FUTURE OPPORTUNITIES & MODERNIZATION OF ICH QUALITY GUIDELINES: IMPLEMENTATION OF THE ICH QUALITY VISION[1] FROM THE ICH QUALITY REFLECTION PAPER[2]
ICH QUALITY DISCUSSION GROUP (2019-2021)

INTRODUCTION

Since its inception, ICH has been a pivotal forum for promoting regulatory harmonisation and establishing mechanisms to improve convergence of regulatory guidance for the development and life-cycle management of pharmaceutical products. ICH Quality guidelines provide a scientific foundational platform and fundamental regulatory paradigms that harmonise standards for control and manufacturing of drug substances and drug products through their respective lifecycles and apply to both innovative and generic medicines. However, continual advancements in science and technology, e.g., complex manufacturing techniques, digitalisation of information, emergence of risk issues impacting pharmaceuticals globally and the advent of new therapeutic modalities, have and will continue to progress rapidly, rendering some of the regulatory expectations described in current guidelines outdated. In addition, the global demand for pharmaceutical solutions in response to unmet medical diseases and needed medicines to contribute to sustainable health care systems, as underscored by the recent global pandemic, warrants timely contemporisation to improve the effectiveness of harmonisation for existing guidelines as well as introduction of new guidelines to address these emerging topics.

ICH's Quality Discussion Group (QDG) was launched in 2018 and serves as a technical discussion forum for issues relevant to the ICH Quality Vision to "develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science" as described in the *ICH Quality Reflection Paper on Advancing Biopharmaceutical Quality Standards to Support Continual Improvements and Innovation in Manufacturing Technologies and Approaches*. In accordance with this vision, the ICH QDG undertook a comprehensive assessment of all existing ICH Quality guidelines to identify gaps and/or need for contemporisation to current recommendations for quality standards and to accommodate new therapeutic modalities and technologies. A summary of the criteria used for the assessment and the results describing the highest priorities from the ICH QDG members are provided in TABLE 2 and TABLE 3 in the Appendix. **Maintenance, modernisation and targeted revision of the Q1/Q5C Stability guideline series and Q6A/Q6B**

[1] The ICH Quality Vision was issued in 2003 with the intent to "*Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science.*"

[2] The ICH Reflection Paper was endorsed at the ICH Assembly on 6 June 2018. An ICH Informal Quality Discussion Group was endorsed by the ICH Management Committee on 13 November 2018. The Informal Quality Discussion Group (IQDG) was changed by the ICH Management Committee to the ICH Quality Discussion Group (QDG) in 2020.

Specifications guideline series were determined as the highest priorities based on an evaluation and recommendations from the QDG. These topics were subsequently endorsed by the ICH Management Committee (MC) during its March 2021 meeting.

From the comprehensive assessment of existing guidelines and in consideration of potential future topics, the ICH QDG identified other priorities that constitute additional recommendations for the future of ICH Quality guidelines. These recommendations, summarised in this report, have two objectives:

1. Provide a perspective of the future Quality landscape of scientific innovations, patient need and associated regulatory expectations.

2. Convey recommendations for the prioritisation of future modernisation to improve, contemporize, and enable consistent implementation of the remaining ICH suite of Quality guidelines (beyond the revisions of the ICH guidelines for Stability and Specifications endorsed by the ICH MC).

FUTURE VISION FOR ICH QUALITY GUIDELINES

ICH Quality guidelines have provided a science and risk-based foundation that, when implemented in an integrated and holistic fashion, provide guidance, and align technical standards globally and foster the development and reliability of a commercial supply of high-quality products. Nevertheless, divergent approaches continue to limit harmonisation and prolong progress in pharmaceutical development and, consequently, the availability of safe, effective, and high quality medicines. In recent years, several factors have prompted the adoption of innovative approaches to product development and stimulated the need for further global harmonisation. Examples include:

- Expedited regulatory approaches to accelerate and increase simultaneous regulatory application approval of medically necessary therapies in multiple countries to improve access to patients globally;

- Advancements in new therapeutic modalities;

- Innovative technologies (e.g., including digital solutions to improve accuracy, transparency, and efficiency of data);

- Expansion of ICH membership and observers has broadened technical and regulatory perspectives in the assessment of existing ICH Quality guidelines and the development of new topic proposals

