

Final Business Plan
Q10: Pharmaceutical Quality Systems
dated 14 October 2005
Endorsed by the ICH SC on 10 November 2005

The issue and its costs:

Currently, there are differences between industry and regulatory agencies in the different regions in the definition and interpretation of quality system terms, principles, application and expectations. Therefore, while the three regions are using various aspects of quality systems and concepts, a strong potential exists for further divergence. This divergence can occur in expectations and interpretations as the quality systems evolve, especially when implementing quality by design, continual improvement and quality risk management. This divergence is not in line with the need for an efficient and effective industry and regulatory processes.

The absence of an internationally harmonized pharmaceutical quality systems guideline that manufacturers can use in assessing their process, products and systems can have the following impact on the patient, regulator and/or industry:

- Fragmented or fundamentally divergent approaches to quality systems are likely.
- Suboptimal deployment of limited resources to identify, enact or support effective elements of a quality system and continual improvement by both industry and regulatory agencies.
- Delays may occur in the availability of medicines to patients around the world.
- Delays in the implementation of innovation and continual improvement for existing products may occur due to different expectations in the three regions.
- Delays in the launch of new products.
- Different approaches between the three regions to compliance inspections.
- Impediments to moving within pharmaceutical manufacturing and associated regulatory processes towards implementing a culture of quality by design, right first time and continual improvement, as practiced within other industries.

Planning:

Because of the broadness and complexity of the guideline and as this guideline will be applicable over the life cycle of the product, it is important that EWG members have expertise in quality systems, compliance, pharmaceutical development, and manufacturing. In order to have the appropriate expertise and to keep the size of the EWG manageable, it is suggested that each ICH partner have the flexibility to nominate up to three experts to allow for a broad range of subject expertise to be adequately represented. The core group would be comprised of these nominees from each of the ICH parties and one representative from each observer (including EFTA, IGPA, WSMI, WHO, and Canada).

It is anticipated that such a harmonised guideline (to step 2) could be developed within an 18 month period, assuming input of 18 man days per expert working group member for essential meetings over this period and 24 man days of input from an appointed Rapporteur. Additional input would be expected from observers. Progression to step 4 is anticipated to be less resource intensive.

Timeline

| | |
|--|---------------------|
| Adoption of topic by Approval of ICH Steering Committee to develop concept paper | May, 2005 |
| Approval of Concept Paper by Steering Committee | November 2005 |
| First EWG – Chicago, USA | November 5-10, 2005 |
| Second EWG – Yokohama, Japan | June, 2006 |
| Adoption of Step 2 Document | Spring 2007 |

Risk Analysis

The main risks associated with this project are the possibility of significant disagreement between the experts who might prevent or protract the development of a harmonised guideline.

Several examples exist for multi-national harmonisation of documents that define quality systems. Therefore the risk of not achieving harmonization is low. In addition, it is expected that the guideline can be modelled after the FDA's recently issued draft guideline entitled "Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations" which serves as a bridge between existing GMP regulations and current understanding of quality systems.

These risks should be mitigated by oversight of the process by the Steering Committee and review against the timelines proposed.

Impact of the project:

Potential Benefit

There are areas where substantial cost benefits are envisaged as a result of the implementation of a quality systems guideline in parallel with it enabling the use of Q8, Q9 and potential future changes to regulations.

- Improved process performance.
- A reduction in the costs of internal failures (rejects, reworks, reprocessing and investigations) as the quality systems guideline drives improvement.
- A reduction in the costs of holding duplicate stock and operating multiple processes as improvements and changes are made more effectively across all regions.
- A reduction in the costs of preparing / reviewing certain regulatory submissions.
- Enhanced assurance of consistent availability of medicines to the patient.

If only a small percentage of these costs could be avoided, then substantial saving of resources by industry and regulators will be realised and the benefits of this project will greatly exceed the costs.

Achieving these savings is possible if industry can fully realize the benefits of ICH Q8 and Q9, and a harmonized ICH quality systems guideline. In a report entitled “The Metamorphosis of Manufacturing, from Art to Science”, published by IBM Business Consulting in May 2005, the authors indicated that their analysis showed that improving the performance of a process from 2.5 sigma (their current estimate of pharmaceutical manufacturing) to 4.5 sigma (their benchmark for “good” pharmaceutical manufacturing) yields a 1,000-fold greater decrease in defect rates when compared to improving the performance of the quality control system (i.e. inspection) from 5 to 5.5 sigma. Furthermore, they estimate that that a resulting decrease in internal failures could reduce the cost of goods by up to 3% and increase process performance significantly. For the top 30 pharmaceutical companies, IBM estimates the annual savings to be in excess of €8 billion.

