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THE REGULATORY FRAMEWORK

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THE EARLY DAYS

The United States Food and Drug Administration (FDA) took the lead in publishing its vision for drug regulations, current Good Manufacturing Practices (cGMPs)) for the 21st Century in 2003 (FDA, 2003) and 2004 (FDA, 2004, 2006). This initiative began in 2002 and pertains to veterinary and human drugs and select human biological products such as vaccines. The FDA's goal is to transform the current chemistry, manufacturing and controls (CMC) review into a modern, science and risk-based pharmaceutical quality assessment, which is expected to result in an increased number of successful drug applications, consequently providing more and better treatment options for patients.

In particular, the Agency's objectives are:

- to encourage the early adoption of new technological advances by the pharmaceutical industry
- to facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance

- to encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas

- to ensure that regulatory review and inspection policies are based on state-of-the-art pharmaceutical science

- to enhance the consistency and coordination of FDA's drug quality regulatory programs, in part, by integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities

We will find these objectives reflected later in the International Conference on Harmonisation (ICH) *(www.ich.or*g) ICH Q8, Q9 and Q10 guidance documents.

Various departments at the FDA are involved with or tasked with activities in support of the desired state.

- In October 2005 the FDA announced the creation of the Office of New Drug Quality Assessment (ONDQA) effective November 1, 2005. ONDQA is a division of the Office of New Drug Chemistry (ONDC) within the FDA's Office of Pharmaceutical Science. ONDQA was created to facilitate the implementation of a modern, risk-based pharmaceutical quality assessment system to replace the CMC review system in ONDC. ONDQA is responsible for evaluating CMC section of Investigational New Drug (IND) Applications, New Drug Applications (NDA), and NDA supplement for drugs regulated by Center for Drug Evaluation and Research (CDER).

- Generic drug applications are managed by the FDA's Office of Generic Drugs (OGD).

- The Office of Pharmaceutical Science (OPS) Process Analytical Technology (PAT) Initiative.

- The Office of Biotechnology Products (OBP) protects public health by assuring the quality, safety, efficacy, availability and security of therapeutic protein and monoclonal antibody products.

The FDA has made a conscientious effort to restructure as needed and to align its operations with the changing regulatory framework. The FDA, like all other agencies, will have to change the way it addresses regulatory submissions/applications. Its assessment will focus on critical quality attributes (chemistry, pharmaceutical formulation, and manufacturing processes) as they relate to product performance.

These three offices in the OPS are focused on facilitating the implementation of Quality by Design (QbD):

- Office of New Drug Quality Assessment (ONDQA)
- Office of Biotechnology Products (OBP)
- Office of Generic Drugs (OGD).

They are developing new paradigms for submission reviews, and in some instances even a new set of skills (Winkle, 2010). The reviewers expect to see evidence that companies, as a result of implementing QbD, use high quality pharmaceutical science and engineering along with a structured set of product and process development tools and an overarching governance and project management process.

All three offices are developing processes which satisfy the needs of their particular regulations and products. However, all three processes have the same objectives, namely a better understanding of product development and manufacturing processes.

In October 2010 FDA published a report titled "Advancing Regulatory Science for Public Health" that stresses again the importance of the Quality by Design initiative:

> **Modernized manufacturing and product quality**
> FDA is leading efforts on "Quality by Design (QbD)," which applies regulatory science to modernize the understanding and control of medical product manufacturing processes. Advances in regulatory science will not only ensure better quality, but could also lower development and manufacturing costs. Areas of investigation supported by FDA include (1) continuous processing, in which materials constantly flow in and out of the equipment and reduce overall manufacturing time and cost; (2) the use of process analytical technology (PAT) to monitor and control manufacturing processes as opposed to just testing products; and (3) new statistical approaches to detect changes in process or product quality. Applying these approaches will help control complex manufacturing processes, enhance their efficiency and provide more reliable products to patients. In addition, new technologies such as flexible manufacturing facilities and the use of modular and disposable equipment can speed production of products in routine and emergency situations.
>
> There is much at stake for public health. FDA will continue to strengthen mission-critical science within the agency while exploring new and exciting partnerships with other government entities, industry, and academia with the intent of transforming lives and safeguarding the public's health.

The European perspective on QbD has been covered in several presentations (Luigetti, 2008), where the current and desired states are described as:

- current state — pharmaceutical products marketed in the EU are of good quality (quality itself is not an issue) but pharmaceutical development and manufacturing can be improved

- desired state — enhanced product and process understanding through enhanced QbD approach to pharmaceutical development

It is important to understand the fundamental differences between the European authority, the European Medicines Agency (EMA) (*www.ema.europa.eu*) (formerly EMEA), and the U.S. FDA as this has led to a different approach in addressing QbD. Unlike the FDA, the EMA co-exists with over 40 national Competent Authorities (CAs) in the European Union/European Economic Area (EU/EEA), forming an integrated network of agencies. The centralised procedure for marketing authorisations (via the EMA) co-exists with marketing authorisation procedures at national level (national procedures, de-centralised procedures, mutual recognition procedures) that are all specific to each member state. The EMA is co-ordinating the existing scientific resources in the member states and provides an interface between all parties and is working towards harmonisation of regulatory and technical requirements within the EU.

