ICH Reflection Paper

Advancing Biopharmaceutical Quality Standards to Support Continual Improvement and Innovation in Manufacturing Technologies and Approaches

Executive Summary

This reflection paper outlines a strategic approach to enhance the portfolio of ICH Quality-related Guidelines to support continual improvement and innovation in biopharmaceutical manufacturing technologies and approaches by continuing to advance 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"*

To enable this approach, this paper outlines recommendations for:

a) The establishment of a theme within ICH on "Advancing Pharmaceutical Quality Standards to Support Continual Improvement and Innovation in Manufacturing Technologies and Approaches" to help identify, plan, and prioritize future harmonization work
b) Drafting of guidance on selected new topics to be undertaken in the near term
c) A comprehensive survey of existing ICH Quality guidelines to determine those in need of revision or modernization
d) A set of other activities to facilitate global efforts, including training

In this context, it should be borne in mind that as the remit of ICH is to harmonise technical standards, ICH should remain focused on technical and scientific aspects and ensure that ICH Guidelines are kept up-to-date with the evolution of science, whilst not striving to drive policy choices for regulations as this falls under the remit of the regulatory authorities in different jurisdictions.

I. Origin of the ICH Quality Vision

In 2003, ICH Members articulated an overarching vision for the regulation of global pharmaceutical manufacturing quality that would ensure the reliable supply of quality pharmaceutical products through striving to "*develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science*." This overarching vision aimed to promote the use of: science and risk-based approaches to product development, dossier submission, review, and post-approval change management to encourage continuous improvement and innovation throughout the product lifecycle and allow effective and consistent global regulatory oversight.

The ICH Quality Vision, as developed in 2003, was the subject of a further review by an ICH Informal Quality Discussion Group (IQDG) in 2014 to examine its ongoing applicability and determine if there was a need for any adjustments. As discussed in greater detail later in this paper, the IQDG reported to the ICH Steering Committee in June 2014 that an update to the ICH Quality Vision was not necessary and that it remained highly relevant, though more efforts would be needed to fully address challenges and strengthen product lifecycle management.

Since then, in 2015, ICH completed a series of reforms to better enable the organization and its members to face the challenges of global pharmaceutical development and regulation, building on a 25-year track record of successful delivery of harmonized guidelines for global pharmaceutical development and regulation. Most notably, the ICH reforms resulted in the opportunity for new regulatory authorities and industry associations to join the ICH as members or observers, requiring new governance processes to meet inclusion and transparency expectations. Further, during its meeting in November 2016 in Osaka, Japan, the ICH Management Committee supported the concept of establishing a set of ICH Themes to help identify areas for future work and better manage ICH resources to achieve desired harmonization outcomes.[1] Therefore, any decisions on further developing the ICH Quality Vision would need to be re-assessed involving all Members and Observers of the ICH Association. In this respect, this paper aims to facilitate the re-assessment of the ICH Quality Vision by the current ICH Members and proposes actions to be taken in order to achieve the agreed goals.

Realizing the ICH Quality Vision

Since 2003, ICH Members have developed the following ICH Quality Guidelines to enable realization of the ICH Quality Vision:

- ICH Q8 Pharmaceutical Development (Parent guideline Nov 2005; Annex Nov 2009)[2]
- ICH Q9 Quality Risk Management (Nov 2005)[3]
- ICH Q10 Pharmaceutical Quality Systems (June 2008)[4]
- ICH Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Products) (May 2012)[5]

These documents provide high level direction with respect to the scope and definition of "Quality-by-Design" (QbD), following the concept that quality should be designed into a product.[6,7] Notably, these guidelines articulate a shift in focus towards future aspirations and potential transformational changes in areas where there is less experience across industry and regulators. This shift is in contrast to previous ICH Quality Guidelines (i.e., ICH Q1-Q7) that were drafted with a scientific and systems orientation, drawing upon documented experiences across industry and regulators with a focus on prescriptive development activities leading to product registration. The shift towards conceptual framework guidelines has become increasingly important given the dynamic nature of the

[1] http://www.ich.org/fileadmin/Public_Web_Site/Meetings/Ass_MC_Meetings_Reports/Minutes_MC_ICH_Meeting_Osaka_Nov2016.pdf

[2] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf

[3] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf

[4] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf

[5] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11_Step_4.pdf

[6] Juran JM. Juran on quality by design: the new steps for planning quality into goods and services. New York: The Free Press; 1992.

