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This article presents the results of a survey conducted by the ISPE United Kingdom/Ireland PAT COP.

The Business Benefits of Quality by Design (QbD)

by Theodora Kourti and Bruce Davis

Introduction

he business case for Quality by Design (QbD) was a hot discussion topic during a meeting of the Process Analytical Technology Community of Practice of United Kingdom/Ireland (PAT COP UK/IR). The discussion concluded with a plan to conduct a survey that would aim to gather actual experiences, examples and candid industry opinions on the business benefits of QbD. The questions were designed to cover a wide range of issues, including the use of modelling and PAT tools. A standardized set of interview questions were produced and sent out with a letter to individuals that agreed to be interviewed. All questions that would lead to commercial bias from vendors, suppliers, or pharmaceutical companies were avoided. The survey topics are listed in Table A.

Survey Topics

- Elements of QbD
 - Does the company apply elements of QbD?
 - What business units apply QbD, i.e., new/legacy products; R&D/manufacturing?
- Drivers for QbD, i.e., regulatory, management, other?
 Benefits of QbD, including metrics and possible examples,
- i.e., regulatory flexibility, cost reduction?
 Additional level of resources and cultural changes to achieve QbD
- Regulatory flexibility, i.e., experiences from ΩbD interactions/filings
- ObD for in-licensed products and third party manufacturers
- Use of modelling in QbD
- Regulatory response to modelling
- PAT tools to support QbD
- Desired sensor technology

•	Future of	ʿ ObD in you	r company	(interviewees	opinion)
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Some of the interviews were conducted with individuals by telephone, while others were conducted with a group of company employees representing different business units who compiled their answers and replied by mail to one questionnaire. Written answers also were produced for the telephone interviews and these were approved by the interviewees. Interviewees were from development, manufacturing and regulatory while the companies range from large and small, both small molecule and biotech.

In total, we received 15 completed questionnaires from 12 companies. The responses were received between November 2010 and September 2011. The companies agreed to have their names listed, but it was agreed that the identity of the individuals or relation between company name and answer would not be revealed. Not all of the comments presented here represent "company" views; some are the opinions of the individuals interviewed. One company response indicated "...that they do not apply QbD..." and this company is not named here as it would be uniquely identifiable. The company deals with early stage cell development and their answer was that "Customers do not ask for QbD." The other 11 companies, listed in Table B, have adopted the use of QbD elements to varying degrees.

Companies in the Survey		
	Abbott (USA)	
	AstraZeneca (UK)	
ł. –	Bristol Myers Squibb (UK and USA)	
	GSK (USA)	
i.	Jazz Pharmaceuticals Inc. (USA)	
i.	Eli Lilly and Company (USA)	
	Merck (USA and Ireland)	
	Pfizer (USA, 2)	
	Centocor Biologics (J&J) (Ireland)	
0.	Vertex Pharmaceuticals (USA)	
1.	United Therapeutics Inc (USA)	
ab	le B. Companies Interviewed that Perform	

Table B. Companies Interviewed that Perform Elements of QbD. Where there are two locations mentioned it indicates that we received a completed questionnaire from each location; from one company we received two completed questionnaires from different groups in the USA (14 questionnaires in total).

Table A. Survey Topics.

Presenting the Outcome of the Survey

The survey responses provided a great deal of revealing material. The interviewees provided candid answers, including interesting case studies and examples. Presenting the answers has not been an easy task because we wanted to retain the richness of the answers as much as possible. So instead of providing charts with numbers, we chose to present the answers in the narrative form. The answers from the companies for most of the questions are listed in Tables, edited for briefness, but presented in such a way that they reflect the context in which they were given. For example, nine out of the eleven companies indicated that *"increased process capability, process robustness, and reduced atypicals*" was seen as a benefit. Rather than simply putting the number (9/11) next to this benefit we also listed the comments associated with the benefit, for example:

- Cpk has increased significantly; demonstrated increased process capability by comparison of Cpk values for legacy products versus QbD products.
- Zero batch failures in a year compared to high batch failures in the past.
- Processes are more robust.
- Batch failures have been reduced significantly.
- Certainly, we see improved process robustness and the potential for improved manufacturing efficiency worldwide.
- Improved process robustness; reduced variability.
- Amount of rejected batches is below industry norms.

In addition, we chose two companies (which we designate as A&B) and we list the answers from interviewees of these companies at separate tables, to the extent that the answers do not identify the company. The objective of this approach was to help the reader develop an appreciation of the responses from interviewees from the same company to several questions. For example, if the interviewees from one company report certain benefits from QbD, what did they tell us about requirements for resources for the same company? What about dealing with third party manufacturers? What type of modelling was used in the QbD framework by this same company? Both companies A& B have embraced QbD as a way of working. For one of them, it was indicated that "Our intent is that 100% of our products will follow the QbD framework" while for the other company, it was stated that "QbD principles (i.e., science- and risk-based approach leading" to product and process understanding) are embedded in all that the company does. It is part of the company philosophy and the way of working."

We encourage the readers to read the document as a whole, rather looking at isolated tables, so that they can get a better appreciation of the relationships between answers but more importantly of the overall prevailing feeling about QbD.

Embracing the QbD Framework

Eleven out of the twelve companies had used elements of QbD to various degrees. Three small companies demonstrated an

impressive QbD record, and the company philosophy is to embrace QbD long term.