The EMA has therefore put its focus first on PAT (see below) and is addressing QbD through involvement in the ICH activities.

PAT AND QbD

These two concepts developed in parallel. Following the CMC pilot program the FDA gained more clarity as to how these are mutually beneficial (Nasr, 2007).

- PAT fits into QbD in the areas of process development, manufacturing and continual improvement. Process development is facilitated via "process monitoring to develop mechanistic understanding, model building and correlations to enhance process understanding, and the establishment of design space."

- For manufacturing, PAT enables "process control to ensure robust and reproducible operations, flexible operation through process controls and real-time release."

The EMA's emphasis is on PAT. QbD approaches often need the use of PAT tools. The EMA described PAT as an enabling tool to a more systematic approach to pharmaceutical development (QbD). PAT can be seen (together with statistical process control) as the control mechanism to maintain the validated state. QbD implementation in the EU is ongoing; however, applications including QbD and PAT elements have been already authorised both in the centralised procedure and within the work-sharing project (variations to nationally authorised products). The PAT team is the key for implementation of QbD in the EU (Luigetti, 2008).

The mandate (general objective) of the EU PAT team is (Luigetti, 2008):

- a forum for dialogue and understanding between the Quality and Biologics Working Parties and the GMDP Inspectors Working Group to prepare a harmonised approach in Europe on the assessment of applications and inspections of products/systems/facilities for PAT, including QbD principles and manufacturing science in the context of PAT.

The team comprises:

- chair; five quality assessors (chemicals and biologicals); four GMP inspectors; chairs of the QWP, BWP and GMDP IWG; an observer from EDQM; EMA staff (four)

- one delegate only (either quality assessor or GMP inspector) per involved country

- representation to cover both human and veterinary products expertise (editor's note: the ICH QbD IWG does not cover veterinary medicinal products).

The team's activities include participation in workshops and conferences, site visits to manufacturers using PAT techniques and training of assessors and inspectors. They have also contributed to the mock submission examples developed by EFPIA and published guidance documents.

It was reported in late 2010 that the EMA is restructuring its PAT team (International Pharmaceutical Quality, 2010b). The team's mandate and membership structure are to change, though there was no official announcement on the Agency's website by mid-October 2010. The key issue is about communication challenges between the various working parties, which are part of the EMA's scientific committees. The PAT team is often not involved in assessments or discussions with submitters where it would be advantageous. It is not yet clear how that team will be reorganised or what its remit will be.

The German central office of German health authorities (Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten (ZLG)) has published an *aide memoire* in 2010, which is unique inasmuch as it describes "continuous validation".

There is no definition of continuous validation yet in any regulation. The terminology is used on the EMA website covering Questions and Answers on PAT (EMA, Q&A: PAT):

> Question: Would the European Medicines Agency consider a validation strategy, which eliminated the need for product equivalence validation (e.g., PQ with 3 batches) if the product/process signature were qualified at the development stage? — Mar. 2006 H+V
>
> Answer: With respect to "Process Signature" please see the answer to question 2 in this section.
>
> We are prepared to accept that where a product is subject to enhanced process understanding and monitoring that a state of *continuous validation* could be achieved. The validation strategy should be adequately justified.
>
> Continuous validation that encompasses the entire lifecycle of a drug product from development until discontinuation of distribution is based on well-founded process understanding and related control strategy. Starting point for process understanding and control strategy is to establish a suitable process design as part of pharmaceutical development in accordance with the concept of Quality by Design, which relies on a systematic and science-based approach and quality risk management.
>
> Process analytical technology (PAT) and statistical process control (SPC) are tools of continuous validation.

The *aide memoire* goes on to explain PAT in more detail, reinforcing the key principle of PAT not merely being used to measure processes, but to exercise control over them.

PILOT PROGRAMS

The FDA was and is aware of industry's hesitance to submit dossiers based on unproven guidance and concepts, which is why the Agency made it clear from the beginning that QbD-related issues would not hold up New Drug Applications (NDAs) or Supplements approval. This created a win–win situation.

In July 2005 the ONDQA announced a CMC pilot program with the following objectives:

- To provide participating firms an opportunity to submit CMC information demonstrating:
  - application of QbD principles
  - product knowledge and process understanding
- to enable FDA to evaluate submissions with PAT and QbD elements and based on QbD concepts
- to enable FDA to seek public input in developing a guidance on the new pharmaceutical quality assessment system (PQAS).