[7] Yu L. Understanding Pharmaceutical Quality by Design. AAPS J. 2014 Jul; 16(4): 771–783.

pharmaceutical industry, including complex global pharmaceutical supply chains, and more product diversity and innovation.

Assessing the ICH Quality Vision and Past Efforts, and Developing a Path Forward

In June 2014, ICH Members and invited interested parties convened during a workshop of the ICH Informal Quality Discussion Group (IQDG) on the margins of the ICH Steering Committee Meeting in Minneapolis, Minnesota, USA. It should, however, be noted that this workshop took place before the establishment of the ICH Association in 2015 and since then, many new members have joined the Association who were not part of the discussions. The purpose of this workshop was to evaluate past efforts and assess the current situation to determine whether additional efforts were needed to meet the expectations of ICH Members to realize the ICH Quality Vision. During this workshop, members of the IQDG noted many successful implementation activities beyond the development of ICH Guidelines to realize the ICH Quality Vision, including the development of follow-on ICH documents (e.g., Quality-IWG Questions and Answers Document[8], Q8/Q9/Q10 Points to Consider Document[9]), ICH Guideline training efforts within and outside of the ICH founding regions, and a variety of implementation activities such as parallel regulatory agency assessment programs, workshops, and the formation of cross-regional discussion groups.[10] The IQDG workshop participants noted that the ICH Quality Vision remained relevant, and did not need to be updated at that time. Additionally, workshop participants identified a set of remaining challenges and opportunities to strengthen product lifecycle management based on stakeholder implementation experiences. IQDG workshop participants also noted that while the ICH Quality Vision was expected to fit into existing regulatory frameworks and procedures, a new "enabling regulatory framework" would be required to fully achieve the ICH Quality Vision. However, experience with the ICH Q12 in 2017 has shown the limits of such an "enabling regulatory framework" as a result of which this approach should be reevaluated in line with the remit of ICH. Further, additional concerted efforts need to be made to ensure that issues relevant to the spectrum of products that may fall within the application of ICH standards are considered during the development or updating of ICH Quality-related guidelines to ensure that the same quality and safety standards can apply to them, as for innovative drug products. Otherwise, the ICH efforts for achieving a globally applicable Quality Vision for all products will be limited.

Ultimately, the IQDG workshop resulted in a recommendation that was presented to and approved by the ICH Steering Committee at its June 2014 meeting for ICH to develop a series of new harmonization work products to address such challenges and continue advancement toward the ICH Quality Vision.

[8] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/Q-IWG_Q_A_R4_Step4_Nov.2010.pdf

[9] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/PtC/Quality_IWG_PtCR2_6dec2011.pdf

[10] https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/UCM553508.pdf

Specifically, the IQDG recommended the following topics for ICH to develop as harmonized guidelines:

- A new guideline on the *Technical and Regulatory Considerations for Pharmaceutical Lifecycle Management*.[11,12] At the time of the drafting of this reflection paper, efforts were under way to develop this guideline by the ICH Q12 Expert Work Group.

- A Questions and Answers (Q&A) document on the *Selection and Justification of Starting Materials for the Manufacture of Drug Substances* which is part of ICH Q11.[13,14] At the time of the drafting of this reflection paper, this Q&A document has been completed through ICH's harmonization process and is published.[15]

- An ICH harmonization work product on *Enhanced Approaches for Development and Utilization of Analytical Procedures* to fully consider the utilization of science and risk-based principles for analytical method design, development, validation, technology transfer, and continuous improvement, and to address the lack of global acceptance of related enhanced approaches. The desired state for such enhanced approaches to analytical procedures would be robust, fit-for-purpose, and consistent in demonstrating and assuring product and process quality throughout the product lifecycle. Further, it is anticipated that updated standards may enable or support detection of unanticipated quality issues and reduce of the probability of product failures. These approaches would also benefit industry in providing opportunities to improve the demonstration of product identity, purity, strength, and quality, while potentially reducing analytical variability. As such, these approaches could facilitate improved method robustness and reliability. At the time of drafting this reflection paper, work has not begun within ICH to develop such a harmonization work product.