The responses from the large pharmaceutical companies and the number of applications in QbD vary, as shown from the following answers:

- Our *intent* is that 100% of our products will follow the *QbD* framework.
- Filed one product with QbD and *intend* to do all time.
- Filed one product and **selectively** apply QbD elements to others.

Overall, interviewees from ten companies indicated that it is their company's intention to apply QbD to **all** new products; one company seems to apply elements of QbD selectively. Five companies also apply QbD on existing products especially when there is transfer to a new site. QbD is applied to both development and manufacturing; when the companies use third parties to manufacture their products, the elements of QbD applied depend on the company, as discussed later in this article.

Elements of QbD

Interviewees were asked to list the elements of QbD that were applied in their company. Table C provides the answers from companies A and B. The answers from other companies were similar and frequent reference was made to the following:

- Principles and concepts as defined in ICH Q8, Q9, and Q10; risk-based approach
- Real Time Release Testing (RTRT)
- Extensive use of statistical and mathematical modelling
- PAT tools
- · Ensuring link to in-vivo understanding
- Risk assessments; Critical Quality Attributes (CQA) risk assessments
- Fundamental process understanding; full mechanistic understanding
- Using science to improve product and process understanding

Elements of QbD Applied in the Company

Company A

 The principles and concepts as defined in ICH Q8, Q9, and Q10 and step 3 of ICH Q11, and all of our products are intended to follow this framework. The science- and risk-based framework and advanced understanding of defining design spaces based on both first principles and empirical understanding. In addition, advanced use of enhanced control strategies has increased, integrating PAT with technology platforms. Modelling is actively used for scale-up and scale down and to confirm our technical understanding.

Company B

 ObD principles (i.e., science- and risk-based approach leading to product and process understanding) are embedded in all that the company does. It is part of the company philosophy and the way of working. The company is aware of ICH 08/09/010 terminology and recognizes the value in use of a common language across the industry. We recognize that during development, data is sparse so we want to build in maximum flexibility and uncover all potential problems during development.

Table C. Elements of QbD - Companies A&B.

Drivers for QbD			
Company A			
 The opportunity in QbD was to showcase a lot of the technical and risk- based approaches we were already doing and extend their practice deeper into our development and supply framework. We felt from a patient's perspective, this was the right thing to do. We see this as a win-win-win for the pharmaceutical industry, health authorities around the world and patients/customers. 			
Company B			
• It's the company philosophy to use QbD principles. It is not for regulatory			

reasons.
The key drivers are being able to produce the product and reliability of supply. We concentrate on "getting the product right."

Table D. Drivers for QbD - Companies A&B.

- Quality Target Product Profile (QTPP) (patient centered design)
- Quality Risk Management (QRM)
- Multi-factorial Design of Experiments (DoEs); parameter risk assessments and prioritizations
- Use of modelling and PAT to guide process development and scale-up
- Integrated control strategies
- Design space
- Raw material attributes and relation to quality

Drivers for QbD

There were several reasons identified as the drivers for em-

Drivers for QbD

- As part of the FDA Pilot program in 2004
- It was not done for regulatory pressure, but it was recognized that the regulators would be inspecting the manufacturing site and so the company wanted to achieve a high level of confidence from the regulators regarding the site's approach and capability.
- It is company policy now, but the history is that the approach was driven by a relative small group of like minded individuals (in early stages using PAT tools to enhance product understanding) and the approach was later accepted by the company as an improved way to work for development of new products; we were involved in the FDA pilot program and learned from this.
- From senior management no pressure from regulatory authorities; the company is a science-based company and applies these principles from late Phase II.
- At early stage, because of the regulatory climate and drive from the FDA. Management policy lead. Now fully integrated as part of our work
- ObD is being used to get a standardized approach across the organization to technology transfer and the introduction of new products/molecules.
- The promise of regulatory flexibility was the drive initially. Currently, it is becoming a norm for developing new products within the firm. Additionally, this (science-based approach) is an expectation from major regulatory agencies.
- The primary driver for the application of QbD is the need to improve product and process robustness and enhance process understanding. Improved product and process understanding enables further changes to a product throughout its lifecycle, including the increase ease in technology transfers between sites. Regulatory flexibility is also a benefit, but lack of global harmonization limits this currently.
- A desire for improved product and process understanding; a more systematic approach across the development portfolio; to continue to improve patient safety and efficiency; to improve manufacturing efficiency; and to improve development efficiency.
- ObD implementation aligned with an internal redesign of the product development process in which ObD deliverables were imbedded into the process. ObD was viewed as an enabler of increased process and product understanding and improved regulatory submissions.

Table E. Drivers for QbD – Rest of Companies.

bracing QbD, including senior management and the need to standardize approaches, while the FDA pilot served as a driver for some companies. However, the main driver for continuing QbD was identified as "process and product understanding and improvement in process robustness."

This response was provided by every single interviewee in different parts of the interview. The answer to whether the reason they started QbD was *regulatory pressure* was negative from all of those interviewed. *Regulatory flexibility* was not a strong driver either and was only mentioned as the driver by few companies. Table D provides the answers from companies A and B, while Table E provides the responses for the rest of the companies.