Taken together, these factors have increased the pressure on regulatory authorities and industry to streamline regulatory approvals across regions and have magnified the urgency to improve patient access to medicines.[3] ICH Expert Working Groups (EWGs) and Implementation Working Groups (IWGs) routinely collaborate with scientific and technical organisations in developing ICH topic proposals and guidelines. In the future, the collective efforts from multiple stakeholders within industry and among regulatory authority networks, e.g., PIC/S,[4] ICMRA,[5] IPRP,[6] ACCESS Consortium,[7] etc., will continue to serve as a critical source for innovative technology and a resource for contemporary expertise. The modernisation of ICH guidelines is inherently dependent on the science and risk-based exercises devoted to continual improvement. ICH QDG believes continued emphasis on leveraging scholarship from these organisations is necessary to ensure ICH Quality guidelines provide the most current and credible scientific and technical criteria for demonstrating product quality assurance.

During the next 10 years, scientific and technical progress in development and commercialisation of new therapeutic modalities, innovative technologies and emerging risk issues, examples of which are provided below, will demand global alignment and stimulate the need for regulatory harmonisation among an expanding ICH membership.

New Therapeutic Modalities:

- Advanced Therapies, including Advanced Therapeutic Medicinal Products (ATMP) and gene and cell therapies among other genetically based platforms, e.g., mRNA/saRNA/siRNA, adeno-associated viral vectors and exosome delivery systems, are currently expanding exponentially and regulatory divergence has introduced challenges to progress these modalities particularly for rare diseases.

- Oligonucleotide products frequently include unique product related impurity profiles that are ineffectively characterised due to gaps within current ICH guidelines, which create differences in regulatory expectations globally.

Innovative Technologies:

- Increased manufacturing is expanding with new technologies (e.g., continuous and portable manufacturing) and the use of sophisticated digital technology to support manufacturing and operational control consistency. This technology is altering the paradigm for

[3] The importance for global harmonization was clearly heightened by the COVID-19 pandemic. By necessity, the magnitude of the impact of the pandemic demanded rapid regulatory actions across multiple regions simultaneously and this hastened the need for global alignment and regulatory transparency. The pandemic also introduced unprecedented provisions for harmonization of regulatory expectations for technical and scientific criteria. While mutual reliance and mutual recognition are beyond the scope of ICH, these concepts offer the opportunity to accelerate patient access to medicines by increasing transparency among regulatory authorities, reducing redundant analytical testing and facilitating pharmacopoeial convergence.

[4] PIC/S = Pharmaceutical Inspection Co-operation Scheme

[5] ICMRA = International Coalition of Medicines Regulatory Authorities

[6] IPRP = International Pharmaceutical Regulators Programme (http://www.iprp.global/home)

[7] ACCESS Consortium = Australia-Canada-Singapore-Switzerland-United Kingdom

demonstrating typical control strategies and their functional relationship to drug product critical quality attributes. The need for incremental modernisation to incorporate these innovations within existing ICH guidelines will be important for maintaining global harmonisation.

- The applications of artificial intelligence and modeling, e.g., product dissolution and *in vivo*/*in vitro* relationships/ correlations, purge and fate of impurities, container/closure integrity, etc., generate comprehensive multi-dimensional boundaries for manufacturing process parameters and material attributes that can control variability and predict product quality. The need for incremental modernisation to incorporate these innovations within existing ICH guidelines will be important for maintaining global harmonisation.

- With the increase in data and sophistication of manufacturing and analytics, approaches to improve knowledge management and access through the establishment of data clouds, structured data formats and comprehensive Quality Overall Summaries for regulatory applications (and subsequent reviews) and inspections should fundamentally be harmonised to ensure integrity and transparency.

- New digital technologies will impact how quality data is generated, utilised and submitted. There may also be requirements linked to product design (e.g., in smart devices).

Accelerated Patient Access for Unmet Medical Needs:

- Expedited regulatory approaches can accelerate and increase simultaneous regulatory applications and authorizations.

- There is a general need to assess training materials and to update key ICH guidance and enable science and risk-based principles. The principles of existing ICH guidelines can be leveraged to expedite development and availability of quality medicines, e.g., the expedited development by industry and authorisation by regulators of needed medicines in response to the COVID-19 pandemic.