In September 2005 a second notice was published, extending the deadline for registering interest in participating to the end of March 2006. NDAs or supplements had to be submitted by end of March 2007. The pilot program provided an opportunity for firms to submit CMC information which demonstrated QbD. The Agency received nine original and three supplemental New Drug Applications (NDAs) (Winkle, 2010). Common factors included elements of design space, use of risk assessment and proposals for regulatory flexibility under the firm's quality system. Applications containing QbD elements outside of the pilot continue to be submitted. As of mid 2010 an additional 12 NDAs, 18 Investigational New Drug applications (INDs) and six supplemental NDAs had been submitted, based on QbD approaches.

ONDQA continues to expand staff skills and knowledge through workshops, case studies, meetings with industry, research and internal training.

A "pilot" was run by the EMA following the publication of the "Work Sharing Procedure for PAT Variations to Nationally Authorised Products" in June 2006, with the assessment of three applications that were all successful (Luigetti, 2008). At a conference in September 2009 the EMA reported it had only received four submissions for solid dose post-approval changes for its QbD trial in previous years and it does not expect more than one other submission for the next couple of years.

The FDA's OBP pilot program was announced in July 2008. The FDA was seeking volunteers from pharmaceutical companies to participate in a pilot program involving the submission of quality (chemistry, manufacturing, and controls) information for biotechnology products. The Agency sought more information on QbD, risk-based approaches for manufacturing biotechnology products. The pilot focussed on products reviewed by the OBP and assisted the FDA in developing guidance for industry on QbD and risk management in pharmaceutical manufacturing.

Requests to participate in the "Quality by Design (QbD) pilot program for biotechnology submissions, including Biological Licence Applications (BLAs), BLA supplements or NDAs reviewed by the FDA's Center for Biologics Evaluation and Research's (CBER) Office of Biotechnology Products" had to be submitted by 30 September 2009 (EMA PAT; International Pharmaceutical Quality, 2010b).

The FDA reported at a conference in September 2009 that it had extended the subscription period to its biologics QbD trial by a year and that results were not expected before 2015 (Concept Heidelberg QbD). As of mid 2010 a total of five BLAs and four post-approval supplements had been received (Winkle, 2010). Unsurprisingly, submissions for monoclonal antibodies (MAb) lead the field.

OBP is developing case studies. One of these, A-Mab: a Case Study in Bioprocess Development is available on the ISPE website (*www.ispe.org*). As with ONDQA, OBP also continues to expand staff skills and knowledge through workshops, meetings with industry, conducting research focused on biotechnology manufacturing science and internal training. However, OBP faces specific challenges:

- the complexity of the products requires additional considerations
- there is difficulty in identifying critical quality attributes
- biological characterisation is anything but trivial
- ensuring safety and efficacy in view of the above.

Though there is no pilot for generic products, OGD has developed a question-based review (QbR) for quality evaluation of generic drug applications (Winkle, 2010). QbR is based on QbD concepts and principles and focuses on product and process design and understanding. All Abbreviated New Drug Applications (ANDA) are now done in the QbR format. Currently OGD is evaluating the implementation of QbR and is determining the next steps for improve the process. Several workshops were held with the goal of understanding QbD for generics. It was agreed that emphasis needed to be on modified release products. Working groups have been established and these are meeting regularly.

In Japan a total of three submissions on real time release were received with regards to QbD. No further information could be obtained.

ICH

The various regulatory agencies have been channelling their efforts for improved and harmonised regulations and guidance through the ICH. ICH developed a suite of guidances that were published in 2005 and thereafter (in chronological order):

- ICH Harmonised Tripartite Guideline Quality Risk Management Q9 (9 November 2005)
- ICH Harmonised Tripartite Guideline Pharmaceutical Development Q8 (10 November 2005)
- ICH Harmonised Tripartite Guideline Pharmaceutical Quality System Q10 (4 June 2008)
- ICH Harmonised Tripartite Guideline Pharmaceutical Development Q8(R1) (13 November 2008)
- ICH Harmonised Tripartite Guideline Pharmaceutical Development Q8(R2) (August 2009).

These three guidance documents are interrelated and form the basis for national and international legislation. This book is predominantly concerned with ICH Q8 (the revision numbers are generally omitted) as it describes the concept of QbD. The ICH Q8 document is related to the Common Technical Document (CTD) format for submissions to the regulatory authorities. This document format has also been developed by ICH.

The ICH Q8 guideline describes the suggested contents for the 3.2.P.2 (Pharmaceutical Development) section of a regulatory submission in the ICH M4 CTD format. This section covers the drug product. The updates to the guideline became necessary as one annex and two appendices were added to the original guideline, providing explanations and examples to help clarify the guideline's intention.