Benefits of QbD

The following statements reflect the feeling among the interviewees regarding the overall benefit of QbD:

• "There has been a knowledge adjustment; undoubtedly applying a QbD process in development has improved process

ObD Benefits

Company	Α

Benefits from Cost Savings

- Saved more than \$60 million
- ObD processes have "zero process atypicals" to date
- Saved API costs in technology transfer
- Advanced enhanced control strategies with global regulatory acceptance that provided greater manufacturing flexibility

Benefits in Process Understanding

- Greater process understanding and greater assurance of product quality
- We gained experience following the science- and risk-based framework and advanced our understanding of defining design spaces based first principles and mechanistic understanding.
- Advanced use of enhanced control strategies by integrating PAT in our technology platforms.

Benefits in Work Practices

- Manufacturing is closer to development
- Improved internal business processes (e.g., technical reviews are much more integrated)
- API and Formulation Development are much closer as a lot of the QbD work is done jointly
- Ensuring we have adaptable quality systems to support advanced scientific concepts and enhanced control strategies (e.g., predictive modelling and PAT)
- We highlight that QbD also can be another mechanism to unleash the scientific and innovative creativity of our scientists

Company B

Benefits from Cost Savings

- ObD processes have "zero process atypicals; we used to have processes with high batch failures in a year"
- Improved product quality
- Improved product robustness
- A stable product with a long shelf life

Benefits in Process Understanding

- Greater process understanding
- Improved formulation design:
 - Simplifying the number of unit operations.
 - In development, we have taken on more complex formulations and made them work (e.g., one development provided a stable product with a long shelf life, whereas initially this was not the case). This was achieved by thorough investigation and understanding of the processes involved.

Table F. Benefits of QbD - Companies A&B.

QbD Benefits				
 Improved Process and Product Knowledge and Understanding It has meant clearer understanding of what matters, improved understanding of the specifications; we are proposing more meaningful specifications Advanced our understanding of defining design spaces based on first principles and mechanistic understanding Helping manufacturing sites understand the potential impact of some changes they might want to make Achieved in some cases full mechanistic understanding which we didn't have in the past Improvement in Product Quality and Product Robustness/Reproducibility Corresponding improvement in product quality has been clearly demonstrated 	 Improved Development Capability, Speed, and Formulation Design Better development processes has been our main gain More structured and using science to improve product and process understanding Capability of development has improved There has been a step change in the capability of the development organization Speedy development Develop a formulation in six weeks rather than six months using knowledge base Reduced experimentation time 			
 Gain also has been in robustness (e.g., avoid bio-equivalence failures) Improved product reproducibility 	 Drug Product Development has data (metrics) that demonstrated improved development efficiency Fast tech transfer to manufacturing 			
 Improved Control Strategy Better process control with on-line techniques demonstrated and established. Have gone through the challenge of validating on-line sensors Advanced use of enhanced control strategies by integrating PAT in our technology platforms Advanced enhanced control strategies with global regulatory acceptance that provided greater manufacturing flexibility Ensuring we have adaptable quality systems to support advanced scientific concepts and enhanced control strategies (e.g., predictive modelling and 	 Our overall goal: double the number of products introduced in half the taken Improved formulation design Simplifying the number of unit operations Converting a cold chain product into a room temperature product In development, we have taken on more complex formulations and mathem work, e.g., one development provided a stable product with a lo shelf life, whereas initially this was not the case. This was achieved thorough investigation and understanding of degradation processes. 			
 PAT) Control strategy is more holistic than just specifications on drug substance and drug product; the control strategies have become more explicit, are more integrated across the entire process, and are focused on patient impact (CQAs) 	Cost Reduction Benefits • Saved more than \$60 million • Leaner and more agile supply chain; reduced stocks • Main benefit is having a leaner and more agile supply chain; reduced cost of supply; drug product has gained via shorter supply chains and we measure this.			
 Fast and Reliably to Market QbD is viewed as a means of reliably getting products to the market. The specific site believes that they have a head start on the other sites and competitors having been through the QbD /tech transfer process before 	 RTRT has given benefits on improved supply chain. Significant stock improvements involving tens of millions of dollars Saved API costs in technology transfer Savings due to reduced number of investigations Improved process inductors indirect product costs 			
 Increased Process Capability/Process Robustness; Reduced Atypicals Cpk has increased significantly; we have demonstrated increase process capability by comparison of Cpk values for legacy products versus QbD products In the manufacturing process, we used to have high batch failures in a year, and now we have zero 	 Improved process robustness improves indirect product costs (investigation time, rejects, etc.) Reduced development cost Reduction in lab expenses for each batch, as a result of RTRT RTRT has had a positive impact on direct product costs due to the reduction in lab expenses for each batch. Yield Increase We are now measurably producing more product. Engaging Science in Profitable Ways We gained experience following the science- and risk-based framework and advanced our understanding. Has provided an awareness of application of PAT methods. (Before QbD, it was somewhat weaker). Use of PAT has provided enhanced understanding of the process. (See detailed section in PAT later). Due to PAT, testing moved upstream and RTRT enabled. (See effect on cost 			
Processes are more robust Batch fails have been reduced significantly				
 Certainly, we see improved process robustness and the potential for improved manufacturing efficiency worldwide Improve process robustness; reduced variability Amount of rejected batches is below industry norms Reduced number of deviations per batch for QbD products. Increased process knowledge and efficiency/robustness. Implications of process robustness leading to process validation QbD processes have zero process atypicals to date 				
Reduce Impact of Raw Material Variability Variability in raw materials has been detected and impact reduced using QbD 	reduction). Improvement in Collaboration between Business Units and Enhanced Work			
 Batch fails due to raw materials have been reduced significantly Broadened the acceptable range of raw materials and developed knowledge of sensitive areas which are then highlighted Better understanding of material quality requirements 	 Practices Two way feedback between R&D formulation and manufacturing/commercial: interchange/discussion on the key parameters to deliver a robust product to manufacture Closer cooperation between development and commercial operations 			
Improved Product Stability A stable product with a long shelf life Greater shelf life stability achieved 	 Manufacturing is closer to development API and Formulation development are much closer as a lot of the QbD work is done jointly Internal business processes (e.g., technical reviews) are much more integrated Better understanding of the process and control strategies for an individual project has lead to a greater shared knowledge resulting in a more consistent approach across functions and projects 			
 Improved Scale Up Efficiency/Speed Applied a blending PAT tool that improved scale-up understanding and efficiency Improved scale-up speed (due to science-based approach) 				
Standardize Ways of Working • Streamlining the process • • Standardizing the platform for bringing new products on stream	 Skill development, e.g., bringing in new skills such as modelling, chemometrics We highlight that QbD also can be another mechanism to unleash the scientific and innovative creativity of our scientists 			

