The State of Quality by Design for Generics

Report on Joint ISPE – European Generics Association Meeting on Applying QbD to Development and Manufacture of Generic Medicines

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Overview

On 27-28 June 2012 in Brussels, Belgium, ISPE co-hosted with the European Generics Association (EGA) the first meeting in Europe to discuss application of Quality by Design (QbD) approaches to developments and manufacture of generic medicines. Over two days there were keynote presentations from eminent EU and US regulators and from the generic medicines industry, as well as workshops with outputs available to participants to discuss the regulatory, technical, and business implications of developing generic medicines and associated processes for both products and active ingredients. Importantly, three case studies were presented showing application of different QbD approaches, which indicated that companies developing and manufacturing generic medicines are very active in, and can derive benefits from, implementing the concept of QbD.

Why Hold the Meeting?

The US FDA has made public statements that from early 2013 US Abbreviated New Drug Applications (ANDAs) applicable to generic medicines should contain QbD elements. Many companies source the US and operate at global level, therefore have activities in both the US and the EU.

The concept of Quality by Design is defined in ICH regulatory guideline Q8 (R2)¹ as:

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

QbD is derived from implementation of harmonized regulatory guidelines in the EU, US, and Japan for Pharmaceutical Development (ICH Q8)², Quality Risk Management (ICH Q9)², Pharmaceutical Quality System (ICH Q10)³, and Development and Manufacture of Drug Substances (ICH Q11)⁴. Some other regions have also embraced these guidelines, e.g., Canada and Australia. It is a voluntary concept which applies to all medicines and active substances and is not intended to create new regulatory requirements. It is equally important to generic and originator medicines. The regulatory expectations in the EU are not clear for many generic (and originator) companies, and it is not clear from the statement in ICH Q8 regarding opportunities for “regulatory flexibility,” what could be achieved.

QbD does have some differences of technical approach compared with a “traditional” approach and the business challenges of investment, given that payback is later in the product lifecycle, are significant:

• How much?
• When in the development program?
• What parts of the process, all or just some steps?

The generic medicines industry operates at a very fast pace, in a very competitive environment, and with the need to file first as a key business goal. Companies obviously want to achieve more robust and efficient manufacturing processes and supply chains but successful companies will be those taking into consideration the dynamics of the generic medicines sector.

Originator companies have reported⁵ significant business benefits when developing new products using QbD, and when applying QbD to make improvements to existing marketed products.

Many practical questions, however, remain open.

Speakers and Structure of the Meeting

The regulatory keynote speakers are leaders for their region. Jean-Louis Robert is chairman of the European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP)/Committee for Medicinal Products for Veterinary Use (CVMP) Quality Working Party and served on the Expert Working Group for ICH Q8, and the Implementation Working Group which produced follow up Questions and Answers, and Points to Consider documents. He works for the Laboratoire National de Santé, Luxembourg. Robert discussed “Demystifying Quality by Design from a Regulatory Perspective.”

Jacques Morenas from the French National Agency for Medicines and Health Products Safety (ANSM) was a member of the ICH Q9 and Q10 Expert Working Groups, was a past chair of PIC/S, and is a global leader from a compliance/inspection perspective on implementation of ICH Q8, Q9, and Q10. Morenas discussed “Implementation of Q9 and Q10 in the EU: A Regulatory Inspection Point of View.”

Keith Webber is Deputy Director of the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (CDER) at the US FDA and has been involved in developing policy in the US for application of QbD to generic drugs. Webber presented “A US Regulatory Perspective on the Implementation of QbD for Generic Drugs.”

Pito Roslansky as Head of Strategic Projects, Global Product Development, Sandoz International GmbH, gave a generic medicines industry perspective on the application and use of QbD in a global context, entitled, “The Quality by Design
Paradigm and the Generics Industry.”

There were also three excellent and relevant case studies explaining the practical application of QbD to different stages of the development of a generic medicine from:

- Francois A. Menard, Watson Pharmaceuticals Inc., US
- Jose Ascensao, Hovione, Portugal
- Jan Ramza, Polpharma SA, Poland

Three interactive Workshop sessions discussed topics relevant to the generic medicines industry using prepared questions based on content from the earlier presentations, these being:

A. Why consider QbD?
B. How do you effectively develop products and processes using QbD?
C. What are the regulatory expectations for QbD submissions?

The meeting was very well attended with representation from large and small generic companies located throughout Europe and the near east, and from a range of relevant disciplines.

**Discussion Highlights**

All speakers included in their content reference to at least one of the four relevant ICH guidelines, Q8 (R2), Q9, Q10, and Q11, and many stressed that all four guidelines are required to achieve the ICH quality vision, which was developed at the Brussels, ICH meeting in July 2003:

“Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasising an integrated approach to quality risk management and science.”

Also relevant are supporting Questions & Answers6 and Points to Consider7 documents and training material8 available from the ICH web site. Particular definitions often referenced were:

- Quality Target Product Profile (QTPP)
- Quality by Design (QbD)
- Critical Quality Attribute (CQA)
- Critical Process Parameter (CPP)
- Quality Risk Management (QRM)
- Control Strategy
- Design Space

An important message from the regulators from Workshop C (What are the regulatory expectations for QbD submissions?) was that industry in both their submissions and internal GMP documentation should use accurate terminology and ideally not use new terms.