The annex elaborates on the central concepts in the ICH Q8 guideline and provides a more comprehensive description of the principles of QbD. Guidance is provided how concepts such as Critical Quality Attributes (CQAs) and Design Space can be applied in practice. There is also reference how the Quality Risk Management (ICH Q9) process can be applied in support of the activities described in ICH Q8. Appendix 1 of the document includes a table that highlights some potential differences between a minimum approach and an extended QbD approach to pharmaceutical development and to lifecycle management. This

comparison table is a key feature of this document. Appendix 2 contains a number of illustrations and examples for clarification.

The importance of the ICH harmonised guidance documents lies in the fact that they are being developed jointly by:

- in the EU by the regulators (EMA, European Commission) and industry associations (EFPIA)
- in the U.S. by the regulators (FDA) and industry associations (PhRMA)
- in Japan by the regulators (MHLW, PMDA) and industry associations (JPMA)
- and observers/interested parties, including regulators (WHO, EFTA, HC) and industry associations (WSMI, IGPA).

Once consensus is reached on a guideline, this will have to implemented into the national regulatory system.

QUALITY IMPLEMENTATION WORKING GROUP (Q-IWG) Q&A

The ICH Q8–10 Implementation Working Group (IWG) has concluded, based on its industry/regulator workshop in Tallinn, Estonia in early June 2010 and the IWG's internal meeting the following week, that refinement of the training model used in the workshop, additional Q&As, and further evaluation of the other ICH quality guidelines for inclusion of Q8–10 principles are needed (International Pharmaceutical Quality, 2010a).

Future areas of focus for the IWG will include examining the remaining technical and regulatory gaps to determine the need for development of further training — potentially including non-ICH regions — and how to proceed with assessment of the other ICH quality guidelines for consistency with QbD principles.

Around 240 participants from 34 countries attended the IWG workshop, which was organised by PDA (*www.pda.org*), but was run entirely by ICH (*www.ich.org*). ISPE (*www.ispe.org*) organised the second event in Washington, USA and PDA were the organisers for the third and last event in Yokohama, Japan. Around 100 assessors and inspectors (about two thirds were assessors) from 32 different health authorities and 140 industry experts representing 45 companies attended. Only 10 authorities sent inspectors, the others only sent assessors. The ratio of assessors to inspectors among the regulators was about three-to-one.

The event focussed on the integration of ICH Q8, Q9 and Q10, not the individual guidances. The first day was reserved for plenary presentations, which centred on a (mock) case study, developed specifically to highlight the potential these guidances provide. The expectation was that the participants would have detailed knowledge of the case study when they attended the event.

The case study followed the application of QbD for both the API and drug product. The API for the product was a single neutral polymorph with low solubility and high permeability, or Class II under the Biopharmaceutical Classification System (BCS). The solubility (dissolution) was affected by particle size, and the API degraded by a hydrolytic mechanism.

The drug product was an oral immediate-release tablet produced by a direct compression manufacturing process. An *in vitro/in vivo* correlation (IVIVC) had been established allowing dissolution to be used as a surrogate for clinical performance. The blending process control options in conventional versus real-time release testing were explored at the workshop.

With the case study as an anchor for the discussions, breakout sessions followed on design space, control strategy, quality risk management, and pharmaceutical quality systems through which the participants rotated. In the breakout sessions, the IWG solicited input from the participants on three primary questions related to the ICH Q8–10 guidances:

- are we clear with the key messages?
- are there practical concerns on implementation?
- where is more clarification required for practical harmonised implementation?

The workshop provided a truly unique opportunity for meetings and open discussions between assessors, inspectors and industry representatives. The following are notes taken by the author during the Tallinn event that are specific to ICH Q8.

Design space

ICH representatives stated that design space is not always an appropriate way to describe the operational limits of a process. In discussions it became clear that processes with only one CQA would be such a case.

No explanation could be given why a design space, which is nothing but a mathematical model, (in the opinion of all the Agency representatives the author

spoke to), has to be at least three-dimensional. This concept excludes all processes that are univariate (i.e., with only one CQA), irrespective of whether these processes are GMP-compliant or not.

It seemed that many attendees struggled with the concept of an n-dimensional space (most think in spheres or surfaces). Also, given the uncertainties of measurements, the design space is only accurate within statistical limits. However, the examples provided depict highly accurate mathematical formulae, which contradict reality.

This highlights the issue that mathematicians, especially statisticians, will need to understand the mathematical descriptions of a design space as this exceeds the comprehension and understanding of those typically involved in GMP and compliance.

Interesting and unanswered questions remained, such as:

- Will the expansion of the design space post-approval result in a simple or a complex variation?
- Is the design space scale independent?
- Is the design space valid based on the design of experiments (DoE), or are validation batches necessary?
- If validation batches are performed, do these have to cover various locations within the design space or can they all be in one location only? For reference, traditional three batch validation would seek to minimise all variation, akin to a single location in the design space. FDA representatives insisted on seeing validation batches from around the design space, though they were unable to explain why.