Table G. Benefits of QbD – All Companies. The table includes answers from A&B to provide a complete picture of the benefits mentioned. Comments under each benefit are verbatim comments from companies.

Additional Resources		
Company A		
 There is pre-investment in training and methodology/tool development. If done well, with strong alignment and support across the entire company, the resource commitment is not as large as one might think. Return on investment is evidenced by the business benefits obtained to date. 		
Company B		
 No additional resource From the outset, we set out to recruit people that have these skills. We expect them to use these skills to ensure products are well understood. 		

Table H. Additional Level of Resources to Enable QbD – Companies A&B.

and product knowledge and understanding."-This comment reflects the view by all interviewed.

- "Control strategy is more holistic than just specifications on drug substance and drug product; improved process understanding and implications on process robustness leading to process validation (PV). The control strategies have become more explicit, are more integrated across the entire process, and are focused on patient impact (CQAs). This has lead to a better understanding of the process and will lead to higher quality products."
- "Greater process understanding and a corresponding improved product quality has been clearly demonstrated. We have demonstrated increased process capability by comparison of Cpk values for legacy products versus QbD products. This same improvement is also demonstrated through reduced number of deviations per batch for QbD products. While improved process robustness improves indirect product costs (investigation time, rejects, etc.), RTRT has had a positive impact on direct product costs due to the reduction in lab expenses for each batch."
- "We gained experience following the science- and risk-based framework and advanced our understanding of defining design spaces based on first principles and mechanistic understanding."

Table F provides the benefits listed by the interviewees for the two companies, A and B; Table G provides the benefits for all of the companies. Some companies provided monetary values. Savings in inventory due to Real Time Release Testing (RTRT) and the cost reduction of API in technology transfer were mentioned. Another very frequent response was the ability to deal with more complex formulations due to better understanding, for example:

- "Converting a cold chain product into a room temperature product"
- "We have taken on complex formulations and made them work (a stable product with a long shelf life, whereas initially this was not the case)"
- "Simplifying the number of unit operations"

"Improvement of process and product understanding" was mentioned in 14 out of 14 questionnaires, as the main benefit of QbD.

A set of metrics was provided together with the questionnaire, which may be used to demonstrate "hard" QbD benefits. The interviewees were asked to consider these metrics when answering. This Table is shown in Appendix I. Most of the companies were not able to provide information based on those metrics, at this point in the interview, but some mentioned that they were developing metrics of their own. Any metrics that were provided are shown in Table G.

Table G lists the benefits by categories. *Shelf life stability improvement* has been mentioned very frequently as

Additional Resources

- The first prototype obviously expends a higher cost. No cost analysis
 was undertaken because the practices tend to be intrinsic to the way the
 company has always worked.
- We have no additional resource, but from the outset we set out to use ObD principles and it was part of the process for designing and specifying equipment.
- I don't believe it is more expensive (we haven't measured it with metrics), but the capability of development has improved. Processes are more robust.
- Initial training and developing the approach has been a significant cost in time (which has been costed using Effort Tracking System). For the ongoing application of these techniques, the additional effort is almost negligible.
- As a personal impression (and we haven't done a cost analysis), the cost and resource in the long term do provide a good return, but one has to appreciate that the benefits only come two to three years post launch.
- Skill development, e.g., bringing in new skills such as modelling, statistics
- No additional resources because QbD is embedded in the production process. It was a good return of investment; we believe that the amount of rejected batches is below industry norms.
- We believe that a more appropriate view is that QbD is a transfer of resources from a down-stream corrective mode to an upstream proactive mode; QbD approaches have already demonstrated that they result in more robust product and processes which reduces the resources needed to investigations, corrective actions and product rejects in commercial operations.
- Added a dedicated Risk Assessment Department
- In drug substance development, mix of chemists/engineers has shifted toward engineers, but no overall increase in resources. In drug product development, mix of pharmaceutical scientist, engineers, and analytical chemist have been important to implement the process; we have not changed these ratios. Have not increased resources. No Data for ROI.
- ObD provides a good ROI.
- A cross-functional governance team was formed to drive implementation
 of QbD. This governance team launched various project teams to address
 certain topics. After the project phase was completed, the associated
 headcount needs were absorbed into normal business. Continuous
 improvement of our programs is being managed through both base
 headcount as well as continuous improvement (6 sigma) headcount. QbD
 is considered to provide a good return on investment; however, an overall
 cost analysis has not been performed.
- For product development, there has been an increase in the degree of experimentation required to define the design space; however, this has not translated to additional people resources. Some resources are required to increase capability, e.g., chemometrics, modelling, PAT.
- From a manufacturing perspective, the additional level of resource is minimal. QbD has manufacturing more involved earlier in the development process which has tended to shift the resource timing and focus, but the "net add" is minimal. Also, during process installation phases (commissioning and qualification), there is some minimal incremental effort increase. As for good investment, it is too early to tell. The benefit has not yet been realized due to minimal experience.

