

Quality by Design and OINDP

Setting the Stage

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IPAC-RS 2008 Conference

Today's Presentation

- QbD – definition
- Setting the stage from an ICH perspective
- **Future Opportunities**

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QbD Definition

Quality by Design: A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.
(ICH Q8R1 – Step 3/4)

- Science and risk-based, holistic and proactive approach to product realisation that focuses on patient needs
- Deliberate design effort from product conception through commercialisation
- Full understanding of how product attributes and process relate to product quality

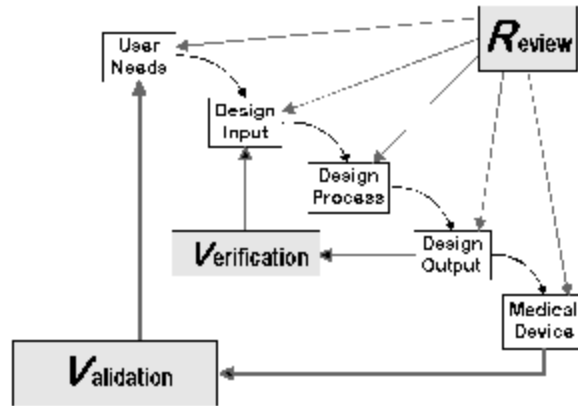
QbD is not new!

Basically not totally new: EU development pharmaceuticals always been done; however the PAT concept allows a better control and monitoring of process and product. The use of risk management in a Q10 type QS environment will optimise the benefit.

This paradigm has been recognised by the European Commission: see Variations Public Consultation Paper (24 Oct. 2007):

'Beyond the notion of 'design space', ICH developments —namely the Q8, Q9, and Q10 guidelines- introduce modern tools (risk management, quality systems) that could facilitate continuous improvement of the manufacture over the products' life cycle, while maintaining a state of control that ensures high standards of quality' .

QbD is definitely not new for Device Manufacturers



Taken from: Design Control Guidance For Medical Device Manufacturers FDA, March 11, 1997

But is QbD for OINDP new?

- Device and Combination Product Regulations and guidelines go back over a decade
- EU
 - Annex 1 Council Directive 93/24 EEC;
 - Pharmaceutical Quality of Inhalation and Nasal Products (CHMP/QWP/49313/2005),
- FDA
 - “Do it by Design” (1996)
 - MDI and DPI Drug Products - Chemistry, Manufacturing, and Controls Documentation (1998 draft)
 - Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing, and Controls Documentation (2002)
 - Guidance for Industry and FDA Staff: Early Development Considerations for Innovative Combination Products (2006)

But many of these guidelines do not support fully current understanding of QbD

- They generally recognise:
 - Systematic approach to design and realisation
 - Quality is closely aligned with device effectiveness and performance
 - Quality must be considered throughout lifetime of device
 - Shared responsibility between stakeholders (including the patient)
 - Absolute safety cannot be guaranteed
- They are almost universally silent on risk.
 - Absent in EU guideline
 - Mentioned only once each in FDA's 1998 draft guidance and 2002 nasal spray guideline (relating to extractables)
- Compare
 - ISO 13485:2003 - Medical devices -- Quality management systems
 - ISO 14971:2007 - Medical devices -- Application of risk management

This looks like an opportunity.....

You all know what the problem is!

And you're looking to QbD thinking to solve the issues

- Bring our industry to the state of the art
- Reduce the cost of quality
- Re-emphasise the importance of manufacturing and manufacturing sciences
- Reduce waste (currently can be as high as 50%)
- Enable us to develop models that predict effects of scale-up
- Gain process understanding that supports root cause analysis of manufacturing failures
- Support global standards
- Support continual improvement and a reduction in regulatory post-approval sub

But some of you are sceptical....