Controversial were statements made by FDA personnel that they insist on failed batches that will verify the boundaries of the design space (edge of failure and beyond). With the exception of some solid dosage form manufacturers, nobody else from industry indicated that they would prepare failed batches on purpose. Nowhere in the current GMPs is there such a requirement. Especially in the case of biopharmaceutical products, this could be cost prohibitive.

Prior knowledge is a key concept for providing evidence when defining the design space. Contrary to common practice and understanding (as for example in the area of intellectual property), the assessors present in the discussions would not consider allowing expert witness statements or any other prior knowledge not published in printed and controlled format.

The assessors refuted the notion that there is much knowledge in industry, especially from the development phase, that is not written down. This illustrated either a lack of understanding many assessors have of industry, or a misconception with regards to the meaning of knowledge (see notes on knowledge management below).

In order to determine and define the design space well planned DoE are required. Most chemists and pharmacists lack the mathematical (e.g., statistical) knowledge to understand how to design multifactoral experiments. Peculiarly, the case study uses univariate DoE to establish the design space.

Real time release testing (RTRT)

This is considered one of the key benefits of applying the principles of ICH Q8, Q9 and Q10. FDA made it clear that it expects companies to develop and validate in parallel all traditional end-release testing methods and perform these on full scale batches. This traditional testing must also, according to FDA representatives, be performed on a statistically significant number of batches. All this is in (seemingly obvious) contradiction to the principles of applying current scientific methods and methodologies. When asked, FDA personnel could not explain what constitutes statistically significant.

Knowledge management

It was quite obvious that the majority of attendees were unaware of the conceptual differences between data, information and knowledge, and how these can and should be managed.

Information related to real time release or design space is no longer a numeric value that can be compared to a specification, but these can be large and complex data, or complex mathematical equations. It is unclear how this can and should be represented in documents, such as submissions, batch records or Certificates of Analysis (CoA). In future, will it require a statistician to release a batch?

Even simple questions, such as the representation of electronically generated data (e.g., where before temperatures were measured once every 10 minutes, now there is a measurement every millisecond) could not be answered by the assessors present in the discussions. These are fundamental questions, independent of any of the concepts discussed at the workshop, simply reflecting today's operational environment. It is unclear how submissions containing e.g., design space elements can be well assessed when there is no clarity on even standard information requirements.

Lifecycle approach

Though it is generally accepted that a lifecycle approach is highly beneficial (e.g., through feedback loops between development and manufacture), no concepts were presented on how this could or should work in an environment with a high percentage of contract development and manufacture.

Though there was little or no explanation of what technology transfer documents should look like (i.e., contents) in order to support the principles of ICH Q8, Q9 and Q10 (e.g., QbD), the expectation is that these documents will have to look very different.

Benefits of applying ICH Q8, Q9 and Q10

As it was a common understanding that submissions based on these documents would be more complex and sizeable, the unanswered question was whether these submissions can and will be reviewed within the same timeframe as traditional submissions. It did not seem that anyone had given it much thought. If the timelines extend, this will mean time to market is extended.

If RTRT requires developing and applying all traditional testing methodology then the value of the methodology is put into question.

If the development of the design space requires the preparation of failed batches, this may become prohibitively expensive.

When asked what they would say to convince industry's leadership of the benefits of applying the ICH concepts, regulatory agency staff responded that this is all very beneficial. However, no data or supporting evidence were provided.

Attendees' understanding of the ICH guidance documents

A large number of Agency personnel expected this event to be a training course on these guidance documents, rather than an event where experts exchange views and ideas. When asked directly what their response would be if they received a submission based on the ICH guidances, several responded (in that sequence): panic, don't know what to do, will call colleagues at another agency for help.

Without close co-operation between assessors and inspectors submissions based on these new principles will face unnecessary delays and complications.

Though there was mention of training needs, no answers were given how the agencies would try and get everyone onto the same level of understanding. Given that submissions on the new paradigms will go through the centralised procedure, this is an important question (at least in Europe assessors and inspectors will not necessarily be from the same agency).

Questions and answers

During a Q&A session the ICH IWG panel provided answers to a series of questions from the audience. These included (FDA stands for FDA representatives and EU stands for EU agency representatives):

Q What will be different in the assessment process for a QbD application?
A The FDA expects a more burdensome process. The EU foresees more burdensome inspections as a consequence of the QbD application.

Q What impact have the differing regulations covering the validation process on QbD submissions?
A The FDA concedes that the current regulations are somewhat inhibiting the application of QbD. The EU would welcome harmonised regulations.

Q What are non-critical process parameters and how do these have to be described in a QbD submission?
A Both FDA and EU answered "you tell us as we don't know".

