

Charting the Course of QbD Implementation

While everyone agrees that QbD makes sense, Europeans and Americans appear to be taking different approaches.

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THE CONCEPT of total quality, promoted by the International Council on Harmonization and encompassed in the idea of Quality by Design, is changing the pharmaceutical sector. Such change is visible in the way in which companies are planning and carrying out the development and commercialization of their products.

The shift from a “quality by inspection” paradigm to one based upon Quality by Design may be thought to have started in America in 2002, when the FDA issued its Pharmaceutical GMP’s for the 21st Century [1]. This document was followed by ICH Guidelines Q8, Q9, and Q10 [2-4] which constituted what may be considered a new regulatory framework for companies around the world that wish to work under QbD.

By definition, the ICH setting is a global one, but it is the duty of the “regional” regulatory authorities to include these guidelines in their standards. These guidelines have already been adopted, and consequently all three ICH regions—the U.S., E.U., and Japan—are in agreement about what it means, on paper, to develop and manufacture drugs with QbD. Concepts such as Design Space, Critical Quality Attribute (CQA), and real-time release have become a part of the lingo of pharmaceutical industry professionals everywhere.

The ICH regulatory framework is designed so that manufacturers who wish to submit variations on the Design Space of an existing process, or their registration of a new product, are able to do so. In June 2008, the European Commission issued new regulations on variations of the Commercialization Authorization, which considers the presentation of a Design Space as a Type II variation.

However, by most accounts, implementation in the U.S. is occurring faster than in Europe. For example,

according to the FDA’s Office of Generics Drugs, by July 2007 approximately 90% of abbreviated new drug applications (ANDAs) submitted for generics participated in the office’s Question-based Review (QbR) process based upon 21st Century GMP and QbD principles [5].

One of the basic differences between the American and European frameworks is that the FDA is being more proactive in encouraging the industry to adopt QbD practices and in training inspectors on all QbD-related scientific subjects. The EMEA has also started similar programs and is encouraging all manufacturers who are thinking of filing QbD dossiers to notify the Agency accordingly in order to establish the suitable support and follow-up mechanisms. However, and despite all those efforts, we in Europe are still quite far from reaching that objective, and some manufacturers continue to report problems when submitting variations—for example, when simply substituting NIR-based controls for traditional HPLC-based methods.

However, the EMEA has quite readily included ICH Q9 and ICH Q10 in its GMP standards. Risk management is now a must within quality management systems [6], and an impending modification has been announced with the purpose of also including the quality system defined in ICH Q10. ICH Q8, the most exacting guideline from a technical viewpoint, is, for the moment, a recommendation for product development.

IMPLEMENTATION OF ICH Q8, Q9, AND Q10

To get a better sense of how QbD is being implemented in different countries, we conducted a survey of professionals involved in QbD at their companies (Box, p. 19). To evaluate ICH Q8 Implementation, participants were asked about the use of Design of Experiments (DoE), risk

Degree of Implementation	Level/Weighing Factor
No, not at the moment.	1
No, but we’ve started educating ourselves and testing small projects.	2
Yes, but in an informal way, or through individual initiatives within the company.	3
Yes, there is a formal project in place.	4
Yes, it is already introduced at the corporate level.	5

TABLE 1. ICH Q8 PHARMACEUTICAL DEVELOPMENT

DEGREE OF IMPLEMENTATION	LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4	LEVEL 5	SCORE	PERCENTAGE RANKING (%)
Design of Experiments (DoE)	7	9	7	8	2	88	42
Risk Analysis in Development	3	5	7	10	8	114	61
Design Space	9	11	5	4	4	82	37
Process Analytical Technologies (PAT)	11	12	4	2	4	75	32

TABLE 2. ICH Q8: PHARMACEUTICAL DEVELOPMENT (REGIONAL DIFFERENCES)

DEGREE OF IMPLEMENTATION	PERCENTAGE RANKING (GLOBAL)	PERCENTAGE RANKING (EU)	PERCENTAGE RANKING (Non-EU)
Design of Experiments (DoE)	42	34	54
Risk Analysis in Development	61	55	71
Design Space	37	29	50
Process Analytical Technologies (PAT)	32	26	40

analysis, Design Space, and PAT within their companies. Results are shown in Table 1. The highest implementation indicator is the one for risk analysis, 61%, followed by DoE with 42%. Design Space and PAT are clearly below those figures, mainly because their implementation appears to be quite recent: either Degree 1 (not done) or Degree 2 (training).

Regarding Q9, the following questions were asked:

- Is risk analysis being used to prioritize critical-to-quality activities?
- Is risk analysis being used to continuously improve manufacturing processes?
- Is there a risk management process in place integrated into the quality system?

All indicators exceeded the percentage ranking of 50, and process risk analysis is least implemented, by a slight degree. This result is reasonable if we consider that ICH Q9 has been a GMP requirement since it was included as Annex 20 to the European GMPs. From this point of view, results may even be lower than expected.

For ICH Q10, questions asked were the following:

- Is the company monitoring manufacturing processes (Six Sigma, SPC, CPKs)?
- Is the company monitoring quality management

processes (indicators, KPIs, etc.)?