Inspections:

- While global harmonisation of inspection standards and approaches are not within the scope of ICH(and this is being addressed by PIC/S), identifying opportunities to ensure connectivity of global regulatory inspections with the concepts described in all ICH Quality guidelines can improve the alignment, integration of concepts and implementation of those guidelines particularly ICH Q7.

ICH Membership and Approach to Harmonisation:

- Enlarging ICH membership expands the breadth of experience and diversity of perspectives, but it can present challenges in achieving consensus on meaningful harmonisation that will provide effective, convergent, consistent, and practical guidance. Increased emphasis on opportunities to establish unilateral reliance/mutual recognition as well as reinforcement on training, implementation and adherence to ICH guidelines will be critical in demonstrating global harmonisation.

These factors will likely influence subsequent generations of ICH Quality guideline updates and accommodations. Innovative policies and scientific and technical progress can introduce regulatory divergence but also provide opportunities for harmonisation. For the immediate future, during the next 10 years the ICH QDG has assessed the scientific and regulatory landscape and compiled specific recommendations in **Table 1** to ensure the current ICH guidelines remain contemporary. However, the ICH QDG recognizes that capacity is limited (refer to Figure 1 below) and therefore, these specific topics are prioritised for endorsement at the earliest opportunity and when requisite capacity is available.

TABLE 1. SPECIFIC RECOMMENDATIONS – PRIORITIES FOR FUTURE ICH QUALITY MODERNISATION

ICH TOPIC	RECOMMENDATION		Endorsed Proposals		Recommended Prioritised Proposals
Stability: ICH Q1A-F/Q5C	The combination and update of ICH guidelines in the Q1 series & ICH Q5C has been endorsed by the ICH MC (March 2021) and ICH Assembly (June 2021). Future timelines TBD by ICH MC.				***In order to address how to most efficiently complete priority updates on stability and specifications, the QDG has performed a detailed gap analysis and review of the current guidelines and made specific proposals. The QDG recommends the ICH members and the MC to encourage the future EWGs to fully exploit the gap analysis, and to follow the detailed recommendations from the QDG and the concept papers. The QDG will ensure these materials are accessible to the new EWGs in the ICH SharePoint.***
Specifications: Q6A/Q6B	The modernisation of these ICH guidelines has been endorsed by the ICH MC (March 2021) and ICH Assembly (June 2021). Future timelines TBD by ICH MC.				
<u>Impurities:</u> <u>M7 (high priority)</u>	The presence of N-nitrosamine impurities in pharmaceuticals has become a global concern for regulators, the pharmaceutical industry and patients. Regulators and the industry have taken measures to mitigate and manage risks associated with these mutagenic impurities that are considered part of the cohort of concern in accordance with the ICH M7 guideline. The QDG acknowledges the priority of developing internationally harmonised approaches to address nitrosamine impurities in pharmaceuticals. Inherent uncertainty in the safety and presence of this family of impurities requires attention. While the knowledge on issues related to nitrosamine impurities continues to increase, the QDG recommends that collaborative work among the ICH parties including safety & quality experts be considered a priority and should be initiated to avoid misalignment and divergence in regulatory expectations for the control of nitrosamine impurities. Leverage the outcome of expert panel discussions (e.g., March 29-30, 2021 FDA Public Workshop, Nitrosamines International Technical Working Group, etc.) to help advance harmonization of key principles and concepts.				
<u>Specifications</u>: Reference Standards for Biotechnological Products	Expand current guidance on establishing and qualifying reference standards for all biotechnological/biological products and chemical entities within the ICH Q6A(R2)/Q6B(R2) guidelines, either: under the QDG's ICH Q6A/Q6B: Specifications topic proposal or as a subsequent subtopic for the development of an annexure on Reference Standards to ICH Q6A(R3)/Q6B (R3), e.g., if this work is too extensive to be covered within the timeframe of the ICH Q6A(R2)/Q6B(R2) update.				