Q What is the assessors' and inspectors' level of statistical knowledge?
A The FDA suggested evaluating if there is a need. The EU said that its staff are challenged.

Q A QbD submission process is most beneficial to new products, but also harbours much uncertainty. Uncertainty and new products do not go well together. How can this be overcome?
A The FDA voiced the opinion that companies would be so pleased to get a better understanding of their products that this would outweigh any disadvantages.

A summary of the Tallinn workshop and subsequent IWG discussions was presented at DIA's annual meeting in Washington, DC in June 2010 by the CDER ONDQA Deputy Director Elaine Morefield (International Pharmaceutical Quality, 2010c). She explained that based on the discussions, "optimized plenary and breakout presentations" and an "improved structure" for the breakout session was being planned, although there would be no changes to speakers or topics for consistency reasons.

Morefield also noted that the initial finding of the IWG "is that there is not a need to directly revise existing guidelines" to include ICH Q8–10 principles but "there are gaps that we should address". The group plans to further evaluate these gaps after the completion of the three workshops, combining feedback from those sessions with its own analysis to chart the course forward.

Although the Tallinn workshop was billed as "integrated implementation training," effectively it was really more oriented toward identifying gaps than resolving issues and developing guidance. Morefield commented that the experience level with ICH Q8–10 implementation was not as high at the workshop as was anticipated. She explained that "the work group decided that true collaboration is a little bit difficult to accomplish in a situation like ICH IWG". Instead of trying to resolve all the guidance challenges in-house, the IWG is considering producing a list of topics where further publication and discussion would be useful and making that list available "so that people could potentially publish on their own in these areas." The IWG will continue to address industry questions through its Q&A mechanism.

The second and third of the IWG "integrated implementation training workshops" will have been held in Washington, DC, 6–8 October 2010, and in Japan on 25–27 October 2010, preceding the scheduled ICH meeting there in November.

The agenda for the November 2010 IWG meeting in Fukuoka, Japan included development of a training summary report, optimisation of training materials for future use, and evaluation of the need for training in non-ICH areas.

At the Tallinn, Estonia meeting MHRA Expert Inspector Ian Thrussell pointed out that "it will be many years before the people in this room and their families take Quality-by-Design medicines. Big pharma may well have been the innovators, but they are not the major providers of the medicines taken by patients today."

CURRENT LEGISLATIVE SITUATION

The U.S. FDA has updated its pre-approval inspection (PAI) compliance program guidance (CPG 7346.832) to better reflect the agency's 21st century quality initiative and the new ICH Q8-10/QbD regulatory paradigm (International Pharmaceutical Quality, 2010a). The new PAI CPG represents a significant overhaul of the program guidance to reflect current agency risk-based thinking and objectives, and is the first major revision since its original release in 1994. FDA has been working on revising the program for some time and has issued interim revisions with more minor changes in the past few years.

The reach of the new version is extended to encompass large molecules, and it includes new sections to adapt the preapproval program procedures to the evolving quality regulatory approaches.

The document also details how the agency intends to assure knowledge transfer between reviewers (assessors) and inspectors: "CDER has initiated a program to enhance the risk-based focus of drug pre-approval inspections. CDER's pre-market assignments and communications will now effectively transfer product and manufacturing knowledge from CDER to ORA inspections. Specifically, CDER staff will alert the inspection team to manufacturing and laboratory issues found during the pre-market application review. CDER/DMPQ will communicate these areas of concern via the Knowledge Transfer Memorandum (KTM) or by initiating other forms of communication, including meetings, telephone calls, or participation on inspections."

In a presentation at the DIA Annual Meeting in Washington in June 2010 Helen Winkle, FDA Director of the Office of Pharmaceutical Sciences, discussed FDA's next steps with regards to QbD. These include:

- defining "design space" and other terminology and determining regulatory pathway for future
- clarifying regulatory flexibility and issue guidance
- defining and codifying incentives
- determining whether to require QbD through regulation
- developing standards by which industry can apply QbD.

Not on the slides, but in her words, Winkle alluded to the fact that the agency considers mandating QbD as industry, and in particular generics manufacturers, are either slow to adopt or even opposed to QbD. She cited the McKinsey report to add weight to her words. Given that there are tens of thousands of companies out there potentially affected by such legislation it is somewhat contentious relying on a report that was commissioned by the FDA and is thus far from being unbiased. The industry survey that McKinsey & Co. conducted for Winkle's office shows that over the past three years most drug manufacturers have been moving through the QbD adoption process. That is in stark contrast to observations by many other industry specialists.

Given that the FDA does not even fully understand or has defined "design space" (see above) it is incomprehensible how mandating it would by default lead

to better and safer medicines, and potentially at lower cost to the consumers. If not, what purpose would such legislation serve?

The design space concept is now incorporated into EU legislation. However, it is *not* mandated.