Table I. Additional Level of Resources to Enable $\ensuremath{\mathsf{QbD}}$ – Rest of the Companies.

	Regulatory Interactions		
Com	pany A		
 F r F b V S V 	Regulatory flexibility is not our primary driver for adopting QbD. QbD is a core element to our overall company Quality Strategy. We have had some regulatory flexibility, but it has been limited to date. Regulatory improvements are harder to quantify than the benefits secured by science and risk based product and process development. Ne have used predictive models in QbD applications and have been successful with regulatory acceptance. Ne developed advanced enhanced control strategies with global regulatory acceptance that provided greater manufacturing flexibility		
Company B			
• 1 	t's the company philosophy to use QbD principles. It is not for regulatory reasons.		

- We have only indirect examples of regulatory flexibility gains. We have products pending approval.
 We note that the example for completent flexibility but to example.
- We use QbD principles not as much for regulatory flexibility, but to ensure we can have the product produced and back on the rails if anything unexpectedly goes wrong.

Table J. Regulatory Interactions and QbD – Companies A&B.

a benefit; the same applies to *increase speed of scale-up*. *Increased process capability, reduced number of deviations, zero atypicals* were used to describe improvement in process robustness. Other benefits were listed that reflect ways of working in the company. The reader will find a plethora of

Regulatory Interactions

- Regulatory flexibility would be considered a benefit, but is not a determining factor in the application of QbD principles.
- A definite regulatory benefit is that QbD provides for a more comprehensive CMC submission and rationale.
- No data on regulatory flexibility, but not expected.
- We do see regulatory flexibility gains, in the sense of giving the regulators confidence that we really understand our products and processes. Regulators will normally keep peeling back layers to investigate. With a ObD approach, when they see these principles being used, their confidence is increased and they realise they don't need to look further.
- The biggest battles are with our internal regulators and the external regulators. Internal regulators say we don't want to open up the file and yet, when we do, in order to use a new approach, in practice it takes longer to gain approval and yet the new approach is clearly much better than the conventional.
- These are great guidances (i.e., reference to QbD principles), but there is sometimes a disconnect between top level/central regulatory messages compared to local demands. In practice, we have to get approval and so we don't have any leverage to say no to the local demands.
- It has meant more questions and challenges from regulators.
- Timeline for approval much reduced.
- The regulatory flexibility is brought mainly via approval of design space. Design space was approved in all major markets. Some other countries have granted further flexibility.
- Some flexibility in post-approval changes has been experienced, but more global harmonization and acceptance is needed to fully realize the potential for continuous improvement.
- ObD submission requires a full explanation that requires learning from company and regulators – a relationship building exercise.
- ObD filing may not be realizing as much freedom as was expected. There
 is a gradual learning on the level of detail required in filing.
- Improvements have arisen: having COAs and CPPs is providing assistance in dealing with regulation.
- More documentation and elaboration are needed for the CMC section; usually we get asked for more data.
- The focus of the site regulatory inspections has shifted to include a blend of review and quality systems type issues. This has lead in some instances to a lack of clarity of what should be in the submission and what is managed within the company's quality system.

Table K. Regulatory Interactions and QbD - Rest of the Companies.

benefits ranging from monetary benefits, to ways of working, to speed to market.

Additional Level of Resources to Achieve QbD

The additional resources required to work in a QbD framework did not seem to be of concern and the overall philosophy of the companies that embraced QbD seems to be summarized by the following statement:

"We believe that a more appropriate view is that QbD is a transfer of resources from a downstream corrective mode to an upstream proactive mode."

The answers from companies A and B are shown in Table H and other sample answers from the rest of the companies are shown in Table I. In general, the feeling was that the Return on Investment (ROI) is very high for the investment to be a matter of concern.

QbD and Regulatory Interactions

Regulatory flexibility was **not** the main driver for QbD adoption according to the responses in all of the questionnaires. According to one interviewee, "QbD has been worth doing irrespective of the regulatory position."

The following statement recognizes the fact that both the industry and the regulators are learning from the process and the advancement of QbD is dependent upon building relationships with each other.

"QbD submission requires a full explanation that requires learning from company and regulators – a relationship building exercise."

There are strong examples cited by some interviewees where regulatory approval was achieved for their companies:

ObD for In-Licensed and Third Parties

Company A

 We apply QbD elements with CMOs and for in-licensed products. The former has primarily been accomplished through DoE driven protocols.

