/ or to support continuous process verification. Such attributes, despite non-critical, may be relevant as product stability indicators or to assess impact of process changes, and therefore it may be beneficial to monitor. They may indicate a product change prior to any CQAs being affected and hence can be considered as sentinels of manufacturing consistency. In general, these tests are not included in specifications but can be executed periodically or as part of change control.

3.2. Establishing Acceptance Criteria

Traditionally, acceptance criteria for attributes in a specification have been defined based on available manufacturing history, often tightened as more lots became available. Such approaches, however, do not necessarily reflect biomedical safety and efficacy considerations and may provide only a limited reflection of the true process capability. In addition, such a traditional approach has additional significant scientific and practical limitations.

For instance, in case of accelerated development scenarios, a limited number of batches are available at the time of registration could lead to inappropriately tight acceptance criteria which would lead to un-necessary batch rejections[18] . In addition, it is likely that acceptance criteria based on process consistency alone will lead to different limits agreed across regions. This anticipated lack of global harmonisation will result in complex lifecycle management and impede innovation/process improvements. Such approaches are not built on patient centric considerations and may not reflect scientific understanding of the process when operated at the limits of input material specifications and the defined process ranges.

The current ICHQ6 guidelines do prescribe that specifications should be linked to manufacturing experience. EFPIA believes that in the interest of globally harmonized specifications and with the help of risk-based clinically relevant specifications, an uncoupling of the manufacturing experience from the specifications is required and that this should be reflected in an ICHQ6 guidelines update.

Definition of acceptance criteria based on product safety and efficacy evidence provides a strong, intrinsically harmonized, justification of acceptance criteria, aligned with Quality by Design principles. It supports accelerated development and manufacturing flexibility, since demonstration of process changes impact on quality would be assessed in an objective way, not necessarily implying a change in specification ranges.

It would be beneficial to clarify the terminology associated to clinically relevant acceptance criteria as part of the ICHQ6 update. Some examples are reported here, for consideration. Clinical justification of acceptance criteria is based on scientific rationale from the totality of information that supports the potential impact of the attribute of safety and efficacy. As previously described, this can include data from clinical/nonclinical evidence along with other available sources of information.

Manufacturing consistency should still be demonstrated, especially post- approval after completion of clinical studies. In this context, demonstration and monitoring of consistency can be achieved relying on internal

[18] WHO Technical Brief: Regulation of COVID-19 Vaccines – Synopsis from the August to November 2020 COVAX RAG meetings, February 2021, https://www.who.int/publications/m/item/1st-technical-brief-regulation-of-covid-19-vaccines-april.

limits (tighter than clinically relevant specifications), managed via pharmaceutical quality system (PQS) and ongoing process verification.

3.3. Specification setting considering analytical method development and lifecycle

The definition of patient- centric specifications should include the CQAs and related requirements as derived from QTPP, and an appropriate analytical procedure should be identified based on the Analytical Target Profile (ATP), as defined in current ICH Q14 draft,[19] as an element of an enhanced approach to analytical procedure development'.

Performance characteristics and related criteria (as described in an ATP), defined at the onset of the development, may need to be revised with progressing development, e.g., due to changes in specification acceptance criteria or based on increasing knowledge in the factors impacting product quality. The use of a patient-centric approach allows the assignment of specification limits which are expected to be unchanged after definition, as they are based on justified impact on product safety and/ or efficacy. This sets the grounds for a robust analytical procedure change management strategy for lifecycle. If that approach is used, it is important to ensure monitoring of analytical performance, e.g., using system suitability and appropriate reference standard and control samples, to ensure that accurate (statistical) control on analytical tests results is in place. Analytical results (based on the selected technology) will be the basis for company monitoring and trending, which will need to be within internal limits, within clinically relevant limits.