The EMA released a revised version of its compilation of community procedures on inspections and exchange of information on the "Conduct of Inspections of Pharmaceutical Manufacturers or Importers" in March 2010 (EMA, 2010) to align with recent revisions to its EU GMP Guide reflective of ICH Q8–10 principles (International Pharmaceutical Quality, 2010a). In this revised document, wording has been added to recommend the use of risk-based planning for inspections, which brings also the inspection process itself in line with the risk-based compliance approach stipulated by the regulations.

At the annual interested parties meeting between the EMA Good Manufacturing Practice (GMP) Good Distribution Practices (GDP) Inspectors Working Group and the Pharmaceutical Industry in September 2010 at the EMA's offices in London, UK, a long list of revisions to the existing European regulatory framework were presented. In particular, the revision to the introduction to the GMP guide will contain references to ICH Q9 and ICH Q10 (personal notes taken by the editor). Other changes necessitated in part by the ICH Q8, Q9 and Q10 guidances will affect Annex 15 on validation and qualification, and Annex 17 on real time release.

ICH is working on the ICH Q11 guideline on drug substance development and manufacture. This guidance will cover manufacturing, which is not covered by the scope of ICH Q8.

A harmonised global approach to QbD, from both an application assessment and an inspection perspective is likely to be a long way away. As most agencies, especially in Europe, are downsizing significantly, smaller agencies will find it even more challenging to cope with QbD applications. Apart from the differences within the various global regulatory systems and the nationally diverse interpretations of the regulations, there is also the matter of (lack of) training and education of agency staff, necessary for achieving harmonisation across the globe.

INDUSTRY ORGANISATIONS AND THEIR ROLES

There are a variety of organisations active in the field of QbD, mostly in Europe and the U.S. Among the key players are the Parenteral Drug Association and ISPE, to name two non-for-profit organisations. The importance of their input is also

demonstrated by the fact that they were the organisers for the ICH Implementation Working Group events in 2010 in Tallinn, Estonia, Washington, U.S. and Yokohama, Japan.

PDA's program Paradigm Change in Manufacturing Operation (PCMO) was launched in 2009. The purpose of this new project is to provide practical assistance to industry for the implementation of the new paradigm as described in the ICH Q8 (Pharmaceutical Development, including Q11), Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality Systems) documents and to highlight inter-relationships. It covers the daily business in operations and manufacturing, and focuses on areas of interest to inspectorates while providing a holistic lifecycle approach towards pharmaceutical manufacturing.

The PCMO program intentions are to:

- enable an innovative environment for continual improvement of products and systems
- integrate science and technology into manufacturing practice
- enhance manufacturing process robustness, risk based decision making and knowledge management
- provide scientific expertise according to new paradigm
- give examples on "how-to-do"
- propose manufacturing topics not covered so far by other organisations
- establish best practice documents/training to assist industry in implementing the ICH Q8, Q9, Q10 and Q11 guidelines
- dialogue with regulators focusing on manufacturing needs.

The project fosters and facilitates communication among the experts from industry, university and regulators as well as experts from the respective ICH Expert Working Groups and Implementation Working Group

This project, which addresses sterile drug products as well as non-sterile drug products and biological products and supply chain issues, is organised into several task forces, covering these themes:

- lifecycle approach

- quality systems
- process management
- quality risk management.

These PCMO task forces identified a series of projects under their oversight, which are open to new volunteers and reviewers. At the end of 2010, the project list is as follows.

- IMP manufacturing and distribution (#L01)
- implementation of quality by design in manufacturing (#l02)
- technology transfer (including discontinuation) (#l03)
- from warehouse to patient (supply chain/good distribution practice) (#l04)
- capture knowledge management during commercial manufacturing (#q01)
- management of suppliers and contractors (including audit) (#q02)
- establishing a Pharmaceutical Quality System (PQS) in a company (#Q03)
- concepts for training (#q04)
- from process validation to process verification (#p01)
- concepts of cleaning validation (#p02)
- how to improve robustness of a manufacturing process (#p03)
- utilisation of statistical methods for production and business processes (#p04)
- corrective and preventive actions (CAPA) (#P05)
- risk-based manufacturing: TR 44 and list of hazards and potential controls (#R01)
- risk-based scheduling of audits (#R06).

The output from these activities may range from publications, such as PDA Technical Reports, technical bulletins, articles in the PDA Journal of Pharmaceutical Science or PDA Letter, to presentations at conferences, e.g., the PDA/FDA or PDA/EMA conferences, to training courses, which may for example be delivered as webinars or through PDA's Training and Research Institute (TRI).

ISPE has named its program "Product Quality Lifecycle Implementation" (PQLI) (Concept Heidelbeg QbD, 2009). The Product Quality Lifecycle Implementation (PQLI) initiative was launched in June 2007 to help industry find practical, global approaches to implementing ICH guidances Q8 (R2)

Pharmaceutical Development; Q9 Quality Risk Management; and Q10 Pharmaceutical Quality System.