- An ICH harmonization work product on Continuous Manufacturing to develop clear expectations of scientific and regulatory approaches and to lower perceived barriers and encourage implementation of this emerging manufacturing technology. Continuous manufacturing technologies offer opportunities for more consistent control of quality and can improve patient access by shortening development timelines of new drugs. Additionally, a number of technical complexities encountered in traditional drug development (e.g., upon scale up) are alleviated by continuous process automation, facilitating rapid commercialization. As such, continuous manufacturing of pharmaceuticals is a rapidly growing approach for production of both active ingredients and finished products. As technology advances and experience increases, harmonization is important to facilitate international acceptance of these technologies across the global supply chain and to prevent potential

[11] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q12/Q12_Final_Concept_Paper_July_2014.pdf
[12] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q12/Q12_Final_Buisness_Plan_July_2014.pdf
[13] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11_IWG_Final_Concept_Paper_10_November_2014.pdf
[14] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11_IWG_Final_Business_Plan_10_November_2014.pdf
[15] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11IWG_Step4_QA_2017_0823.pdf

disharmony through development of region-specific expectations or regulatory guidances. The current regulatory framework does not prevent implementation of continuous manufacturing since a number of continuous manufacturing processes have been successfully registered. However, provision of ICH guidance would prevent regional divergence and provide a clear framework and expectations such that continuous processes could be reliably filed. At the time of drafting this reflection paper, work has not begun within ICH to develop such a harmonization work product.

II. Establishing an ICH Theme: Enabling a Strategic Portfolio Approach to Achieve the ICH Quality Vision

During its meeting in November 2016 in Osaka, Japan, the ICH Management Committee supported the concept of establishing a set of ICH Themes to be actualized through a strategic portfolio approach with the goal of aligning future harmonization work to ICH's current resources in order to achieve desired harmonization outcomes in light of the recent ICH reforms and participation of new Members and Observers.[16] Such an approach should be applied to ICH's efforts moving forward in achieving the ICH Quality Vision to enhance the management of the finite resources of the ICH Association and its members in order to balance these efforts against other harmonization work in other areas with the growing membership of ICH. As such, to fully achieve the ICH Quality Vision, most future ICH Quality harmonization activities and other supporting efforts should be aligned to the ICH Quality Vision and should be managed and assessed over time as an interconnected portfolio rather than as individual guideline efforts. The ICH Quality Vision should be used as a framework to proactively identify, assess, and prioritize new quality topics for harmonization or revisions to existing ICH Quality Guidelines and should be integrated into the ICH annual process for selecting new topics in the future, notwithstanding other exceptional needs to develop ICH Quality-related Guidelines.

III. Recommendations

The following recommendations outline a set of steps to establish such a strategic portfolio approach to advancing the ICH Quality Vision. Of note, recommendations related to near-term harmonization efforts, the survey of existing ICH Quality-related guidelines, and other activities to facilitated global efforts are expected to proceed in parallel.

a. Formally Establish an ICH Quality Theme

Establishing an ICH Theme on "Advancing Pharmaceutical Quality Standards to Support Continual Improvement and Innovation in Manufacturing Technologies and Approaches" will serve to formalize the ICH Quality Vision within the new ICH Association and to garner support for implementing the proposed strategic portfolio approach. Further, establishing an ICH Theme will help familiarize new ICH Members and Observers to the series of activities ICH has undertaken since 2003 to realize this vision. Additionally, establishing an ICH Theme will promote the use of the ICH Vision as a framework

[16] http://www.ich.org/fileadmin/Public_Web_Site/Meetings/Ass_MC_Meetings_Reports/Minutes_MC_ICH_Meeting_Osaka_Nov2016.pdf

for the identification, assessment, and prioritization of future harmonization work to continue advancement toward the ICH Quality Vision.