The implementation of this approach for the analytical method lifecycle (as per ICH Q14) ensures further control on the method performance during routine method application. In this context, batch test trending should always be reviewed in conjunction with manufacturing variability as part of the overall consistency assessment. Companies' PQS should ensure method performance information is reviewed on a regular basis and should identify any drift in process during lifecycle (eg due to process changes or new data). In this context appropriateness of ATP (regarding method performance requirements) should be reviewed.

The use of platform method approaches is highly recommended, as it reduces the risk for unexpected method variability issues, sets the basis for consistent acceptance criteria and supports comparability assessment between clinical and commercial batches.

Real Time Release Testing (RTRT) (when available) and conventional off-line testing of the same attribute are typically both filed, provided that the RTRT is demonstrated to reliably monitor product quality; this happens, for instance, in case of availability differences across multiple testing sites, unavailability of PAT-based model, emergency scenarios with limited prior knowledge. Replacement of off-line test has therefore to be decided on a case- by – case basis as part of the overall control strategy.

The introduction of PAT-based methods for real time release testing requires different approaches for sampling and specification acceptance criteria. Use of PAT-based methodologies require acceptance criteria based on a statistical, risk-based approach to account for the extensive dataset and sampling frequency of PAT-based methods compared to off-line testing. Revisions to ICH Q6 should account for new testing technologies and outline at a high-level consideration for justification of real time release testing specifications.

3.4. Stability considerations

While specifications must be met during drug substance/product shelf-life, product considerations may drive the establishment of distinct release and stability specifications.

When an attribute changes over shelf-life, it may be required to set a separate stability (or shelf-life) specification to confirm that the product remains in specification during the entire shelf-life, therefore

[19] ICH Q14 Guideline (Step2): Analytical Procedure Development- draft version March 2022

ensuring the product is safe and efficacious through the in-use period up to and including the point of use. As such, a change in quality attributes during shelf-life should be considered when setting acceptance criteria for batch release. When the release and stability specifications are different, the release specifications may be managed internally by the sponsor. When the changes over time are not significant, the release specification of the product may apply for stability studies. In addition, different test methods may be appropriate for release and stability testing in some scenarios, when supported by appropriate analytical bridging. For example, real-time release testing performed during the manufacturing process may require different methods than are performed for stability. While ICH Q6B allows for different release and stability specifications, ICH Q6A does not include this allowance and the revision to ICH Q6 should clarify the approach can be applied to chemical substances and biologics.

Accounting for attribute changes that are expected to be observed over the product expiry can be challenging for products that have small datasets due to limited storage duration. This scenario poses challenges if the specification is required to be tightly linked to the range in the available stability dataset. Incorporation of a patient centric approach for establishing stability specifications would enable ranges that account for expected changes over the desired shelf-life if such ranges can be sufficiently justified to ensure that there will be no impact to safety and efficacy within the range.

While patient-centricity is the overarching principle for establishment of a proposed shelf-life limit, prior knowledge and risk-based stability (modelling) can also be used to support the specification for shelf-life by extrapolation of available data. Modeling approaches are well established for small molecules and can also be considered for biologics.][7, 16, 20,21] These models can be especially useful where limited stability data with respect to batches and/or time is available for a product under accelerated development. The data utilized for these models can originate from laboratory-scale data; product and nonproduct-specific prior knowledge, platform knowledge and various development studies under various real time and/or accelerated conditions. The statistics should be justified by the Sponsor.

By extrapolating the stability profile (trend) of the attribute to the worst-case release value, stability models can support the integration of stability data from drug substance and drug product up to the point of administration. The adoption of an integrated stability approach should ensure connectivity between the drug substance, any intermediates and drug product stability data, shelf-life and the specifications. This would ensure that a batch released at the worst-case drug substance specification will still meet the drug product specification at shelf-life, including any in-use stability prior to administration.

Ultimately, the specification, as supported by stability data, should be demonstrated to be able to appropriately monitor product quality, considering the intended performance of drug substance and drug product throughout shelf life.