Estimated Implementation Costs

The proposed quality systems guideline is focused on industry practice and will not itself define a new regulatory framework. The broad implementation of Q8, Q9 and a quality systems guideline may facilitate the initiation of changes in regional regulations; however, the nature of those changes is not within the scope of this guideline. Therefore, there will be no significant implementation costs for regulatory agencies aside from participation in the guideline

development, education and publication processes. This cost will be mainly related to training of inspectors.

The estimated cost to industry will vary across a very broad range based on a number of factors. The guideline is intended to be voluntary, and a firm may choose not to implement because they consider their current quality system a suitable alternative to that defined in the quality systems guideline, or because they choose to maintain the status quo. In this case, the cost to a firm could be zero. By maintaining the status quo, the firm chooses to operate within the current regulatory processes and may not benefit from any flexibility that may be associated with implementation of the guideline.

If a firm decides to implement the quality systems guideline, the factors that will drive implementation cost include:

- Current state of the firm's quality system and extent of internal harmonization across sites
- Complexity of operations
- Number of operating sites

The cost to implement a modern robust quality system should be viewed as an investment in efficient, high quality operations. Therefore, there will be a return on investment in cost savings resulting from efficiency improvements and lower internal reworks and rejects. In general, it can be assumed that the greater the opportunity to improve, the higher the cost savings resulting from the implementation.

The costs of implementing a new or enhanced quality system are associated with 4 discrete steps:

- Assessment of existing corporate quality system versus ICH QS Guideline
- Design, redesign or enhancement of existing corporate quality system
- Assessment of required changes at operating sites to comply with updated corporate quality system
- Implementation of changes required at operating sites

The range of man-days for these activities can be very roughly estimated. The estimates below are based on input from an independent quality system/GMP consulting firm. These estimates assume that a firm is compliant with existing GMPs and has at least a basic internal quality system.

Assessment of existing corporate quality system versus ICH QS Guidance

It is estimated that it would require between 10 and 20 man-days to complete an assessment and gap analysis of the current quality system versus a new ICH Guideline. The range is dependent on the size and complexity of the firm and the current state of the quality system.

Design, redesign or enhancement of existing corporate quality system

Enhancement of an existing quality system would be addressed through normal continuous improvement processes in accordance with a plan and timeline defined by the company. The cost for an enhancement is estimated to be nominal. If a partial redesign is needed, up to 160 man-days could be required to complete. The development of a totally new quality system could require up to 320 man-days for a larger, complex firm.

Assessment of required changes at manufacturing sites to comply with updated corporate quality system

For smaller firms with one or two manufacturing sites, the site assessment can be incorporated into the assessment of the corporate quality system and there will be minimal incremental costs. For larger firms, a separate site assessment may be warranted. It is estimated that it will require 20 – 40 man-days to conduct a comprehensive assessment against a newly designed or significantly redesigned corporate quality system. For enhancement to the corporate quality system, site assessments will be handled through the normal continuous improvement process at nominal cost.

Implementation of changes required at manufacturing sites

This number will vary greatly based on the current state of the corporate quality system, the extent of global implementation, the size of the firm, and the complexity of operations. An accurate estimate can only be established with a finalized quality system guideline and an assessment of the firm's current quality system versus the guideline. We can roughly estimate the time requirement to develop a comprehensive site quality system for firms with limited quality systems. For smaller and less complex sites, up to 200 man-days could be required to develop and implement all elements of a robust quality system at a site. For larger more complex sites, up to 800 man-days or more could be required. Firms will likely leverage the site development and implementation activities and each site will not have to incur this level of investment.

The table below illustrates the estimated range of costs (measured in ‘man-days’ that can be expected for each phase.

| | Small Company | | Large Company | |
|--------------------|---------------|----------------|---------------|----------------|
| | Limited QS | Robust QS | Limited QS | Robust QS |
| Assess Corp | 10 | 10 | 20 | 20 |
| Design | 160 | nominal | 320 | nominal |
| Assess Site | 20 | nominal | 40 | nominal |
| Implement | 200 | nominal | 800 + | nominal |
| Total | 390 | 10+ | 1180+ | 20+ |

The actual monetary cost will depend on the region and whether internal resources or external consultants are used to complete the work. Under any situation, the implementation costs within a company are greatly exceeded by the potential benefits highlighted in the IBM report referenced above.

Post-hoc evaluation:

The results of implementing a harmonized quality system guideline can be measured in at least two areas; (1) improved process performance (sigma) resulting in lower rejects and (2) regulatory inspection findings that verify the robustness of a manufacturing site’s quality system.

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