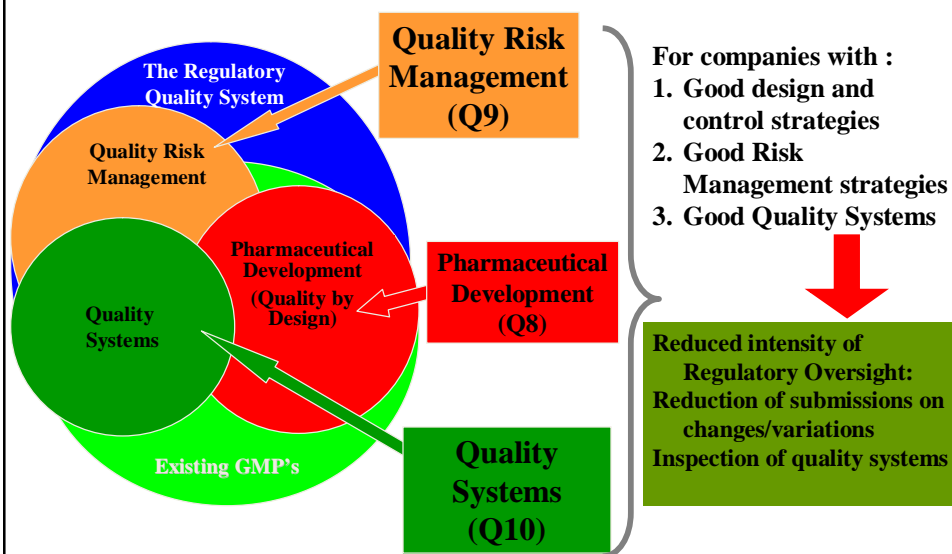
Background:
To help us all, we developed the ICH
Pharmaceutical Quality Vision

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

Bruxelles July 2003

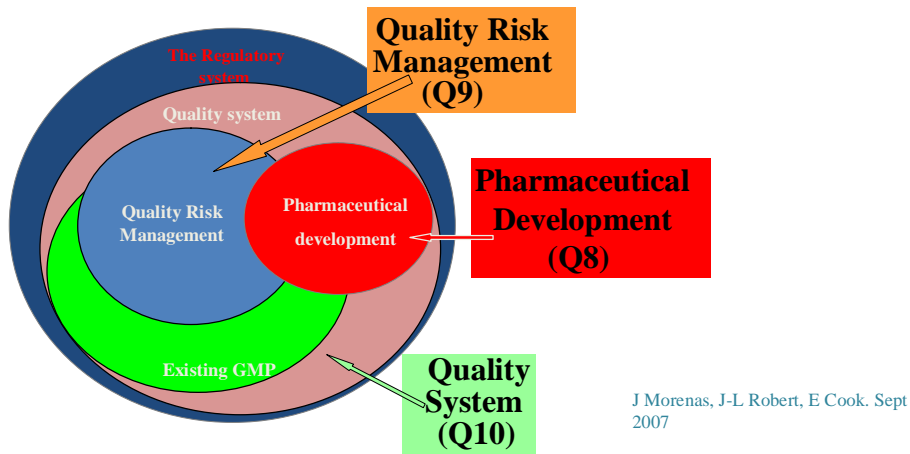
- Q8: Pharmaceutical Development (step 5)
- Q8: Annex (step 3)
- Q9: Quality Risk Management (step 5)
- Q10: Pharmaceutical Quality System (step 5)
- Q11: Manufacturing process development (step 1)