4. Use of Prior and Platform Knowledge

The definition of tests and acceptance criteria in specifications should be based on a sound scientific justification, clinical relevance, patient-centric attributes and platform or prior knowledge**.** An update of ICH Q6A and Q6B provides the opportunity to set specification criteria based on science and risk-based approaches and the totality of product, quality attribute and process understanding, including the

[20] M. Scott Furness, Hong Cai, Sithamalli Chandramouli, et al. Modeling Approaches to Reimagine Stability (MARS) for Enabling Earlier Access to Critical Drugs for Patients with Unmet Medical Needs. AAPS PharmSciTech 24, 35 (2023)
[21] Cristiana Campa, Thierry Pronce, Marilena Paludi, Jos Weusten, Laura Conway, James Savery, Christine Richards, Didier Clénet, Use of Stability Modeling to Support Accelerated Vaccine Development and Supply. Vaccines, 9(10), 1114 (2023)

appropriate use of platform and prior knowledge, if justified and demonstrated to be relevant for the product.

"Prior knowledge" includes knowledge from development and manufacturing experience (both product experience and knowledge obtained from analogous molecules (like-molecules), products and processes) as well as reference to scientific and technical publications or application of established scientific principles. A "Platform specification" is derived from harmonized specifications applied to similar compounds and/or dosage forms based on prior knowledge and may include compendial specifications. The updated ICH Q6 guideline should be clear in providing options to use prior and platform knowledge as part of a holistic control strategy and to accommodate accelerated development and regulatory pathways where acceptance criteria are derived from limited batch experience. It is therefore recommended to rebalance the reliance on specific batch data by indicating that specification setting can be based on (1) scientific understanding and justification of the links between specific quality attributes and safety and efficacy, and (2) utilization of prior knowledge to allow for specification to be set beyond the manufacturing experience of specific clinical lots, when justified.

The use of prior and platform knowledge can be extremely valuable for setting phase appropriate specifications, especially when product specific data and manufacturing experience are limited, and a plethora of prior knowledge may exist for molecules of similar modality/mechanism of action. These similarities make the experience and learning from any individual molecules highly translatable to other relevant candidates. Overall, prior and platform knowledge can be grouped into four general categories.

1) Established principles and available published experience

The ICHQ6 guidelines should clarify that prior knowledge gained from previous molecules can be leveraged for new molecules, which share similar biological principles. For example, an established relationship between a biochemical attribute and a biological activity for similar molecules can support the use of a biochemical test as a part of a molecule's control strategy. In addition, the linkage of specification setting to existing platform technical knowledge in the public domain should be addressed.

2) Established manufacturing experience

The guideline should address the possibility to leverage prior manufacturing experience for new product CQA assessments where similar cell line, culturing conditions and purification processes are used. In addition, the guideline should address the approach to potentially remove redundant specifications if consistent process performance is demonstrated.

3) Forced degradation studies

The guideline should address the use of prior knowledge from forced degradation studies to support molecule potential degradation pathway assessments for similar molecules.

4) Platform specification

Utilising a platform specification offers the benefit of facilitating early development and for accelerated development scenarios (e.g., PRIME, Breakthrough or Sakigake designation), while ensuring the attributes that are directly related to product safety and quality are still adequately controlled using specifications derived from prior experience. Even though ICH Q6 guideline is intended for commercial licensure, it could be helpful to address when the principles of using platform specifications: scope, generation, justification, and adaptation of the platform limits, could be applicable in product development.

Prior and platform knowledge principles proposed are applicable for biologics and chemical substances, inclusive of using a patient-centric approach and/or modelling to justify widening specifications when appropriate.