Robert said that QbD is not totally new in the EU, referring to the previous CHMP Guideline on Development Pharmaceutics9. However, he insisted that a sound, more systematic development approach with use of more formal risk management should facilitate the process to achieve quality and should automatically generate more knowledge. He pointed out that QbD does not require establishment of a design space or necessarily lead to real time release testing. Independent of the level of development (“minimum” or “enhanced, QbD”) a control strategy is always required. Additionally, he stressed that a conventional specification is still required and acceptance criteria are likely to be set using a balance between clinical relevance and process capability.

Webber said that implementation of QbD is essential to ensuring the availability of affordable, high quality generic drugs in the US. He indicated that QbD goals were to reduce product variability and defects, to increase product development and manufacturing efficiencies, and to enhance post-approval change management. The minimum ICH Q8 expectations are to define a QTPP, identify and control CQAs of drug product, determine CQAs of drug substance and relevant excipients, select an appropriate manufacturing process, and define a control strategy. He also elaborated on what could be involved if an enhanced, QbD approach were chosen, for example, drug substance and excipient properties to consider. He stressed that a basis of the enhanced, QbD approach was development of process understanding whereby there is linkage of critical material attributes and CPPs to relevant drug product CQAs.

Morenas concentrated on implementation of Q9 and Q10 in the EU and the potential impact on current EU GMP guidelines. He said Q9, Quality Risk Management (QRM) provides principles and a framework for science-based decision making. It is guidance introduced in Part III of the EU GMP guide and it is not an “SOP.” It is simple, flexible, not mandatory, facilitates communication and transparency, and supports build-up of trust between regulators and industry. He discussed an example of the application of QRM in the GMP inspection environment by referencing the work currently being undertaken by the CHMP Safety Working Party to develop toxicological guidance for use in risk identification in the manufacture of different medicinal products in shared facilities.10 He also described the ANSM approach to risk-based GMP inspection planning, which was derived from the recommended model elaborated by PIC/S QRM Experts Circle.11 With regard to Q10, Morenas identified those parts of the EU GMP guide which are being or have been revised based at least in part on ICH Q10. He concluded that Q10 allows global harmonization of a Pharmaceutical Quality System (PQS), that a PQS is mandatory to comply with EU GMP, and ICH Q10 reflects current expectations for EU GMP.

Roslansky showed examples of how there can be different QbD strategies and that use of prior knowledge can be very effective to reduce development time and resources. For the
generic industry there are significant challenges applying a 
QbD approach, for example, compatibility with the business 
need to be first-to-file in the US. For the globally-sourcing 
industry, there are challenges with: global regulatory align-
ment; alignment with the new US process validation guidance; 
low amounts of drug substance during early development; 
and unavailability of excipient samples for quality attribute 
evaluation. Nonetheless, the enhanced, QbD approach should 
lead to improved product and process understanding with the 
concomitant benefits.

All three case studies emphasized the need to balance 
the business environment and regulators’ expectations with 
the amount of work and its timing in the development pro-
gram and with the anticipated benefits. All described their 
company’s iterative science- and risk-based approach, which 
can, however, be summarized in Figure 1 taken from ISPE’s 
PQLI Guide, Part 1 – Product Realization using Quality by 
Design: Concepts and Principles.\textsuperscript{12}

Menard from Watson showed with two generic drug prod-
uct case studies of complex products how matching the CQA 
of dissolution profile of the originator product from an osmotic 
delivery system and from a coated multi-particulate system 
could be achieved successfully using a QbD approach. Use 
of advanced analytical methods and development of process 
models were described. Significant business benefits were 
described, such as better process robustness, less deviations/ 
rejections, improved cost of goods, and customer service.

Ascensao indicated the “Hovione Way” to QbD implemen-
tation using spray drying of an API as an example. He particu-
larly emphasized the important role of risk management to optimize 
the number of variables to study in statistically-designed stud-
ies, as well as to optimize the number of experiments, and in 
each experiment, the range and intervals of variables to study.

Ramza explained Polpharma’s decision to apply QbD to 
chemical process development of APIs. Polpharma uses risk 
management to select the critical steps of the process on which 
to apply the QbD approach. For other steps, conventional 
studies to determine proven acceptable ranges are performed. 
New equipment and software was required to implement QbD, 
as was new documentation and training of people in many 
disciplines. Goals for the project were achieved.

The main points from the Workshops were:

A. Why consider QbD?
   - Develop your own business case.
   - Consider a pilot project.
   - Involve all disciplines.

B. How do you effectively develop products 
   and processes using QbD?
   - New tools and expertise required 
     – knowledge management, Process 
     Analytical Technology (PAT), risk as-
     sessment, multivariate experiments 
     and analysis
   - PAT tools may be more suitably ap-
     plied in development.
   - IT software and infrastructure re-
     quired

C. What are the regulatory expectations 
   for QbD submissions?
   - Assessors want a well-written, clear 
     story. Internal peer review is recom-
     mended.
   - No real difference for inspections
   - Use accurate terminology.

Conclusion

The main conclusions from the meeting were:

- QbD is feasible for the generic medicines sector and there 
  are benefits.
- Such meetings create the necessary platform for dialogue 
  between regulators and industry experts to clarify miscon-
  ceptions.
- It is essential that implementation by the various regions 
  remains harmonized, otherwise the divergences might 
  defeat the initial purpose.
The State of Quality by Design for Generics

The EGA looks forward to more opportunities to address QbD with regulators and will work jointly with other trade associations to organize a workshop with EMA in 2013.

Guidance on technical aspects of implementation of QbD approaches is given in Part 1, Concepts and Principles, and Part 2, Illustrative Example, of the ISPE PQLI Guide series.

References

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