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26-28 March 2008 • San Francisco



*Quality by Design: An Attempt to Jumpstart
Innovation Into the Manufacturing Process*

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GMP in the 21st Century

- Quality by Design (QbD) is part of Critical Path initiative and GMP's in 21st century driven by FDA
- Driven by resources
 - **Small increase in FDA staff and dollars**
 - **PDUFA restrictions and guarantees**
 - **Increase in supplements**
 - **In spite of slowing of New Molecular Entity approval**



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What is “Quality by Design”?

- Quality
 - “Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes.”
- QbD
 - “Means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches.”

Janet Woodcock (2004)

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Linking Structure, Function and Controls

- In a QbD system:
 - The product is designed to meet patient needs and performance requirements
 - The process is designed to consistently meet product critical quality attributes
 - The impact of starting raw materials and process parameters on product quality is understood
 - The process is continually monitored, evaluated and updated to allow for consistent quality over time
 - Critical sources of variability are identified and controlled
- Appropriate control strategies developed

Duffy (2007)

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Quality, Continuous Improvement Process (CIP) and QbD

- Proactive approach to continual improvement and innovation instead of reactive compliance approaches
- Manufacturing experience and knowledge provides opportunity to evaluate and improve processes
- Manufacturing experience and product knowledge can be used to establish a “design space”
- Introduction of innovative processes and controls is encouraged and will be facilitated
- Robust Pharmaceutical Quality System (PQS) is essential to implement scientific risk based change control

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Duffy (2007)

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QbD and Linkage into ICH

- Quality Design
 - Not testing in but creating quality by designing in
 - Linked very much with ICH Q8, 9, 10
 - Heavy into CIP and risk

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ICH Q8, Q9 & Q10

- Q8 – Pharmaceutical development
- Q9 – Risk based judgment
- Q10 – Quality Systems – inc CIP

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Not all QbD is the Same

- Principle behind is really to understand what makes good products and then make sure process is within areas of success to yield good product
 - **For drugs easily understood**
 - Tablet properties, API is very clearly defined
 - **For biologics less easily understood**
 - Characterisation less than complete, immunogenicity, carbohydrate changes
- From this key parameters that govern Critical Quality Attributes (CQA)
- Process topology / topography

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QbD can lead to Regulatory Relief

- Good product → CQA → process parameters → process controls and inputs
- Process topology/topography understanding
- Define process controls and inputs → process parameters → CQA → good product
- If that done will get regulatory relief and this helps industry and regulatory bodies
- Less number of supplements
 - **Simpler and less demanding supplements**
 - **Less number of and shorter inspections**

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Regulatory Relief

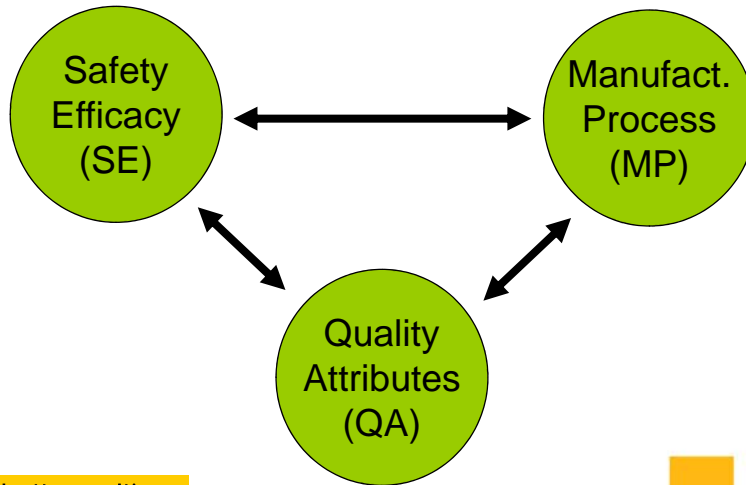
- | | | | |
|----------|--|------------------|--|
| • PAS | | PAI/PLI/biennial | |
| • CBE 0 | | decrease length | |
| • CBE 30 | | elimination | |
| • AR | | reduced cycle | |
| • NR | | | |

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Linkages



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Continuous Improvement Links into QbD