The Brussels 2003 Agreement Evolved and Was
Confirmed in 2006

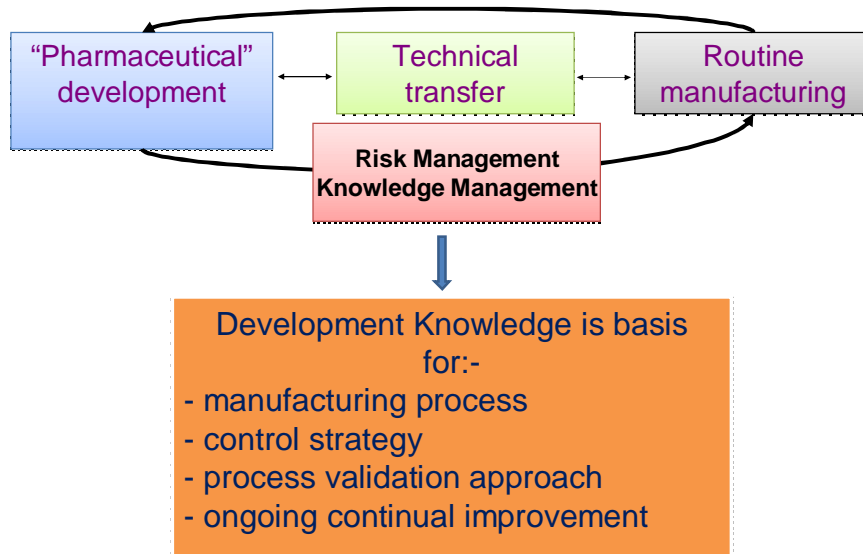


EU Regulators' Vision of ICH

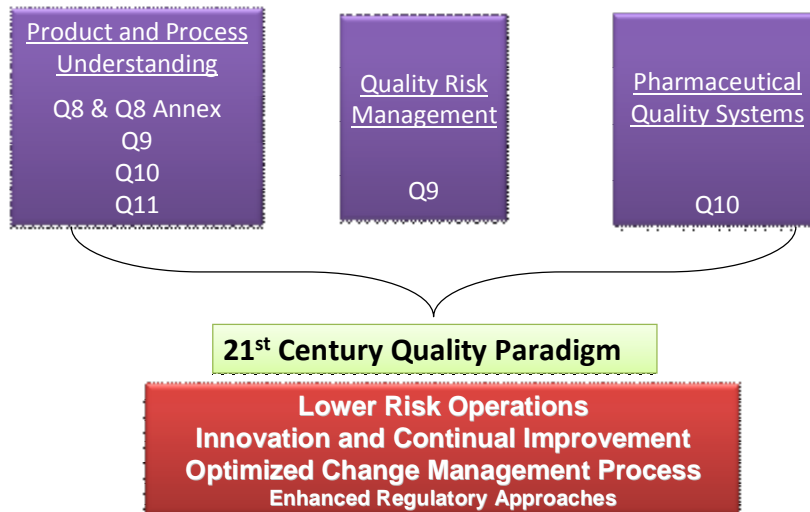
The EU regulatory point of view on integration of different ICH quality concepts



Q8/9/10 Support Lifecycle Goals



The new Qs underwrite the new quality paradigm



ICH Q9: Quality Risk Management (QRM) is straightforward

- A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.
- To ensure both industry and regulators have common understanding of Quality Risk Management (QRM)
 - To facilitate moving to the “**Desired State**”
 - To facilitate communication and transparency
 - To move from ‘fire fighting’ to management of risk
- ICH Q9 explains
 - A common process and language
 - Where QRM can add value

Principles of QRM

Two primary principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge (Q8) and ultimately link back to the protection of the patient.
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

Basically nothing new EXCEPT to encourage use of QRM

Q10: Pharmaceutical Quality Systems

- Guideline dedicated to industry-
 - Complements ICH Q8 and ICH Q9
 - Augments GMPs
 - Encourages a science & risk-based approach to quality decisions
 - Not mandatory
- Applicable to:
 - “This guideline applies to pharmaceutical drug substances and drug products, including biotechnology and biological products, throughout the product lifecycle.”
- Two ‘enablers’
 - Knowledge Management and Quality Risk Management

PQS Objectives

Achieve Product Realisation

- To establish, implement and maintain a set of processes that provides a product with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with marketing authorisations) and internal customers.

Establish and Maintain a State of Control

- To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes. Quality risk management can be useful in establishing the monitoring and control system.

Facilitate Continual Improvement

- To identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations, and pharmaceutical quality system enhancements, thereby increasing the ability to consistently fulfil quality needs. Quality risk management can be useful to identify and prioritise areas for improvement.

Not much new for OINDP

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Which leaves ICH Q8 – Why?