Through PQLI, ISPE is spearheading the effort to provide the technical framework required for the implementation of these guidelines as well as the more-recently initiated topic Q11 Development and Manufacture of Drug Substances, including a better understanding of the "enhanced Quality by Design (QbD) approach".

PQLI is projected to be at least a five-year initiative that has started with highly interactive fact-gathering sessions held in locations in the three ICH regions; with working groups that will continue to collect and process that information for distribution as white papers for comment.

ISPE mention on its website that PQLI:

- demonstrates there are many right ways, not just one way, to successfully implement ICH guidances in a global environment and throughout the lifecycle of a product
- focuses on science- and risk-based approaches to product realisation and manufacture
- welcomes contributions from all scientists, engineers, regulators, and industry leaders committed to supporting these principles.

An ISPE PQLI Good Practice Guide (GPG) Series is being developed. The series will consist of the following:

- overview of product design, development, and realization
- critical quality attributes and critical process parameters
- design space
- control strategy
- a small molecule illustrative example.

A biotech team is developing a Guide to extend and expand the concepts discussed in the A-Mab case study. This document, titled "A-Mab: a Case Study in Bioprocess Development" was released as version 2.1 on October 30, 2009.

The first document in this series is the "Overview of Product Design, Development, and Realization, a Science- and Risk-Based Approach to Implementation" document, released in 2010. Its Table of Contents is as follows:

It is helpful to understand the relationship between PDA's Paradigm Change in Manufacturing Operations (PCMO) and ISPE's Pharmaceutical Quality Life Cycle Implementation (PQLI) Initiatives. Whereas ISPE's PQLI initiative focuses on regulatory (CMC) aspects, PDA's PCMO program focuses on the implementation in the commercial manufacturing part of the lifecycle with a link to inspection activities.

PDA and ISPE have performed a detailed analysis of their two key initiatives PCMO and PQLI in order to ensure coordination and prevent unnecessary duplication. As a result, program leaders have determined that there is no significant overlap between the efforts of each organisation. In those cases where overlap has been identified, agreement was reached to realign the scope and to work together to avoid any duplication of effort.

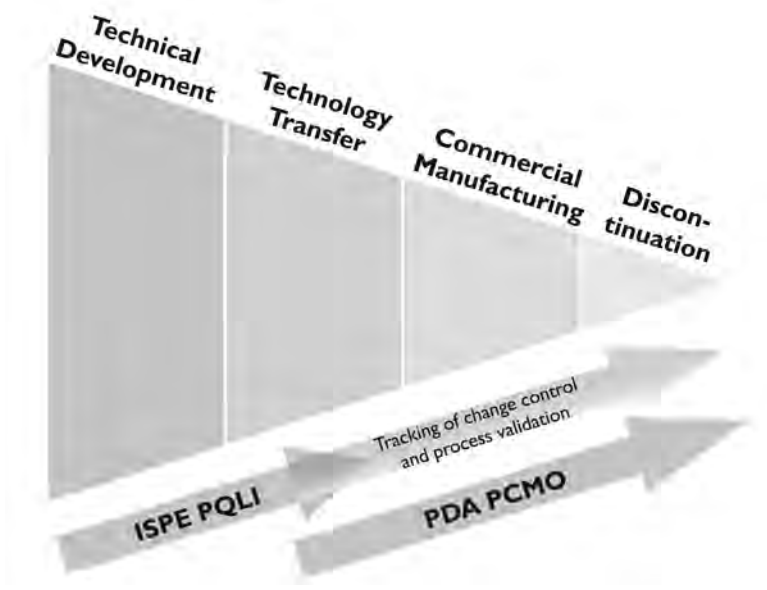
In summary, both PDA and ISPE have agreed that the PCMO and PQLI deliverables are:

- different
- complementary and
- not in competition.

With this in mind, we are determined to utilise the expertise of two organisations to find practical approaches for the changing pharmaceutical environment according to the new paradigm laid down in ICH Q8 (Q11), Q9 and Q10 (PDA, 2010).

Figure 2.1 illustrates the relationship between the ISPE and PDA programs.

Figure 2.1 PCMO and PQLI along the lifecycle



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WHO *www.who.int*

WSMI *www.wsmi.org*

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Siegfried Schmitt, Principal Consultant, joined PAREXEL Consulting in 2007. He provides consulting services to the medical device and pharmaceutical industry on all aspects of regulatory compliance, particularly the design and implementation of Quality Management Systems and Competitive Compliance.

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Dr Schmitt is an active member of various industry associations, including DIA, PDA, RAPS and ISPE, conference presenter and organiser of international events. He is also an accomplished author and editor, having won the coveted "distinguished PDA author/editor award" for 2008.

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