5. Accelerated scenarios & phase- appropriate specifications

For products undergoing accelerated development timelines, product and process knowledge (e.g., uncertainty on the criticality of attributes, their control by the manufacturing process, and analytical capability) will likely still be evolving at the time of the marketing authorization application. Thus, the amount of data available to support specifications at the time of approval may be reduced compared to a product undergoing a standard development, and a flexible, science and risk-based approach is critical to allow establishment of the specification. In addition, and especially in health emergency scenarios, it is also important to avoid wasting good lots due to over- restrictive specification limits set with limited or not fully representative batches.

As such, the following considerations, applicable to all scenarios, will become more significant:

5.1. Identifying CQAs

Early identification of CQAs will enable the specification setting, however data may be limited. Consideration of all available science and prior knowledge from similar product and processes will be key to identifying CQAs when only limited data is available. Consideration should be given to how the CQAs will be reviewed in the early lifecycle and updates made, if needed (eg addition or removal of CQAs). Unnecessary controls on attribute in the specification will lead to a higher risk of rejecting safe and efficacious batches and may lead to waste of valuable product due to unnecessary testing.

5.2. Acceptance criteria

It is expected that there will be fewer batches and less data in accelerated scenarios, which may prevent a meaningful statistical analysis. Alternative data sources such as prior knowledge, in-vitro data, animal data, platform knowledge, CQAs from related programs, etc. would form the basis for establishment of patient-centric acceptance criteria. If using information from other products, a comparison and justification for any differences between products should be provided.

As well as relevant prior knowledge, data from all development batches should be considered to enable a full scientific assessment of the process capability in setting the specification. This may mean lab or pilot batches play a significant role, and the use of data generated using alternative analytical procedures with limited validation, may also be important.

5.3. Use of dose finding

In an accelerated development scenario, dose-ranging studies may be designed to support evolving product knowledge and future changes during development and lifecycle. During development, the target active ingredient amount in the final product should be higher than the minimum active dose demonstrated in the clinical trials of the active ingredient under study, if there are no safety concerns. In this scenario, if the real target active ingredient amount, in the presence of variant(s) impacting efficacy, is lower than the target but still higher than the minimum active dose, the product will still be effective. Of course, the control over the variants to appropriate levels (including stability considerations, as applicable) should be ensured. This strategy was also discussed at the EMA/ FDA Stakeholder workshop on support to quality development in early access approaches, such as PRIME and Breakthrough Therapies. [5] The meeting report highlighted the following: ”as a prerequisite and where no impact on safety is seen, the aim for somewhat higher doses for the commercial product compared to what has been used in clinical trial will add a safety margin to compensate for residual risks and can be considered. It was proposed that companies seek SA and/or discuss with the responsible agencies during development such innovative approaches."

5.4. Additional controls

If necessary, consideration should be given to how the acceptance criteria will be reviewed in the early lifecycle and updates made, if needed. One option to enable wider acceptance criteria may be to include additional controls such as additional orthogonal testing or in-process tests at the time of filing and to gather

the required knowledge after approval. Tighter control on the process to reduce variability (eg narrower parameter ranges) may also be a consideration. However, such controls would need to consider any potential impact on supply and utilised appropriately within the context of benefit/risk. Use of ICH Q12 tools [22] would support establishment of lifecycle plans in support of specification evolution.

Overall, in accelerated scenarios, an assessment of the specification as part of the holistic control strategy and in the context of benefit/risk and patient centricity, coupled with review and updates during the lifecycle, will be critical to the supply strategy. Tools such as Post Approval Change Management Protocols (PACMP) can enable the lifecycle management.

Post-approval, additional batch data will be available to demonstrate manufacturing consistency, however patient centricity and scientific understanding (including relevance of the attribute to safety and efficacy and prior knowledge) combined with quality risk management should remain the focus of the justification, rather than batch data. Ongoing process verification will ensure demonstration of manufacturing consistency and proactively manage trends and deviations.

6. Link of specifications to comparability and reference standard strategy

6.1. Comparability

It is recommended to have more explicit mention of the relationship between specifications and comparability, considering the proposed changes towards patient- centric approaches and manufacturing consistency management through PQS.