Company B

- For in-licensed products, we find we have to do more work in-house to ensure the formulation meets QbD principles.
- For contract manufacturing, it is difficult to get companies to do fundamental work. We find it best if we set out our expectations early and then expect them to meet these. We employ our own specialists who know how to manage the external supply base. We often have to put our own resources into contractors to manage the early stages of a contract and ensure the product will be made successfully. We expect for example use of control charts by the third party. We do have a philosophy to build long term relationships with many third party manufacturers.
 - For manufacturing, we have quarterly meetings with our contractors and collect the usual metrics such as yield, customer complaints, etc.
 - We find drug substance third parties entities are more sophisticated when it comes to PAT and modelling than drug product ones, as the latter seem less flexible to new approaches.
 - Third party manufacturers would expect us to pay them to develop their own use of PAT tools; it is hard to justify for us.

Table L. QbD for In-Licensed and Third Party Manufacturers – Companies A&B.

In-Licensed and QbD

- Often we carry out further development work (DOE) to ensure robustness
 of the product, before putting it into commercial manufacturing; we have
 improved bought-in products this way.
- If they are acquired early, then they would be part of the QbD development process; sometimes they are acquired too late to be influenced by QbD principles, other than by post-approval.
- We apply QbD for in-licensed.
- Some limited aspects (COA and DOEs) applied to in-licensed product; an assessment of the ObD elements during due diligences for in-licensing candidates is often done, but is not an expectation.
- We apply QbD for in-licensed, for drug substance (could not comment about drug product); ensure we are involved in the development and understanding of products using QbD tools and develop risk assessment based on this knowledge.
- We apply QbD (Interviewee was not able to provide details, but he believes it is based on the overall company's QbD approach.)
- Intent would be to make use of these approaches with in-licensed products, but timeline will determine whether that is achievable, both for drug substance and drug product.
- In-licensed product to be filed, all based on risk assessment; in some cases, the partner or originating company also has taken a QbD approach. Where this is not the case, QbD principals are applied to in-licensed products according to a risk-based approach. The risk analysis will consider the current level of process robustness, the level of process understanding, as well as the expected time remaining to gain approval. In many cases, QbD approaches are applied to certain higher risk areas of the process, as opposed to a more holistic approach for a fully in-house developed product. In some cases, it also may be determined that a product developed by a partner is suitable for launch, but that additional process improvements can be gained post-launch. In these cases, QbD tools are applied during the commercial phase of the products lifecycle

Third Party and QbD

- ObD is applied. An example where we imposed ObD principles: they (third party) didn't believe they had a problem, as their processes on average yielded 95% or better. But they couldn't explain why some batches yield was 99% and some 96% so we insisted on investigating this to find root cause. The process is now more consistent and more productive.
- We don't have our own plants and we use external third parties for manufacturer of our products. QbD is done for this purpose
- Generally, they (third parties) are not expected to apply ΩbD principles.
- Third party contractors: QbD is applied but on a case by case basis. Main area is aspects of control that we expect or want.
- Third party contractors, they do not need to be ObD enabled; they are required to work within the boundaries of the license.
- ObD is applied; this has primarily been accomplished through DoE driven protocols.
- DbD is applied; interviewee was not able to comment too much on how this is being done, but he believes it is based on the overall company's ObD approach.

Table M. QbD for In-Licensed Products and Third Party Manufacturers – Rest of Companies.

- Advanced control strategies (global acceptance)
- Predictive models
- Design space (approval by all major markets)

There are still concerns for the following issues:

- Lack of harmonization
- Lack of clarity as to what should be in the submission and what is managed within the company's quality system
- Lack of flexibility for post approval changes to realize the potential of continual improvement.
- Amount of data required for a QbD submission

Use of Modelling

Company A

- · Models have been used for direct prediction of CPPs/CQAs.
- Predictive models for assessing stability of the product.
- Verification at commercial scale
- For PAT models, yes.
 - For first principle or mechanistic models, no.

Company B

- Models have been used in development.
- Kinetic modelling for improving stability: understand rate of formation of degradants.
- Simulations of what we expect dosage form to be in the human body IVIVC models
- Manufacturing have used a lot of DOE (re-establish operating range if changes are made to the process)
- Have used models or earlier analysis to push testing as early as possible in the process rather than (testing) the final product.

Table N. Use of Modelling in QbD – Companies A&B.

QbD for In-Licensed Products and Third Party Manufacturers

When asked whether their company applies QbD principles for in-licensed products, the interviewees gave a variety of answers; however, the following sentence captures a reasonable argument of when a company would consider QbD:

"If the in-licensed products are acquired early, they would be part of the QbD development process; sometimes they are acquired too late to be influenced by QbD principles, other than by post-approval."

For third parties, some companies do not expect QbD; however, some are keen to provide support to the third parties:

"We often have to put our own resources into contractors to manage the early stages of a contract and ensure the product will be made successfully."

"We used an external contract manufacturer, and much to their chagrin, we imposed QbD principles on them. They didn't believe they had a problem, as their processes on average yielded 95% or better. But they couldn't explain why some batches yield was 99% and some 96%, so we insisted on investigating this to find root cause. The process is now more consistent and more productive."

The responses from companies A and B are listed in Table L. Responses from the rest of the companies can be found in Table M.