Pharmaceutical Development and Manufacturing: Q IWG Points to Consider (PtC)(R2), Q8/9/10/11/12	Emphasise training and improve implementation of ICH Q8 – Q12 after ICH Q12 integration for implementation is completed. Reinforce holistic integration of control strategy concepts and accommodate ICH Q13 and Q2(R2)/Q14 concepts in a Points to Consider document to ensure integration of advanced manufacturing criteria across ICH Quality guidelines, e.g., Pharmaceutical Quality Systems (PQS) accommodations for robotics, digital calibration using AI, environmental monitoring, container closure integrity testing, autonomous and portable manufacturing.
Impurities: Oligonucleotides	Accommodate impurity qualifications within annexures of ICH Q3A/Q3B and/or ICH Q11 and incorporate fundamental impurity management within a drug product control strategy.
Biotechnology: Q5B, Q5D, Q5E & ATMPs/Cell and Gene Therapies	Contemporise all ICH Q5 guidelines to incorporate relevant criteria associated with ATMPs, as appropriate, with consideration and accommodation for emerging ATMP and cell and gene therapy technologies (after ICH Q5A and Q2/Q14 updates are completed). Leverage work of IPRP (http://www.iprp.global/home) and other expert groups and anticipate emergence of local ATMP guidelines as a basis for harmonised guidance to be introduced in the future as a separate guideline within the ICH Q5 series of guidelines on biotechnology.
Impurities: Q3A(R2)/Q3B(R2)	Opportunity to clarify and incorporate clinical relevance of thresholds with respect to patient centric benefit/risk, modelling approaches and control, and new technologies in future maintenance updates and provide reference in ICH Q6A(R2)/Q6B(R2) targeted revisions and Q&As
GMPs for API's Q7	Consider specific training activities, e.g., in accordance with PIC/S based on PQS expectation (ICH Q10), ICH M7 accommodations for nitrosamines and clarification of risk management ICH Q9(R1) such as, to reinforce expectations for outsourced activities (Q7/Q10), controls for recycled materials, etc.
Analytics: Dissolution	Develop recommendations for dissolution methodology and to harmonise dissolution acceptance criteria for solid dosage forms in existing ICH guidelines to address gaps and differences in regional expectations, i.e., ICH Q6A and ICH M9.
Manufacturing: Process Validation	Contemporize to incorporate lifecycle approaches and statistical quality control in ICH Q8, Q10 and Q11 annexures complementary to the ICH Q-IWG Point to Consider (PtC).
Pharmaceutical Development:	Develop a new scientific Multi-disciplinary guideline topic to align and harmonise on technical content for reporting of criteria for device design and in-patient use of drug device combination products.

Drug Device Combinations	
Training & Monitoring	Reinforce the need for a systemic approach to establish a curriculum for implementation and training for all ICH quality EWGs. Enabling consistent understanding and interpretation of the portfolio of ICH Quality-related Guidelines requires efforts to educate and train the users of these guidelines across industry and regulator stakeholders. A feedback loop should be built in in order to monitor the effectiveness of training materials and activities. ICH established in 2016 a standing Training Subcommittee under the ICH Management Committee to identify a series of training priorities and enable connections to trusted training providers across the entire portfolio of existing ICH Guidelines, including ICH Quality-related Guidelines, based on a survey of ICH Members and Observers conducted in 2016. This was revisited and updated in 2021 recognizing the QDG asks and aligns with the ICH training subcommittee remit. As part of the proposed strategic portfolio approach, it is recommended that the ICH Management Committee bring this report to the attention of the ICH Training Subcommittee, in concert with any recommendations from the QDG, to reassess its training priorities for ICH Quality-related Guideline i.e., the tier 1 guidelines Q1/Q5C and Q7; and the training priority tier 3 guidelines Q8-Q11 as well as enforcing the development of training by existing EWGs/IWGs namely e.g., Q12, Q13, Q9(R1).

Overall, based on the current and approved workplan for ICH Quality (and related M) guidelines (see Figure 1 below) there remains a clear need to develop and manage a holistic plan for updates and additions to the ICH Quality guidelines and align with available capacity. **Figure 1** provides a current snapshot of activities and known or anticipated timelines.[8]