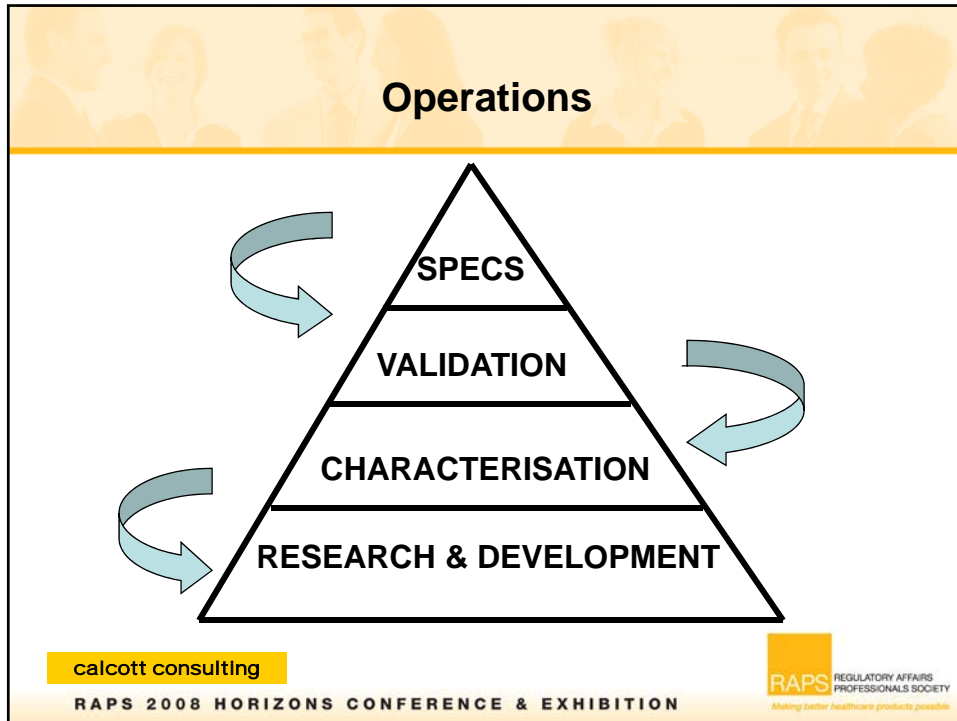


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Duffy (2007)





- ## Two Issues for Success of QbD
- It is really two fold
 - 1 – do we understand the process landscape? – science
 - 2 – can we **communicate** it effectively?
 - Can we tell the story?
 - Is it believed?
 - This is communication and trust
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Generics, Drugs and Biologics are Different

- QbD not the same for generics, drugs and biologics
- Generics – same compound, specs approval. Little process development, just confirming. Little understanding of Quality attributes.
- For generics – science is the issue
- Changes are quite laborious and dependent on the established drug
- Drugs and biologics more complex approvals
- Generics→Drugs→Biologics

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Generics Approach

- Quality by Review (QbR) has made FDA's expectations clearer - limited experience
- Guides product and process development
- Promotes communication among different functions within the company
- Points to the need for good knowledge management systems
- Will and should improve technology transfer

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Mundkur *et al.* (2007)

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Generics Approach (cont.)

- QbR questions have changed the information gathering and data reporting of generic drug development
- Move development activities upfront; more product and process understanding reduces risk of process scale-up
- Technical support and technical writers added
- Deficiency questions are science-based and are used to re-direct R&D activity for future ANDAs

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Mundkur *et al.* (2007)



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Generics Approach (cont.)

- QbR encourages forward thinking of QbD elements and principles
- Define the target of generic product quality profile pharmaceutically equivalent to drug
- Understanding of properties of drug substance and product design
- Understanding of manufacturing process
- Development report is now more product and process design focused

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Mundkur *et al.* (2007)



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Generics Approach (cont.)

- QbR has changed the quality assessment within OGD and has generated positive comments from the reviewers
- Office of Generic Drug (OGD) stated that QbR is being developed for microbiology review and to a certain degree, bioequivalence review

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Mundkur *et al.* (2007)

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Generics Next Steps

- **How much more information and knowledge on development activities is needed for filing?**
- **More clarity of FDA's expectation**
- **Developing a risk based approach to achieve OGD's goal of up to 80% CMC supplement reduction**
- **Develop metrics beyond the preliminary risk assessment strategy proposed by OGD**
- **Can post-approval data be evaluated upon review or inspection and used for regulatory relief?**
- **For some sponsors, additional development work (e.g. process) will be needed to fully address QbR prior to submission**

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Mundkur *et al.* (2007)

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Drugs

- Science is there
- Issue is communication and trust
- Develop NDA that is comprehensive and science driven
- Success story for some innovators

