Roundtable Session 2 – Table 7 – ICH Q6(R1): Challenges and Opportunities for Using an Enhanced Approach to Lifecycle Management of Specifications

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Abstract:
ICH Q6(R1) is being developed to consolidate and modernize specification (ICH Q6A and Q6B) principles, shifting from specifications as fixed endpoints toward a science- and risk-based framework. The revision emphasizes how product knowledge, process understanding, attribute characterization, and analytical maturity can inform the establishment and evolution of specification criteria across the lifecycle. This approach is particularly relevant for advanced modalities where inherent variability or modality-specific biology limits the ability of early datasets to reliably inform specification setting.

This roundtable will focus on the scientific considerations that influence specification design. Participants are invited to discuss how expanded evidence—such as mechanistic understanding of CQAs, prior knowledge, platform experience, and/or modeling outputs—can guide the lifecycle evolution of specifications as product and process understanding matures. Modalities such as gene therapies, cell therapies, and conjugated biologics will serve as illustrative examples, particularly where heterogeneity challenges conventional specification methodologies.

Discussion will focus on which forms of scientifically grounded evidence best characterize quality attribute performance over time. The goal is to explore how science—beyond empirical limits—can support clinically meaningful and resilient specification frameworks without oversimplifying modality-specific complexity.

Discussion Questions:

(1) When datasets are limited, how should prior knowledge and emerging product-specific evidence be combined to inform specification strategy—and how should this balance evolve as knowledge increases across the lifecycle?

(2) Where has mechanistic linkage between process parameters and CQAs provided sufficient confidence to reduce reliance on end-product testing, and what level of supporting evidence was required to make that scientifically credible?

Notes:

(1) Participants acknowledged that for early phase development, when there is a small data set, traditional statistical approaches (e.g. ±3 SD) are not meaningful. Wider specification ranges are scientifically justifiable when supported by platform knowledge, prior knowledge from similar molecules, and structure-function characterization.

Specifications in early-phase development should focus on attributes critical to safety and mode of action (MoA), rather than attempting to control every potential quality attribute. In that context, potency assays are particularly important when batch history is minimal.

Participants stressed that specifications must be grounded in clinical context, considering the intended MoA, known adverse events, and exposure ranges used in clinical trials. Strong cross-functional collaboration with safety and clinical pharm colleagues is encouraged to gain the knowledge to be able to justify the specifications.

It was recommended to start building the knowledge from early clinical development to prevent surprises when setting commercial specifications. It would be useful to bring some diversity with regard to certain CQAs in clinical batches, to build variability into pivotal batches and patient exposure. This could be achieved by intentionally manufacturing material at the high end of an attribute to gain clinical experience and support wider commercial limits. Another option is to use end-of-shelf-life batches as part of the pivotal studies. Finally, dose escalation studies could be leveraged to justify specifications. Again, cross-functional collaboration, especially with Clinical Operations, is key for these strategies.

The participants discussed some other elements that could be used to set and justify the specifications, such as analytical platform knowledge, method variability, and experience with process controls and continued process verification.

As development progresses and more data is available, specifications should gradually shift from reliance on benchmarking to molecule-specific structure-function relationships. Participants opposed the idea of tightening specifications simply because manufacturing consistency is observed (e.g., reassessment after 30 batches) if broader ranges remain clinically safe.

There were some examples provided by the participants where Health Authorities (HAs) were not accepting the justifications, and in some instances, this could be about specific reviewers.

(2) Some participants shared that they have been successful in using process validation to justify the elimination of routine, lot-release testing for DNA and Protein A by providing scientific evidence that the purification process consistently removes these contaminants to safe levels.

Most participants shared that the same approach is not feasible for HCP testing, and they will add it as DS release testing or an in-process control. One participant shared a recent success in not including HCP testing as a release or IPC for EMA.

Some participants also shared that they have been successful implementing fill weight checks as an IPC in lieu of the release method for extractable volume. For PFS and AI, they confirmed that functional testing for deliverable volume is still required.

There were some discussions about how to set up specifications for early development studies when experience is limited. Suggestions included using the QTTP and linking it to the criticality of the attribute. For certain CQAs, citing relevant literature is also sometimes helpful.

Additional Questions (not discussed at session):

**For advanced modalities, which product attributes are most scientifically meaningful to specify, and how are ranges justified when inherent heterogeneity is expected?*

**As analytical methods mature (e.g., functional assays, multi-attribute approaches), how should scientific progress inform the criteria for determining whether improved sensitivity warrants specification changes, and how do we ensure those changes continue to reflect patient benefit?*

**How can modeling or multivariate approaches meaningfully contextualize variability and support specification decisions, and what additional evidence is needed to build confidence in their use?*