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Personal Commentary

ICH Q12 Should Build on the ICH Q8 Design Space

By Mark F. Witcher

The current draft of ICH Q12 appears to have taken several steps backward in the pursuit of the manufacturing excellence initiated by ICH Q8 (R2) pharmaceutical development and expanded by FDA's 2011 process validation guidelines.

The first step backward involves controlling process changes by building an additional layer of information around vaguely defined "explicit and implicit" ECs structured using a PACMP within a PLCM. These requirements are over-and-above the information in the existing CMC/CTD structure for defining product attributes (QTPPs/CQAs/ECs) and providing the manufacturing process information contained in the DS and CS descriptions.

The justification for the draft Q12 approach might indicate a lack of trust between regulatory agencies and the development and change control methods currently used by the industry. An understanding of these issues might be gained by further evaluating and discussing the following sentence starting at line 8 in the draft ICH Q12 document:

> *"Experience with implementation of recent ICH guidelines has revealed technical and regulatory gaps that limit the full realization of more flexible regulatory approaches to post-approval CMC changes as described in ICH Q8 (R2) and Q10 Annex I."*

If the industry is not doing its job, then we need to fix the gaps by diligently improving the application of the existing DS, lifecycle PV, and QbD approaches. Why add programs and requirements that may hamper already challenging process development and improvement activities, especially for the next generation of advanced therapy products and intensified manufacturing processes? The industry needs to fix problems by improving existing systems and current methods rather than potentially masking the underlying problems by adding more complex programs to achieve the same objective. To be most effective, the CQAs/ECs should be identified during the PV design stage using scientific, experimental, and QRM methods, and then specified, along with their CSs, in the process's DS information.

The draft ICH Q12 also appears to abandon the ICH Q8 DS concept of providing operating flexibility gained from a comprehensive, regulatory-approved, science-based DS created using QbD within the PV lifecycle—another step backward. The activities and effort of developing the DS is crucial for establishing the excellent process understanding and control necessary for manufacturing very high quality products.[1] While regulatory communication and approval is important for changes that impact product safety and efficacy, such collaboration should be based on evolving the original product and process understanding established in the initial approval process using the DS and lifecycle PV.

As ICH Q12's title implies, "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management" is a golden opportunity to strengthen the entire product development and manufacturing lifecycle, including process improvements, by utilizing the naturally occurring lifecycle stages described in FDA's lifecycle PV guidance. Development and subsequent modifications should be driven by QbD during the process design stage to build and manage comprehensive DS information, knowledge, and analysis, especially for assessing product risks associated with process improvements.[2]

Striving for very high levels of process control and product quality is critical to the long-term success of the industry's quest for good patient care. These medical patients deserve Six Sigma product quality levels by achieving FDA's stated goal of "a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight."[3] Regulatory agencies and the pharmaceutical industry must work together to rigorously improve the existing methods of defining and communicating the DS and CSs necessary for meeting the challenges of the 21st century.

ACRONYM KEY		ICH	International Conference on Harmonisation
CMC	Chemistry, manufacturing, and controls	PACMP	Post-approval change management protocol
CQAs	Critical quality attributes	PLCM	Product lifecycle management program
CSs	Control strategies	PV	Process validation
CTD	ICH M4 – Common technical document	QbD	Quality by design
DS	Design space	QRM	Quality risk management
ECs	Established conditions	QTPPs	Quality target product profiles

References

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