Use of Modelling in QbD

It became evident from the responses that all the eleven companies are using Design of Experiments (DOE) and empirical modelling. Mechanistic/first principles models are also used by the majority of companies (9 out of 11). Use of modelling in existing products also has been mentioned as for example, "composition of an oral solid formulation was modified, based on a model." A company mentioned that "the use of both empirical and mechanistic models has improved

Use of Modelling

- Composition of an oral solid formulation was modified, based on a model
 Model used for RTRT
- · For adjusting process parameters (in feed forward mode)
- For energy input to granulation
- PAT models
- DOE to establish design space
- Use of modelling in development is increasing, e.g., predicting operating space.
- Haven't got to the stage where it is being used for release.
- Extensive use of models
- Models are used at full scale and developed with data from clinical batches at full scale.
- Small scales (e.g., viral spiking and viral removal studies) are being carried out in downstream processing. Model studies have not been used for upstream (cell culturing and bio-fermentation) processes.
- Modelling and PAT were used to guide process development.
- · Modelling was used to predict scale-up parameters.
- Both mechanistic and empirical (statistical) models have been developed and used to improve product and process understanding
- For PAT based methods
- Development of design space
- Deliver early warning of problems (drug substance) but not being deployed in RTRT at present.
- RTRT models have been deployed in drug product manufacturing.
- Extensive use of modelling across the company including the investigation and demonstration of scale independence
- Statistical and mechanistic models are employed based on suitability to a
 particular product or process.
- Significant use of DOE modelling
- Use of engineering first principles and modelling
- Statistical and first principles models are primarily used to define and describe the design space and justify experiments and scales selected to map the design space.

Table O. Use of Modelling in Rest of Companies – Grouped to Indicate Use by Company.

product stability." Comments related to use modelling by the two companies A and B are shown in Table N. Examples

Modelling and Regulatory Interactions

- We have used predictive models in QbD applications and have been successful with regulatory acceptance.
- Small scales (e.g., viral spiking and viral removal studies) are being carried out in downstream processing. Regulators have accepted model data.
- Regulators have demonstrated their acceptance of the concept of modelling although they expect the use of a model to be strongly justified for each instance of its use.
- We have experienced challenges, e.g., for mechanistic understanding. Challenge also has been verifying model at scale. Regulators want data to show it works at full scale, though level of this scrutiny depends on what the model is being used for, e.g., more scrutiny if being used for release testing.
- Use of model for post-approval flexibility was not accepted by regulators. The regulators do expect to see model verification studies at commercial scale.
- The regulatory agencies have struggled to understand and accept the validity and scalability of the models (interpolation versus extrapolation).
- Statistical and first principles models are primarily used (in our company) to define and describe the design space and justify experiments and scales selected to map the design space. Regulators have stated that this approach seems acceptable and full scale verification is not required; however, this is yet to be verified.
- We have experienced challenges (for modelling) with inexperienced regulators, but for those with experience and understanding of models, the models have been accepted.

Table P. Regulatory Response to Modelling – All Companies.

of modelling use from the rest of the companies, grouped by company, are given in Table O.

Comments related to the acceptance of modelling use by the regulatory agencies are listed in Table P. Please note that the different level of scrutiny described by some interviewees is related to the impact of the models involved in their submissions; according to ICH points to consider for modelling [1], models that are used as sole predictors of quality (i.e., for product release) are considered high impact and therefore a higher level of scrutiny may be expected.

Use of PAT to Support QbD

All the eleven companies use PAT. The majority of the companies answered that they use PAT both in R&D to gain product and process understanding and also in manufacturing. Only two companies answered that although they use PAT in R&D, they rarely use PAT in manufacturing. One of them uses it mainly in drug substance manufacturing. *"We rarely use it in manufacturing, as conventional end product testing is a lot cheaper than using PAT tools for our products today. We have used PAT tools more in drug substance (where it has been longer established by the industry) and less so in drug product."* The other company uses third party manufacturing so the comment was *"Third party manufacturers would expect us to pay them to develop their own use of PAT tools so it is hard to justify for us."*

The thought process behind PAT choices is accurately reflected in the following statement:

"PAT tools are used in various applications including development and commercial control strategies. In a development setting, PAT tools can be used to gain process understanding and may not be necessary in the commercial setting. In other cases, PAT tools may be appropriate as an element of the commercial control strategy. These decisions are based on risk assessments of the specific product and process."

Desirable PAT Sensors

- A means of 100% integrity check of sealing on aluminium overwrapping pouches for BFS.
- Non-destructive way to measure tablet properties and an efficient at line HPLC measurement
- Not fully utilizing all the available PAT devices commercially available for manufacturing environment
- A tool to measure residual ethanol in wet granulation would be useful
- One area we struggled with somewhat was in dry granulation (roller compaction) – ribbon porosity is difficult to measure on-line, this is a gap in the market. Apart from this, most tools are available, but are expensive to operate and validate.
- Lack of sensors in vaccines and biologics. For small molecule solid dosage forms we lack suitable on-line technology (including sensors) for degradate and impurity analysis. Accurate moisture sensors.
- Sensors to examine resin contamination.
- Non-destructive measurement of oxygen/water in opaque blisters or tablet bottles. More specific and sensitive sensors for reaction monitoring applications.
- Microbial counts in process streams rapid fluorescent method being examined. Rapid and robust cell density measurement linked to automated sampler.

Table Q. Desired Sensor Technology not Currently Available – All Companies.