FIGURE 1: STATUS OF ICH QUALITY (AND RELATED MULTIDISICPLINARY) GUIDELINES

Status	ICH gui	Title	Connectivity	Type of activity	Focus	Current Driver	Major gaps to be addressed in a regulatory guideline by ICH (max 2)	Jun 21	Nov 21	Jun 22	Nov 22	Jun 23	Nov 23	Jun 24	Nov 24	Jun 25	Nov 25	Jun 26	Nov 26
running	QDG	Quality Discussion Group	all Q topics	members	maintenance	ICH-MC	see ICH QGD remit 22 October 2018	◆											
running	Q3C	Residual solvents	Impurities	IWG	maintenance	ICH-MC	see concept paper												
running	Q3D	Elemental Impurities	Impurities	IWG	maintenance	ICH-MC	see concept paper	Step 4											
running	M7(R2)	Mutagenic Impurities & Nitrosamine	Impurities	IWG	Q&A	ICH-MC	Concept paper and current workplan	Step 4											
running	Q12	Lifecycle Management	Development/Manuf	IWG	training	ICH-MC	Concept paper and current workplan	close											
running	Q13	Continuous Manufacturing	Development/Manuf	EWG	new	ICH-MC	Concept paper and current workplan	Step 2			Step 4								
running	Q14/Q2	Analytical Procedure Development/Validaton	Analytics/Spec	EWG	new	ICH-MC	Concept paper and current workplan	Step 2			Step 4								
running	Q9(R1)	Quality Risk Management (QRM)	Risk Management/GMP	EWG	revision	ICH-MC	Concept paper and current workplan		Step 2			Step 4	Training						
running	Q5A	Viral Safety	Biologics	EWG	revision	ICH-MC	Concept paper and current workplan		Step 2			Step 4							
running	Q3E	Extractables & Leachables	Impurities	EWG	new	ICH-MC	Concept paper and current workplan				Step 2				Step 4				
endorsed by MC	M4Q	CTD-Q & Structured Quality Submission	Regulatory Pathway	EWG	revision	ICH-MC	Quality overall summary / QbD		if Q13 #2									Step 2	
QDG priority	**M7(R3)?**	**Mutagenic Impurities / Nitrosamines**	**Impurities**	**IWG**	**maintenance**	**QDG**	**Nitrosamines; Annex to M7 or others e.g. Q&A**		*anticipated timeline*										
endorsed by MC	**Q1/Q5C**	**Stability for new DS and Drug Products**	**Stability**	**EWG**	**targeted revision**	**QDG**	**Innovation leveraging QbD / access**				Step 2		Step 4						
endorsed by MC	**Q6A/Q6B**	**Specification DS / DP / Biologics**	**Analytics/Spec**	**EWG**	**maintenance**	**QDG**	**Innovation leveraging QbD / access**					step 2		Step 4					

Reflecting on most current timelines as communicated in the ICH workplans

[8] For a complete and up to date list of the status of all ICH Quality (and related M) guidelines, please refer to the ICH web site (https://www.ich.org/page/search-index-ich-guidelines).

APPENDIX

BACKGROUND

An Informal Quality Discussion Group was convened in 2014 and focused on improving implementation of an integrated approach to quality risk management through the product lifecycle largely in conjunction with the adoption and implementation of ICH Q8 – Q10. The current ICH Quality Discussion Group was established in 2018 in response to the ICH Reflection Paper, *Advancing Biopharmaceutical Standards to Support Continual Improvement and Innovation in Manufacturing Technologies and Approaches*.[9] The QDG was established and convened on behalf of the ICH Management Committee to ensure that the ICH Quality guidelines remain contemporary and continue to fulfill the objectives of the ICH Quality Vision,[10] to identify and remove globally divergent barriers to continual improvement and innovation in manufacturing technologies and approaches and develop harmonised regulatory outcomes that lead to mutual reliance or mutual recognition between regulatory authorities.

The remit of the ICH QDG has been to "*serve as a technical discussion forum for issues relevant to the ICH Quality Vision, to develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science and to ensure that ICH guidelines are kept up-to-date with the evolution of science*." The scope of the ICH QDG included the following activities:

- Review and recommend the need for new ICH Quality-related harmonisation work;
- Review and recommend training needs related to the content and/or implementation of ICH Quality guidelines;
- Review and recommend any necessary updates to the ICH Quality Reflection Paper and ICH Quality Vision statement;

In its assessment of the applicability and currency of existing ICH Quality guidelines the ICH QDG agreed to prioritise activities based on the following principles:

[9] The ICH Reflection Paper was endorsed at the ICH Assembly on 6 June 2018. An ICH Informal Quality Discussion Group was endorsed by the ICH Management Committee on 13 November 2018. The Informal Quality Discussion Group (IQDG) was changed by the ICH Management Committee to the ICH Quality Discussion Group (QDG) in 2020.
[10] The ICH Quality Vision was issued in 2003 with the intent to *"Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science."*

- *Is the guideline outdated due to new technologies/techniques?*
- *Is the guideline up to date with current scientific understanding and principles?*
- *Are there gaps in the guideline?*
- *Will an update/revision address issues/alignment with other ICH guidelines?*
- *Will an update/revision to the guideline address patient need and accelerated access?*
- *Will changes to the guideline drive alignment, e.g., clarify differences in criteria, replace regional-specific guidance, support implementation in new regions?*
- *Is training sufficient to ensure harmonized adoption of the guideline?*

During 2019 and 2020, the QDG completed a comprehensive assessment of current ICH guidelines and introduced specific proposals for targeted revisions to modernise, integrate, consolidate, and update ICH Stability (ICH Q1 series / ICH Q5C) and Specification ICH Q6A/ ICH Q6B) guidelines. As a result of the comprehensive assessment several other priorities were identified for future consideration as ICH topic proposals and a heat map reproduced in **TABLE 2** was developed. This map reflects input from all members of the ICH QDG and provides a directionally aligned list of topics from which the specific recommendations in **TABLE 1** were consolidated.

TABLE 2. HEAT MAP OF ICH QDG TOPIC PRIORITIES

	ICH Member and Observer Priority (1-4, high-low)																		Totals	Total #1's Very High Priority	Total #2's High	Total very High and High Priority	Total #3's low Priority	Total #4's Very low Priority
M4Q	4	3	4	2	2	3	4	2	4	4	3	1	4	4	3	3	4	4	58	3	3	6	5	9
M4Q	2	4	3	4	4	3	4	2	4	4	3	3	4	4	3	3	3	4	61	0	2	2	7	9
Q8(R2)	4	4	3	4	4	1	2	1	4	4	4	2	4	4	3	3	4	4	59	2	2	4	3	11
Q9	4	4	4	4	4	1	4	1	4	4	4	3	2	4	2	1	4	4	58	3	2	5	1	12
Q10	4	4	4	4	2	4	3	4	4	4	4	2	4	4	3	3	4	4	65	0	2	2	3	13
Q-IWG Q&A (R4)	2	4	4	4	4	4	4	4	4	4	4	2	4	4	4	4	4	4	68	0	2	2	0	16
Q-IWG PtC (R2)	2	4	3	2	4	4	4	4	4	4	4	2	4	4	4	4	4	4	65	0	3	3	1	14
Q11	4	4	4	4	4	1	4	4	4	3	4	2	4	4	3	4	4	4	65	1	1	2	2	14
Q11 Q&A	2	4	4	4	4	4	4	4	4	4	4	2	4	4	4	4	4	4	68	0	2	2	0	16
Q12	4	4	4	4	4	4	3	4	4	4	4	4	4	4	4	4	4	4	71	0	0	0	1	17
Q13	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	72	0	0	0	0	18
Q5A(R2)	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	72	0	0	0	0	18
Q5B	4	4	3	2	4	4	2	4	4	4	3	2	4	4	4	3	4	4	63	0	3	3	3	12
Q5D	4	4	3	2	4	4	2	4	2	4	3	2	4	4	2	3	4	4	59	0	5	5	3	10
Q5E	2	3	4	4	4	4	4	4	4	4	2	2	4	4	2	3	4	4	62	0	4	4	2	12
Q7	4	4	3	4	2	1	4	4	4	4	1	4	4	4	2	2	4	2	57	2	4	6	1	11
Q7 Q&A	4	4	2	4	4	4	4	4	4	4	1	4	4	4	4	2	4	4	65	1	2	3	0	15
Q4A	4	4	4	4	4	4	4	4	4	4	4	1	4	4	4	4	2	4	67	1	1	2	0	16
Q4B & 16 Annexes	4	4	4	4	4	4	2	4	4	3	4	4	4	4	4	1	2	4	64	1	2	3	1	14
Q4B FAQs	4	4	4	4	4	4	4	4	4	2	2	4	4	4	4	1	2	4	63	1	3	4	0	14
Q6A	1	4	2	1	4	2	2	1	4	3	2	1	4	4	1	2	4	4	46	5	5	10	1	7
Q6B	2	2	2	1	4	2	3	4	4	2	3	1	4	4	2	2	4	4	50	2	7	9	2	7
Q14	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	72	0	0	0	0	18
Q2(R2)	4	4	4	4	4	4	1	4	4	4	4	4	4	4	4	4	4	4	69	1	0	1	0	17
M9	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	72	0	0	0	0	18
Q3A(R2)	2	2	3	4	4	3	4	3	4	1	2	1	4	4	2	3	3	4	53	2	4	6	5	7
Q3B(R2)	2	2	3	4	4	3	4	3	2	2	2	1	4	4	2	3	3	4	52	1	5	6	5	6
Q3C(R6)	4	4	3	4	4	4	4	4	4	3	4	4	4	3	3	3	4	4	67	0	0	0	5	13
Q3D(R2)	4	4	4	4	4	4	4	4	4	3	4	4	4	3	4	4	2	4	68	0	1	1	2	15
M7(R2)	4	4	4	4	4	1	4	4		4	4	4	2	4	4	3	1	4	59	2	1	3	1	13
Q1A (R2)	1	1	1	1	2	2	1	1	1	1	4	1	4	1	1	1	4	4	32	12	2	14	0	4
Q1B	1	4	4	1	4	4	1	3	4	4	4	4	4	2	1	2	4	4	55	4	2	6	1	11
Q5C	1	1	1	1	2	2	1	4	1	4	4	1	4	4	1	2	4	4	42	8	3	11	0	7
Q1C	4	3	4	4	4	4	4	4	4	4	4	1	4	4	1	2	4	4	63	2	1	3	1	14
Q1D	4	4	1	4	4	4	4	4	4	4	4	1	4	1	1	2	4	4	58	4	1	5	0	13
Q1E	1	1	1	1	4	3	2	4	4	3	4	1	4	1	1	2	4	4	45	7	2	9	2	7
Q1F	4	4	4	1	4	4	4	4	4	4	4	1	4	4	4	4	4	4	66	2	0	2	0	16