In this context, success of comparability exercise is very much dependent on product understanding and on the specifications setting strategy: a patient- centric approach, reinforced by extensive product characterization, sets the basis for assessing the impact of process evolution on the quality, safety and efficacy of the medicine or vaccine. The use of prior knowledge and the development of an appropriate control strategy help defining which process steps may impact CQAs and assess the overall quality risk associated to a process change.

For biological products, ICH Q5E [23]states that comparability is an exercise to ascertain that pre- and post-change drug product are comparable in terms of quality, safety, and efficacy. “The extent of the studies necessary to demonstrate comparability will depend on the relationship between quality attributes and safety and efficacy, based on overall nonclinical and clinical experience”

As per ICH Q5E, the specifications are an essential element of evaluating comparability due to the linkage of quality attributes to safety and efficacy based on overall nonclinical and clinical experience. The manufacturer should confirm that the specifications after the process change are appropriate to ensure product quality. Results outside specification acceptance criteria would generally not be considered comparable.

ICH Q5E notes that results within the established specification acceptance criteria, but outside historical manufacturing control trends, might suggest product differences that warrant additional study or analysis. If specifications are set according to patient- centric approach, and manufacturing history/ consistency is evaluated through internal limits/ PQS, the relevance of post- change differences observed during comparability studies can be rigorously evaluated, and the need/ dept of additional analysis can be assessed. For instance, such analysis could include additional characterization and verification of risk of out of specification in case the post- change values are closer to specification limits. Also, when some CQAs are

[22] ICH Q12 Guideline: Technical and regulatory considerations for pharmaceutical product lifecycle management
[23] ICH Q5E Guideline: Comparability of biotechnological/ biological products subject to changes in the manufacturing process

removed from the specification panel as supported by an appropriate control strategy pre- change, it is opportune to include those CQAs in the comparability assessment. The CQAs and their relationship to nonclinical and clinical experience should be considered.

Any change in analytical methodology should be evaluated to determine potential impact to specifications. If method changes are occurring simultaneously with process changes, careful interpretation of results requires scrutiny to disambiguate the potential contribution of analytical changes from the process comparability assessment.

6.2. Reference standard strategy for biologics

Reference standards play a critical role in specification tests that assure product quality, safety, and efficacy. Specification criteria such as identity, content, and potency are determined based on a comparison or calibration with a qualified reference standard. For biologics, biological activities such as potency are commonly reported relative to a qualified reference standard. In addition, reference standards are included in comparability assessments to support evaluation of process changes as described in ICH Q5E.

Although ICH Q6B includes information regarding reference standard use and relevance, further guidance should be considered on this topic, to ensure alignment with other ICH guidelines, and support definition of patient- centric quality expectations.

Per ICH Q7[24], a primary reference standard is defined as "a substance that has been shown by an extensive set of analytical tests to be an authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognized source, (2) prepared by independent synthesis, (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material." For biologics, rather than using an ultra-purified material as reference (which may not be available for newly developed products) ICH 6B states that "an appropriately characterized in-house primary reference material [should be] prepared from lot(s) representative of the production and clinical materials" or traceable to clinical trial material qualification against previous reference materials.

Phase 3 clinical materials or equivalent are considered as the primary reference standard to support Process Performance Qualification (PPQ) and early commercial materials testing, especially for potency assessment. This ensures a clear link to patient (clinical efficacy and safety) and represent further element of patient centric specification strategy. For this reason, it is important to define appropriate storage conditions to preservation to the integrity of reference standard, which may be different (i.e., more preserving) than the DS and DP storage conditions. The stability of reference materials should be monitored to detect drift in relevant critical quality attributes.

For biologics reference standards, a two-tiered system is recommended, consisting of a primary reference standard and a working (or secondary) reference standard. A single lot of primary reference standard may be maintained throughout the product lifecycle, unless there is a specific need to replace it (i.e., degradation observed or supply depleted). Multiple lots of working reference standard may be prepared throughout the product lifecycle as needed. Working reference standard should be representative of current manufacturing process material at time of qualification.