Regulators said that, where industry acquires extensive, systematic understanding about their product and its manufacturing process **and shares this understanding with them**

- Submissions could focus on knowledge rather than data
- Enhanced science and risk-based regulatory quality assessment will be possible
- Specifications become safety & efficacy focused
- New approaches to product release and process validation would be considered
- Post-approval processes would be examined to support innovation and continual improvement



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Q8: Key Principles

- Quality cannot be tested into products; i.e., quality should be built in by design.
- The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.
- The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls.
- Information from pharmaceutical development studies can be a basis for quality risk management.

Q8 Expectations



It's important to tell a compelling story

- At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified.
- Critical formulation attributes and process parameters are generally identified through an assessment of the extent to which their variation can have impact on the quality of the drug product.

Q8 Additional Opportunities

- can choose to conduct development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options and process parameters.
-additional information provides an opportunity to demonstrate a higher degree of understanding of material attributes, manufacturing processes and their controls.
 - This scientific understanding facilitates establishment of an expanded design space.

Q8 Additional Opportunities

In these situations, opportunities exist to develop more flexible regulatory approaches, for example, to facilitate:

- Risk-based regulatory decisions (reviews and inspections)
- Manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review
- Reduction of post-approval submissions
- Real-time quality control, leading to a reduction of end-product release testing

But only if you describe this all in your submission

Q8(R) Objectives (Step 2)

- ...an annex to ICH Q8 .. and provides further clarification of key concepts outlined in the core guideline. In addition, this annex describes the principles of quality by design (QbD).
-shows how concepts and tools (e.g., design space) outlined in the parent Q8 document could be put into practice by the applicant for all dosage forms.
- Where a company chooses to apply quality by design and quality risk management (ICH Q9, Quality Risk Management), linked to an appropriate pharmaceutical quality system, then opportunities arise to enhance science- and risk-based regulatory approaches (see ICH Q10, Pharmaceutical Quality Systems).

An enhanced, quality by design approach to product development would additionally include the following elements

- A systematic evaluation, understanding and refining of the formulation and manufacturing process, including:
 - Identifying, through e.g., prior knowledge, experimentation, and risk assessment, the material attributes and process parameters that can have an effect on product CQAs
 - Determining the functional relationships that link material attributes and process parameters to product CQAs
- Using the enhanced process understanding in combination with quality risk management to establish an appropriate control strategy which can, for example, include a proposal for *design space(s)* and/or real-time release
- ... this more systematic approach could facilitate continual improvement and innovation throughout the product lifecycle (See ICH Q10)

Design Space: First referenced in FDA PAT guidance

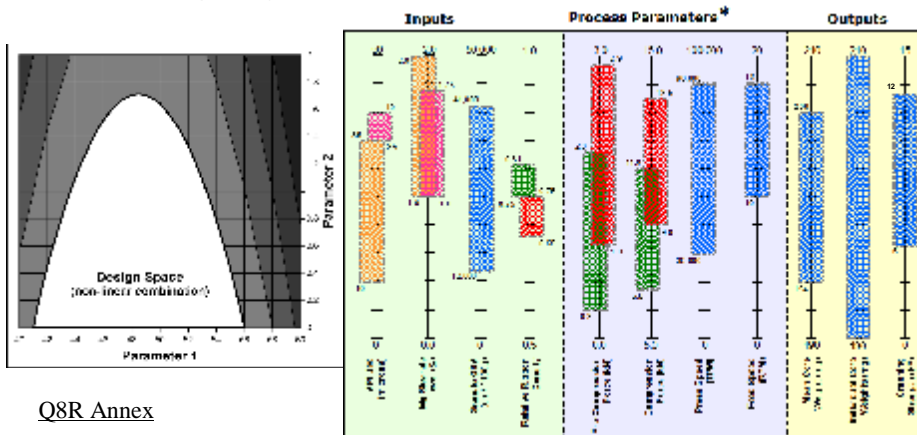
Design Space: the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Stop worrying so much about design space

Design Space can be simple or complex



Q8R Annex

ACE case study
www.conformia.com

I can feel you thinking about all the challenges

- Need understanding and agreement on terminology (e.g., design space)
- Need to determine what relevant data is needed in applications
- How do we get uniform global implementation?
- Need to determine how best to handle legacy products in line with those products developed and filed under QbD
- Need a “regulatory agreement” or post-approval management plan
- We’re not sure how review, inspection, compliance etc fit together
- Everybody needs training – industry and regulators
- OINDPs are unique - Q8 (QbD) is just for small molecules and simple drug products (Q6A)

Who should address the challenges?