- Is there an ICH Q10-type Quality Manual in place?

All three factors were quite even. It should be noted that approximately 20% of the participants do not use process monitoring, have no Quality Manual, and have no project in store. Therefore, it appears that participants are polarized at the extremes for Q10 implementation.

REGIONAL DIFFERENCES

Tables 2-4 also illustrate differences in Percentage Rankings between EU and non-EU manufacturers. We must caution that this sample is hardly representative—the EU contribution is concentrated in companies based in Spain, for example. Had manufacturers from Germany, France, and the U.K. been represented, QbD adoption (and thus Percentage Rankings) would likely have been higher.

In general, Q8, Q9, and Q10 have higher ranking for non-EU countries (which may be considered to be an area of FDA influence). Differences are more evident in the following practices: DoE, Design Space, and monitoring (both manufacturing process and quality systems). While risk management is also something that is not practiced as frequently in the EU, it is implemented elsewhere.

Table 3. ICH Q9 RISK MANAGEMENT (REGIONAL DIFFERENCES)

DEGREE OF IMPLEMENTATION	PERCENTAGE RANKING (GLOBAL)	PERCENTAGE RANKING (EU)	PERCENTAGE RANKING (Non-EU)
Critical to Quality Prioritization	65	64	67
Manufacturing Process Risk Analysis	59	49	63
QRM Integration in QS	63	56	73

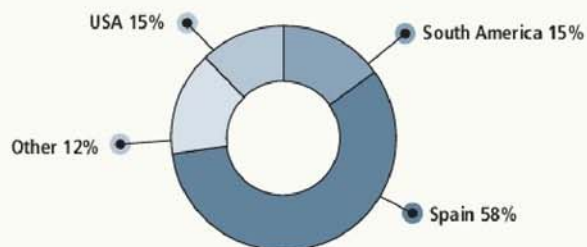
TABLE 4. ICH Q10 PHARMACEUTICAL QUALITY SYSTEM (REGIONAL DIFFERENCES)

DEGREE OF IMPLEMENTATION	PERCENTAGE RANKING (GLOBAL)	PERCENTAGE RANKING (EU)	PERCENTAGE RANKING (Non-EU)
Manufacturing Process Monitoring (Cpk's, SPC)	56	46	71
Quality Monitoring (indicators, KPI's)	57	46	73
Quality Manual (ICH Q10)	55	50	62

LOOKING AHEAD

From written responses to our survey, we learned that one of participants' greatest worries is understanding the criteria for evaluation and inspection of QbD activities. How is a Design Space evaluated? The answer to this question is by no means straightforward. Establishing a multi-dimensional space of input material and process parameter attributes, frequently interrelated, that defines the "secure" working area is considerably complex and demands specific knowledge of multivariate statistics and chemometrics.

Both FDA and EMEA have set up working groups that include evaluators, inspectors, and industry representatives in order to make joint progress towards the scientific understanding of such methods, and the development of criteria for their evaluation. However, it would indeed be good for the European national authorities to also participate in the opening



of indispensable communication pathways with those companies that have prepared QbD projects and need further clarification on which is the scenario for evaluation and inspection of these products.

The comments received by this survey point to great expectations regarding ICH Q8, Q9 and Q10 guidelines implementation in the sector. Professionals view the guidelines as extremely useful for process improvement and for decision making on quality-critical issues. The degree of implementation of Q9 and Q10 is clearly higher than that of Q8, probably due to the greater technical complexity of the latter.

Interestingly, the guideline that will likely yield the greatest financial return is ICH Q8, as it establishes the foundations of development based on process knowledge, which paves the way for a robust and flawless commercial manufacturing process. One factor delaying the adoption

of ICH Q8 is uncertainty about how QbD processes will be evaluated and inspected by regulators.

The purpose of QbD projects is twofold: to launch safer products into the market, thus showing that process and product risks are under control, and to reduce the product development costs. This is a scenario in which everybody gains something: the regulatory authorities and public gain peace of mind, and manufacturers gain competitiveness. In every part of the world, therefore, the implementation of QbD is worth the effort.

About the Authors

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References

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2. ICH Q8 (R1): "Pharmaceutical Development". Step 5, November 2008.
3. ICH Q9: "Quality Risk Management". Step 5, November 2005.
4. ICH Q10: "Pharmaceutical Quality Systems" Step 5 June 2008.
5. OGD Update on Question-based Review Submissions http://www.fda.gov/cder/ogd/QbR/QBR_submissions_upd.htm
6. EudraLex Volume 4 EU Guidelines to GMP's Part 1.Chapter 1: "Quality Management".

ABOUT THE SURVEY

Our survey was answered by representatives of 33 companies in 9 different countries (Graphic at left). Participation was indeed limited, but the diversity of the participants, and their objective comments, lend significance to the results.

It should be emphasized that participants were from companies with QbD projects underway. Companies without QbD projects in progress did not take part, so the results should not be used as a measure of the degree of QbD implementation within the sector.

The survey asked participants to rank implementation on the basis of five levels of implementation (Box, p. 17). The score is obtained by multiplying the frequency of each degree by the weighing factor. This final score is transferred to a 0–100 scale to establish a Percentage Ranking.