Both Primary reference standard and working reference standard should be qualified using a comprehensive test panel, including routine release testing as well as extended characterization testing. Qualification of reference standards should ensure homogeneity across a batch.

[24] ICH Q7 Guideline: Good manufacturing practice guide for active pharmaceutical ingredients

7. Pharmacopoeias & Regulatory harmonization

Pharmacopoeial monographs cover test methods and acceptance criteria for a number of product and product types. ICHQ6A notes that "*Whereas differences in pharmacopoeial procedures and/or acceptance criteria have existed among the regions, a harmonized specification is possible only if the procedures and acceptance criteria defined are acceptable to regulatory authorities in all regions. The full utility of this Guideline is dependent on the successful completion of harmonization of pharmacopoeial procedures for several attributes commonly considered in the specification for new drug substances or new drug products*"

The ICH Q6 update is an opportunity to clearly define principles for justification of specifications which link to safety and efficacy, considering ICH Q8(R2) recommendations. In this context, adherence to patient-centric strategies would intrinsically help harmonization across different (ICH) regions, because it would avoid different interpretations on consistency- driven criteria (e.g., number of lots, relevant statistical approach, historical data, ...), which is often a key element of disconnect across different Authorities. Harmonization driven by clinically relevant specifications would bring significant benefit not only for companies (one set of specifications for all relevant regions) but also for patients (more reliable access to safe and efficacious products). g

The ICH Q6 update could also set the basis for further review and harmonization. Of national Pharmacopoeia's. Pharmacopoeias represent a relevant guidance for the definition of analytical strategy and for chemical substances, specifications. It would therefore be ideal to see a dialogue among the national Pharmacopeias to define common approaches especially on cross-product CQAs (eg endotoxins, identity, ...). Further addressing the need for pharmacopoeia harmonization, beyond monographs for analytical procedures, in ICH Q6 would also benefit non-ICH areas, for which specific strategies often need to be defined to address local requirements.

At the same time, it would be important to enable flexibility, with the control strategy being product specific and based on the actual product knowledge. An updated section on pharmacopoeias could also enable the introduction of up-to-date analytical technologies and overall control strategy. An explicit mention of such flexibility can help addressing the harmonization issues which companies often face for the same product/ attribute to be characterized for different countries. [25]

In some cases, companies have observed expectations linked to national pharmacopoeias which are not aligned with ICH guidance (e.g., endotoxin limits as reported in the IQ survey on globally accepted specifications-[26]), leading to a lack of harmonization in specifications.

8. Drug- device combinations

Increasingly, newer medical products are being developed containing a delivery device element, especially following a patient centric approach which suggests including a delivery device along with the medicinal products to allow patients to take the medicine easily.

Globally, there is divergence in the regulatory definition of drug/device combination product, and not all ICH territories have a legal regulatory definition. Although the medical devices directly are outside the scope of ICH, many of these products are governed as a medicinal product on the basis of the primary mode of action. As such, they are viewed as being in scope of ICH and principles related to manufacturing and control for these medicinal products with a drug delivery component should be considered. Therefore, it is

[25] Beierle J, Cauchon NS, Grau Tl, Hedberg Y, et al Toward a Single Global Control Strategy: Industry Study, Pharmaceutical Engineering, January/ February 2022

[26] Dow Y, Towards Globally Accepted Specifications of Pharmaceutical Products: A Summary of the Current State (IQ Consortium), IABS Conference on Global Harmonized Specifications: current state and future opportunities, Basel, January 10-12, 2023

recommended to expand the scope of the existing ICH Q6 to include some considerations specifically for medicinal products with a drug device component in the principles of ICH Q6 guideline. The section below will provide an illustration on the rationale for inclusion.