In parallel, the ICH QDG provided targeted evaluations and recommendations for new ICH Quality topic proposals submitted to the ICH Management Committee in 2019 – 2021, integrating these into the long-term strategy where appropriate. A total of 9 new ICH Quality topics were reviewed and prioritised. The topics with highest priority were reported to the ICH Management Committee and the following topics were endorsed to proceed.

- Revision of ICH Q9 Guideline on Quality Risk Management
- Revision of ICH M13 Bioequivalence for Immediate-Release Solid Oral Dosage Forms
- New Guideline: ICH Q3E Extractable and Leachables for Pharmaceuticals and Biologics
- Revision of ICH Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Line of Human or Animal Origins
- Revision of ICH M4Q Common Technical Document (CTD) & Structured Product Quality Submissions

In accordance with these evaluations the ICH QDG also developed a process to systematically assess and prioritise all future ICH Q topic proposals. Prioritisation Decision Criteria are provided in **Table 3**.

TABLE 3. PRIORITISATION DECISION CRITERIA

Type of Action	Choose When…	Consideration
New Guideline	Harmonization on this topic would have a high impact/provide substantial benefit; Harmonization focus can be either prospective (e.g., digital health, cell and gene therapies) or retrospective	High(est) effort; must demonstrate a clear need and have a significant level of regulator support
Revision of an Existing Guideline	Scientific issues with current version; Full revision would have a high impact/provide substantial benefit	High (to medium) effort; must demonstrate a clear need and have strong regulator support
Annex or Addendum	New information needs to be added to an existing guideline without amending the existing text	Medium effort
Maintenance of an Existing Guideline	Only specific chapters require an update, but a full revision is not needed	Medium to low effort
Q&A	Additional guidance is needed to help the interpretation of the guideline to ensure consistent implementation	Low effort; Q&A may not have same impact as revision
Implementation	Existing guideline is adequate, but industry feels interpretation/adoption varies across regulators and guideline implementation has not yet been assessed via ICH survey	Low effort; No *formal* process within ICH to request an implementation assessment
Training	Existing guideline is adequate, but interpretation/adoption varies across regulators	Medium effort; Training can be conducted independent from ICH (e.g., APEC Centers of Excellence.