The Future of **QbD**

- It will continue it is part of our company's way of working.
- ObD will be the norm within 10 years and manufacturing efficiency will be significantly improved – but remember we're not a commodity industry.
- I think it will continue to grow and become more embedded as it is applied more in production we will get better at it. We will use more prior knowledge and more risk-based approaches.
- ObD will become the norm.
- Quality by design is already expanding its scope into new paradigms such as RTRT, continuous quality verification, analytical QbD, lean stability approaches and others. We expect this trend to continue.
- We will continue using QbD principles to guide the development and manufacturing of commercial APIs, but how QbD plays out in registration remains to be determined. In drug product, we are constantly reviewing our QbD implementation process to determine how the process and underlying tools can be improved to make the implementation as practical as possible.
- I am a supporter of QbD as it brings enhanced product and process understanding internally. The biggest risk is that people will give up if we don't see movement from the regulators and all this benefit will be lost. It is very disappointing to have to say that at the moment while I fully support QbD as a development principle, I cannot see a logical business case to justify including this information in a regulatory submission.
- Since we are not driven to do QbD solely for regulatory benefits, we see QbD as the way we will develop and supply all our products.
- The value of the QbD principles is clear and will continue to be integrated into the product development processes. It provides a systematic approach to product development, a common language, increased integration of patient requirements, and an advanced control strategy for increased process and product understanding, and a strong rationale for the control strategy.
- ObD will be a far bigger part of operations and activity at the site now. Six sigma to align with ObD with PAT as the enabler is the approach being pursued.

Table R. Response to the question *"What is the Future of QbD?"* – All Companies.

Desirable New PAT Sensors

The interviewees were asked for a "wish list" of sensors that could be applicable for PAT at their businesses and that are not currently available; this list is given in Table Q. The following two statements summarize the overall feeling about the state of PAT in the pharmaceutical industry:

"As a general statement, our experience has shown that PAT tools are more advanced than our current understanding of how to fully utilize them. PAT tools are typically developed and implemented outside of the pharmaceutical industry and then adapted to the pharmaceutical setting. This implication is that our ability to utilize new approaches often lags behind the technologies themselves."

"In the future, if one established 'real QbD,' this would mean flexible manufacturing processes that responded to these tests to feed forward/feedback, i.e., attribute based controls to assure product output would be of the required quality, even though input materials varied."

The Future of QbD

Overall, the interviewees indicated positively that QbD is here to stay, not for regulatory flexibility but because it is the right thing to do. This is evidenced from the responses listed in Table R. The following statements summarize the feeling: "The value of the QbD principles is clear and will continue to be integrated into the product development processes. It provides a systematic approach to product development, a common language, increased integration of patient requirements, and an advanced control strategy for increased process and product understanding, and a strong rationale for the control strategy"

"Quality by design is already expanding its scope into new paradigms such as RTRT, continuous quality verification, analytical QbD, lean stability approaches and others. We expect this trend to continue."

Concluding Remarks

QbD seems strongly embedded in the companies interviewed. The benefits realized have met the expectations set by companies when they embraced QbD "...improved product and process understanding; a more systematic approach across the development portfolio; continue to improve patient safety and efficiency; improve manufacturing efficiency; and improve development efficiency." Additionally, significant cost benefits have been reported from QbD developed products. QbD is being applied in development and manufacturing, in new and also established products. No significant overall increase in resources is expected, but a shift from resource upstream and requirement of additional skills (e.g., statisticians, chemometricians) and multi-disciplinary working. The use of models and PAT is commonplace. For in-licensed products and third party manufacturing, the degree of QbD implementation is varying. The opinion about the future of QbD is unanimous: QbD is here to stay.

Reference

1. ICH Quality Implementation Working Group Points to Consider (R2); ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation, Document date: 6 December 2011, can be downloaded from http://www.ich.org.

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Appendix I: ISPE PAT COP: Business Case for Quality by Design					
Business Benefit Category	Sub-Category	Metric	Benchmark (Traditional)	Benchmark (QbD)	
Robustness	Process Performance, CpK (for all end of process and within process measurements	СрК			
	Reduced OOS Product	Batch Fails			
	Re-Work/processing				
	Acceptable Range of Raw Material Specification				
	Time on incident analysis	Manhours			
Production Cycle Time	Cycle Times (Predictable) (for each individual production unit and across whole process)	Cycle Time, Average and Std Dev			
	Work in Progress				
	JIT, RFT , Reduced Inventory	£			
Manufacturing	Energy Efficiency	Cost per Unit			
Efficiency	Reduced Cycle Times	Time			
	Reduced Cleaning/Setup times	Time			
	Reduced Manpower	£			
	Stock Turn				
	Right First Time	%			
	Overal Equipment Effectiveness	%			
	Yield	%			
Speend to Market and	Reduced time from filing to market				
Sustainability	Regulatory Flexibility (through improved Process monitoring and understanding)				
	Continuous Improvement (Operational Excellence activities)				
	Cumulative Benefits year on year				
	Quantify reduced or increased documentation				
	Process Development Time (Stage 1, 2, 3)				
	Risk Assessment (Time, People, etc.)				
Return on Capital	Initial Capital Costs	£			
Employed or RUI	Lifecycle Capital Costs	£			
	Cost of QC	f			
	New Product Efficiency	%			
	Product Extensions (speed to market)	IRR			
Strategic	Diversity – able to produce products at different sites worldwide				
	Showcase	Number of Publications? PR			
	Transferability (through Improved Process Understanding)				
	Environmental Benefits	Carbon Footprint			
	Regulatory Agency Interaction				
	Process Understanding of material, offering flexibility in supply chain	Reduced Risk			
	Real Time Release	Reduced Cost of QC			

This set of metrics was developed and kindly made available to ISPE PAT COP UK/IR by David Lovett, Perceptive Engineering, UK.