The delivery device is provided in form of:

- Single integral drug-device combination – where the delivery device forms a non-separable component of the medicinal product, such as single use prefilled pen injector or a prefilled syringe
- Co-packaged combination – where the medicinal product is presented in the same secondary packaging as a medical device for the preparation or administration, such as injection needles
- Cross-labelled (Reference) combination – where the medicinal product requires a specific medical device (e.g. an autoinjector that is independently placed on market) and is shown to be compatible with the medicinal product and aids treatment with the medicinal product.

For single integral drug device combination product, the assessment of CQAs for the control medicinal product must also include attributes of the device component as they relate to functional performance to ensure safe and effective use of the medicinal product.

For co-packaged or cross-labelled (referenced) drug products, the drug physicochemical properties may impact the selection and usability of the medical device. e.g., device compatibility and ability to deliver accurate dose. As there are a huge number of combinations possible, the aim would be to align in principles in defining CQAs to demonstrate performance to ensure safe and effective use of the medicinal product. This information is required to provide within the marketing authorisation applications.

Future revisions to ICH-Quality guidelines should consider device related CQAs within the manufacturing and controls and where relevant, form part of formal specifications for release and shelf-life testing to ensure appropriate functionality and patient safety. Although the manufacturers of such products may apply the ICH Q8 based holistic-control strategy approach, including a specific reference under ICH Q6 revisions will provide assurance that relevant device attributes that relate to safety, performance and functionality will be adequately included in the release specifications. Current practices for DDC specification development already focus on patient/user driven considerations and often lean on human factors/usability data.

The potential CQAs linked to the device component could be summarised as follows:

- Device Functionality: device functions essential to the intended use of the device (i.e. initiation and completion of delivery of the medicinal product)
- Integration of Device and Medicinal Product: medicinal product CQAs that could impact device functionality (e.g., sterility)

In order for the drug product manufacturer to place a safe and effective medicinal product that contains a single integral drug/device combination product or a co-packaged drug/device combination product on the market, it is important these performance characteristics are appropriately controlled via control strategy for corresponding critical process parameters based on the principles highlighted in ICH Q8 using a holistic approach to control strategy and establish alignment between QTPP / device design input and CQA / device design output. It is recommended that such a concept is also built in the next revision of ICH Q6.

Concluding remarks and future directions

In this paper, EFPIA has reported key proposals on how to define product quality expectations addressing patient needs, accelerated access, and global harmonization in ICH Q6A/B. It is proposed to focus on:

1- Product understanding for justification of specifications:

- identification and selection of the Critical Quality Attributes (CQAs) and their impact on safety and efficacy

- CQA ranges or limits that are not exclusively based on (clinical) manufacturing history
- holistic CQA acceptance criteria that consider the overall quality of a product, with safety and efficacy justified; for instance, by attribute understanding, clinical relevance, reliance on nonclinical (*in vitro-/ in vivo*) and *in silico* models, use the of prior knowledge (e.g., on safety of some impurities, to be used across different products)
- analytical approaches, considering selection and development of fit-for-purpose analytical methods to monitor a CQA during specification testing and/or overall characterization, to support the whole product lifecycle
- risk- based approaches for development of specifications in accelerated scenarios

2- Control Strategy development and manufacturing consistency demonstration through:

- knowledge of the impact of process parameters on CQAs (process understanding)
- defining limits based on prior knowledge and process understanding – less reliance on batch data
- definition of analytical performance expectations based on product and process needs, and demonstration that selected procedures are fit for purpose
- reliance on the Pharmaceutical Quality System to monitor and demonstrate manufacturing consistency through trending analysis

This paper has also the purpose to build a clear narrative about ICH Q6 Guidelines update, to support consolidation of a shared vision on modern specifications setting strategies, as a basis for harmonized implementation at launch and during lifecycle. Communication of this shared vision is key to support the cultural shift that will allow full implementation of patient- centric specifications.

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