- It’s up to Industry to grasp the initiative and begin to lead the regulators
 - Articulate the good science and quality risk management at conferences like this
 - **And in your submissions**
 - Be ready to contribute to revised guidance and implement it
 - Encourage the regulators to focus on science and risk-based reviews and facilitating continual improvement
- We will then achieve the desired state
 - A greater assurance of quality, improved supply reliability and security, and reduced costs.



Future Opportunities



QbD is here, it is now, and you can use it!



An ICH Satellite Meeting in 2007 debated whether the principles of Q8 were applicable only to drug products from chemically derived APIs

Points for consideration & common understanding

- Product lifecycle – are there elements which should be separated out for different consideration?
- New Development Paradigm? – applicable to substances?
- Elements of Quality by Design – product specific?
- Interrelation Development / Risk management /Quality System
- Control Strategy applicability
- Design Space – is it for drug products only?
- Future opportunities for science and risk based approaches (e.g. Real Time Release)
- Opportunities for extension

Extensions ???

.... the principles described are considered to be similarly applicable to the development of active ingredients. However, taking into account the complexity of biological molecules and processes, the application of these concepts to biological molecules will require careful consideration, and could lead to more limited use of this approach.

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Extensions ???

Many of the principles are also similarly applicable to the development of analytical procedures. Adoption of the principles in this guideline can support the justification of alternative approaches to the setting of specification attributes and acceptance criteria as described in Q6A and Q6B. For example, with appropriate product and process understanding, acceptance criteria can be based on patient needs such as safety and efficacy, rather than simply on the process capability.

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Meeting conclusion

- QbD principles are applicable to everything we do
- Nothing is totally unique
 - It's just about complexity
- Agreement to progress Q11

More coming today.....

IPAC-RS Strategic Plan – Great ideas!

QBD INITIATIVES	6
A. OINDP MATERIALS WORKING GROUP.....	6
B. MODEL OINDP WORKING GROUP	6
C. QBD ANALYTICAL METHOD DEVELOPMENT WORKING GROUP.....	7
D. QBD CORRELATIONS WORKING GROUP.....	7
E. RISK MANAGEMENT WORKING GROUP.....	7
F. QBD LEACHABLES & EXTRACTABLES FEASIBILITY GROUP.....	8
G. SHELF LIFE STABILITY WORKING GROUP (through PQRI)	8
H. SUPPLIER QC WORKING GROUP.....	8
I. CASCADE IMPACTION WORKING GROUP	9

B. MODEL OINDP WORKING GROUP

Objectives

To consider and explain how initiatives such as Quality by Design may be applied to OINDP. The focus of this group will be two-fold: internal, through industry discussion and education, and external, through dialogue with regulatory authorities and standard-setting bodies.

Activities

Developed P2 Points to Consider document providing guidance on content of P2 section of CTD for OINDP under a QbD paradigm.

Visit the poster and ask how you can help!