b. Proposed Near Term Harmonization Activities

In line with the recommendations from the 2014 IQDG workshop, ICH proposes that the following harmonization activities conducted by ICH Expert Working Groups should begin in the near term on the following topics: *Continuous Manufacturing*, and *Enhanced Approaches for Development and Utilization of Analytical Procedures*. These topics should be considered in line with this reflection paper during the annual ICH new topic selection process, with final decisions taken in consideration of overall consensus priorities, according to applicable ICH Rules of Procedure and Standard Operating Procedures, across new topic proposals submitted from the ICH Quality, Safety, Efficacy, and Multidisciplinary domains.

c. Survey of Existing ICH Quality-related guidelines for Revision or Modernization Work

As new guidelines are being developed, application of continuous improvement principles would suggest that ICH should also comprehensively assess and potentially update a number of existing ICH Quality Guidelines to incorporate new science and any regional implementation learnings. Importantly, revision or modernization work to existing ICH Quality-related guidelines should take into account any potential unintended consequences to the supply chain if several widely used guidelines are revised or modernized in a particular timeframe, and should be prioritized to meet to the needs and priorities of all current ICH Members. To compile a comprehensive list of existing guidelines appropriate for assessment and possible revision, ICH should endeavor upon a survey of existing ICH Quality-related Guidelines among its Members and Observers in the near term. The survey should also include recommended approaches on how to efficiently update existing Quality-related guidelines (e.g., Q&A approach, revising a guideline, bundling similar types of updates to multiple existing guidelines using one ICH Expert Working Group, etc.). The survey results should be presented to the ICH Assembly to inform a set of next steps that would include evaluating the priority of revising existing ICH Guidelines against the framework of the ICH Quality Vision. The agreed priorities should be captured in an updated reflection paper.

d. Other Activities to Facilitate Global Efforts

As articulated in the "Origin of the ICH Quality Vision" section of this paper, the ICH Quality Vision calls for effective and consistent regulatory oversight across and between regions. Enabling coordinated planning, consistent understanding and interpretation of the portfolio of ICH Quality-related Guidelines requires efforts to dialogue, educate and train the users of these guidelines. As such, three areas of focus are envisioned to further facilitate the ongoing global efforts for the development, maintenance, and implementation of the ICH Quality Vision and ICH Quality-related Guidelines over time:

i. **Establish a new Quality Discussion Group (QDG)**: It is recommended that ICH establish a new Quality Discussion Group to facilitate necessary planning dialogue between ICH Member experts. The proposed remit of this group is detailed in the attached Annex. The ICH MC will exercise oversight over the QDG. The QDG could

primarily interact through email correspondence and teleconferences, or via face to face meetings, as appropriate.

ii. **Training and Monitoring**: 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. The QDG would be responsible for prioritizing topics and organizing the required training materials. 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. As part of the proposed strategic portfolio approach, it is recommended that the ICH Management Committee periodically directs the ICH Training Subcommittee, in concert with any recommendations from the QDG, to reassess its training priorities for ICH Quality-related Guidelines

iii. **Maintenance of the ICH Quality Reflection Paper**: The new Quality Discussion Group should periodically review and update this paper to reflect progress made in achieving the ICH Quality Vision, and recommend updated priorities and strategies for endorsement by the ICH governance bodies, as appropriate. As such, any agreed revisions to this reflection paper should be used as a point of reference in the annual ICH new topic selection process moving forward.

Annex: Remit of the Informal Quality Discussion Group

General Description

The Informal Quality Discussion Group (IQDG) will 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" as described in the ICH Quality Reflection Paper on Advancing Biopharmaceutical Quality Standards to Support Continual Improvement and Innovation in Manufacturing Technologies and Approaches.

The IQDG will operate in line with the applicable ICH procedures, similar to other ICH Technical/Discussion Groups, under the oversight of the ICH MC, and with reporting to the ICH Assembly. As the remit of ICH is to harmonise technical standards, the IQDG should in its work remain focused on technical and scientific aspects and ensure that ICH Guidelines are kept up-to-date with the evolution of science, whilst not striving to drive policy choices for regulations as this falls under the remit of the regulatory authorities in different jurisdictions.