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Drugs Next Steps

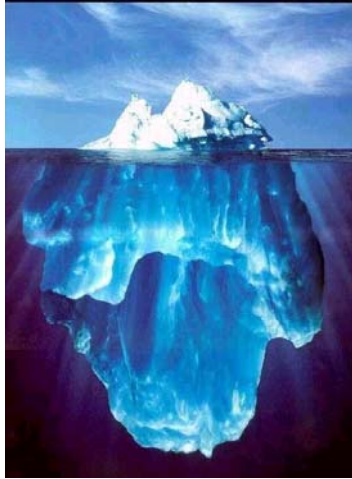
- Drugs – processes are simpler than biologics
- Unit operations
 - **API – properties, RM for next step, granulation, physical properties, how much variability is acceptable for next step – edge of failure**
 - **Granulated API – tableting to get quality properties**
 - **Tablet properties**
 - **Controlled delivery devices and prolonged release formulations**
- Pfizer has successfully done this – relief from inspection for drugs

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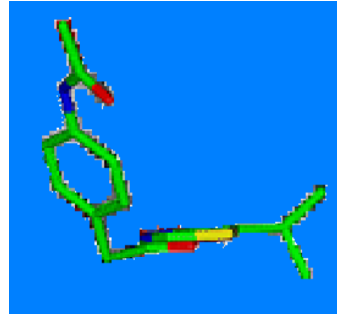
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Drugs versus biologics



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QbD for Biologics

- Biologics – much more complex process
 - Cell bank to fermentation to Biological Drug Substance to viald product
 - Again – unit operation – RM controls and end product for next step
- QbD is not new for biologics – without it we would not have processes.

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What are the issues?

- For biologics, issues surface
 - **Lack of complete characterisation – structure not 100% known**
 - **Lack of linkage of Bioactivity measurement and chemical potency**
 - **Significant change in chemistry (carbohydrate/glycosylation) yet no change in potency and also no changes seen in chemistry but potency changes seen**
 - **Changes in immunologic reactions – relevance**
 - **Pharmacodynamic/Pharmacokinetic differences**

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The Real Underlying Issue

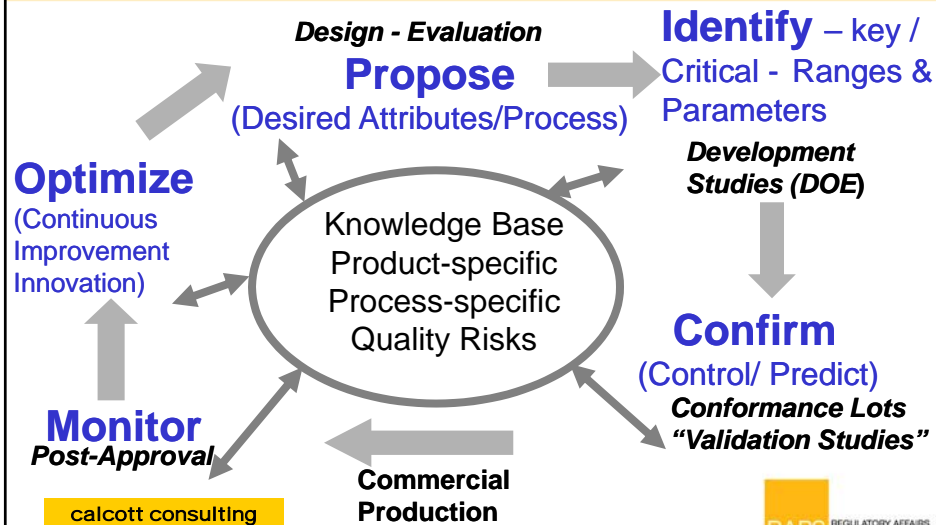
- **Biologics issue is science, communication and trust**
- **For well characterised products comparability protocols step in right direction – partly QbD – predicting outcomes**
- **QbD – Genentech and others are doing this but still a work in progress**
- **Generic biologics will challenge the paradigm**

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Quality Life Cycle by Kozlowski (2007)



Take Home Messages

- QbD is different in industry (generics→biologics)
- QbD philosophy leads to
 - Stronger linkage between departments within companies
 - Improved success in product approval
 - More robust, efficient commercial operations
 - Decreased production failures
 - Decreased regulatory burden
 - Improved relationship with regulatory bodies
 - Science driven compliance

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Q & A

Any questions?

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