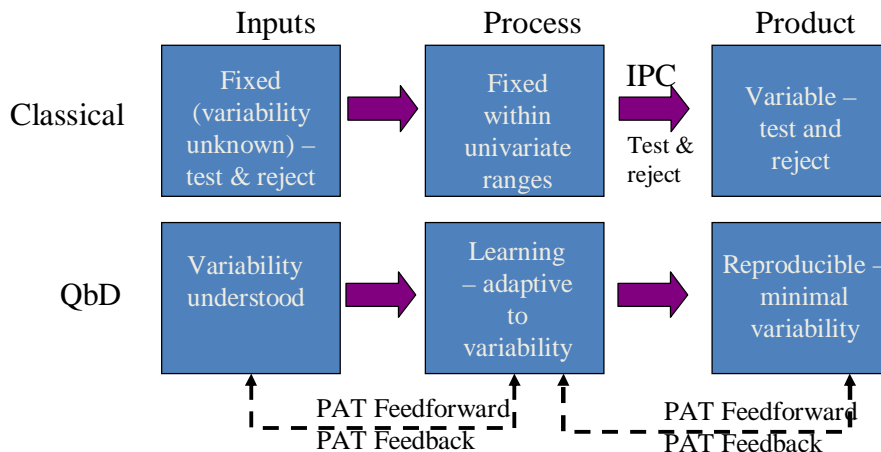
IPAC-RS 2006: Stream A – PAT

- “Unclear benefits”
- “QbD offers more benefit than PAT”
- AT is a SYSTEM with wide applicability both in development and manufacturing
- AT tools are key to gain enhanced process understanding
- AT supporting QbD and “Benign by Design” gives synergistic savings (1+1=2)

More in Tuesday morning sessions!

AT is a component of QbD, not an alternative

QbD process can capitalise on different control strategy



QbD with PAT can support Real-time Release

Quality Risk Management is more than Design Space

“To make use of the design space concept” (Q8)

- A powerful tool for driving rational decisions within an organisation
- A great vehicle for facilitating culture change
- When documented appropriately, provides a transparent record
- One of the two enablers for pharmaceutical quality systems
- A critical component of every future regulatory submission
 - Rapidly becoming the ‘norm’
 - But do it properly!

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IPAC-RS 2006: Stream C – Control Strategies

- How do you link control strategies to safety and efficacy

– No one could suggest realistic way

But Regulators expect it!

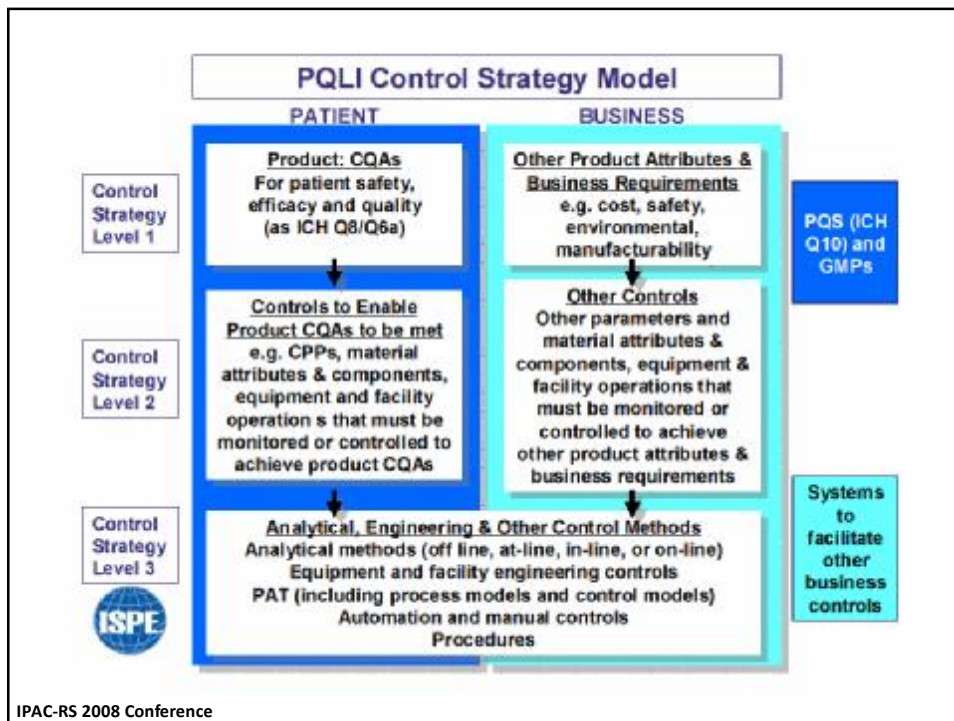
- ONDC reorganisation: The new system will focus on critical pharmaceutical quality attributes (chemistry, pharmaceutical formulation, manufacturing process, product performance) and their relevance to safety and efficacy.
- EU/HC guide: Significant variations in the delivered dose and/or fine particle mass should be fully discussed in terms of the safety and efficacy of the product.