Scope of Activities

The Informal Quality Discussion Group will:

- Review the need for new ICH Quality-related harmonization work.
    - In this regard, upon requests from the New Topic SubCommittee, the IQDG will discuss and recommend approaches to advance new ICH Quality topic proposals through the development of ICH Guidelines (e.g., new guideline vs. Q&A vs. revision to an existing guideline, etc.) and the logical sequencing of new ICH Quality topics to efficiently achieve harmonization and the ICH Quality Vision. Any new topic proposal recommended by the IQDG would need to be submitted through the ICH annual new topic process, per the applicable Rules of Procedure and Standard Operating Procedures.
    - In support of reviewing the need for new ICH Quality-related harmonization work, the IQDG will review all existing ICH Quality (and relevant Multidisciplinary) Guidelines with the goal of identifying and recommending those that need updating. In addition, this activity should include developing and maintaining a priority list all Quality-related (and relevant Multidisciplinary) harmonization work that is to be sequenced, including existing Guidelines subject to updating and new topics proposals, for review by the ICH Management Committee in order to facilite efficient planning and deployment of experts across several related ICH EWGs.
- Review and recommend training needs related to the content and/or implementation of ICH Quality Guidelines. Training needs might additionally be based on feedback data collected through periodic surveys and interactions with the ICH Training Subcommittee on how effectively and consistently ICH Quality-related Guidelines are being interpreted and applied across various ICH regions.
- Review and recommend any necessary updates to the ICH Quality Reflection Paper and ICH Quality Vision statement as needed. Any approved updates should also be reflected in the priority list of all Quality-related harmonization work to be maintained by the IQDG, as appropriate.

Type of Expertise Needed and Resources

The IQDG should be comprised of a diverse group of strategically-oriented experts that collectively have extensive knowledge of the scientific and regulatory aspects of all the ICH Quality Guidelines and others under development. Expertise should be balanced across a number of scientific (e.g., pharmaceutical sciences, process analytical technologies, quality manufacturing systems, and modelling, etc.) and regulatory (i.e., cGMP, CMC requirements and approval standards, etc.) aspects of the product-types subject to ICH Quality Guidelines, including small and large molecules, and vaccines.

It is envisioned that the IQDG should be comprised of experts from Members and Observers of the ICH Assembly, in accordance with the applicable Articles of Association, Rules of Procedure, and Standard Operating Procedures. ICH Members and Observers participating in the IQDG should be allowed to nominate standing experts and alternate experts to enable an appropriate balance of expertise while keeping the size of the IQDG manageable, in accordance with the applicable Standard Operating Procedures.

Operating Model and Term

The IQDG should complete its activities in a virtual setting via email and teleconference. In exceptional cases, the ICH Management Committee may consider granting a face-to-face meeting of the IQDG during a biannual ICH Meeting upon approval of a specific work plan in line with current practice for other ICH Working Groups.

The leadership of the IQDG should be comprised of a Rapporteur and a Regulatory Chair, in accordance with the applicable Standard Operating Procedures.

The IQDG will operate within an initial 2-year term beginning on the date upon which the Remit of the IQDG is approved by the ICH Management Committee, further to the ICH Assembly approval of the ICH Quality Reflection Paper. The IQDG should provide an update of its activities and progress biannually to the ICH Management Committee and the ICH Assembly, in line with current practice for other ICH Working Groups. Further to the recommendation of the Management Committee, the ICH Assembly will consider whether to grant an extended term to the IQDG within 6 months of the end of the initial 2-year term.

In support of the IQDG Scope of Activities, the IQDG should specifically endeavour upon completing the following actions in its first calendar year:

- Assess the impact of ongoing ICH Quality Topics on future ICH Quality harmonization work envisioned under the ICH Quality Vision (i.e., the impact of ICH Q12 on other ongoing or newly proposed ICH Quality topics)
- Consider ICH Quality topic proposals envisioned under the ICH Quality Vision that have not been endorsed by the ICH with the goal of assessing how the proposal could be strengthened for reconsideration
- Design and recommend to the ICH Management Committee for execution a survey of existing ICH Quality Guidelines in need of revision