This remains a key topic for all involved in the new paradigm

Control strategy should be universally applicable

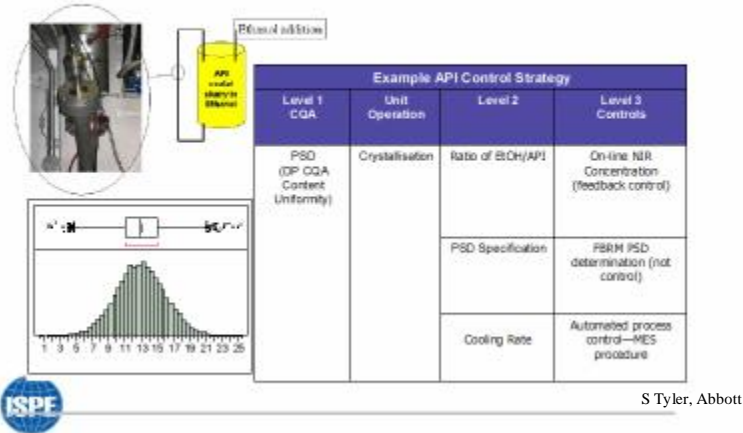
Control strategy : a planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10 EWG)

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The ISPE model in action

Crystallisation – Control Strategy



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ICH Implementation Working Group (IWG)

November 2007 ICH meeting

- Steering Committee endorsed establishment of implementation working group
- Concept paper developed and conditionally approved
- IWG started June 2008

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Implementation Issues Identified

Technical Issues & Related Documentation

- Technical examples and case studies
- Level of detail to include in dossier
- Common understanding of terminology
- Inter-relationship between Q8, Q9, Q10
- Application to both review and inspection
- etc.

Implementation Issues Identified (2)

Communication and Training

Additional Implementation Issues

- Scope of implementation:
- Ensuring a harmonised approach in these 3 areas
- Updating of existing guidelines

No shortage of opportunities here!

Other opportunities?

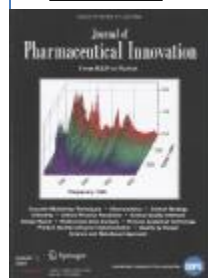
- Harmonised standards
 - Is the HC-EU guideline a potential basis for ICH?
 - Does Q6A meet your needs?
 - Does Q8 + Annex give sufficient guidance & flexibility?
 - Pharmacopoeial discussion group
 - Q4B
- Case studies
 - Everybody is doing them!
 - Examlpain (NCE) and Mockestuzumab (biotech) – EFPIA
 - Analytical methods – EFPIA and PhRMA
 - Product quality lifecycle implementation (PQLI) – ISPE
 - Acetripitan (NCE), and biotech - Conformia
 - Mock QOS (PMDA)
- Pilot study focused on OINDP?



Pharmaceutical Development
Case Study: "ACE Tablets"

Prepared by Conformia OMCIM Working Group
March 13th, 2008

Version 2.0
www.conformia.com



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In conclusion:- Carpe Diem

- Seize the opportunity and begin to realise the benefits of Q8, Q9 and Q10 (Q11)
 - Provide significant benefit to your company NOW within the current regulatory framework
- Don't sit back saying, 'I am not going to do it until I see the regulatory flexibility'
 - Ignore the 'carrot' of regulatory flexibility and make savings now even within the restrictions of today's regulatory environment
- Congratulate Regulators for their initiatives
 - FDA's PQAS, PMP, 314.70 rewrite
 - European Commission new variation regulations which recognise Q8/9/10
 - Includes dialogue with the FDA to try to harmonise on the categorisation of change
 - Welcome start but still a way to go to achieve truly innovative regulatory approaches
- Lead and Contribute – there are so many opportunities!
 - PhRMA, EFPIA, JPMA, IPAC-RS, PDA, AAPS, ISPE, PQRI & other consortia

There is plenty to be done, let's get on with it!

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