QbD / PAT Conference 2012

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QbD and PAT - an Analysis of the Current Situation

The University of Heidelberg

Ajaz S. Hussain, Ph.D., Chief Scientific Officer & President Biotechnology

WOCKHARDT n.D.

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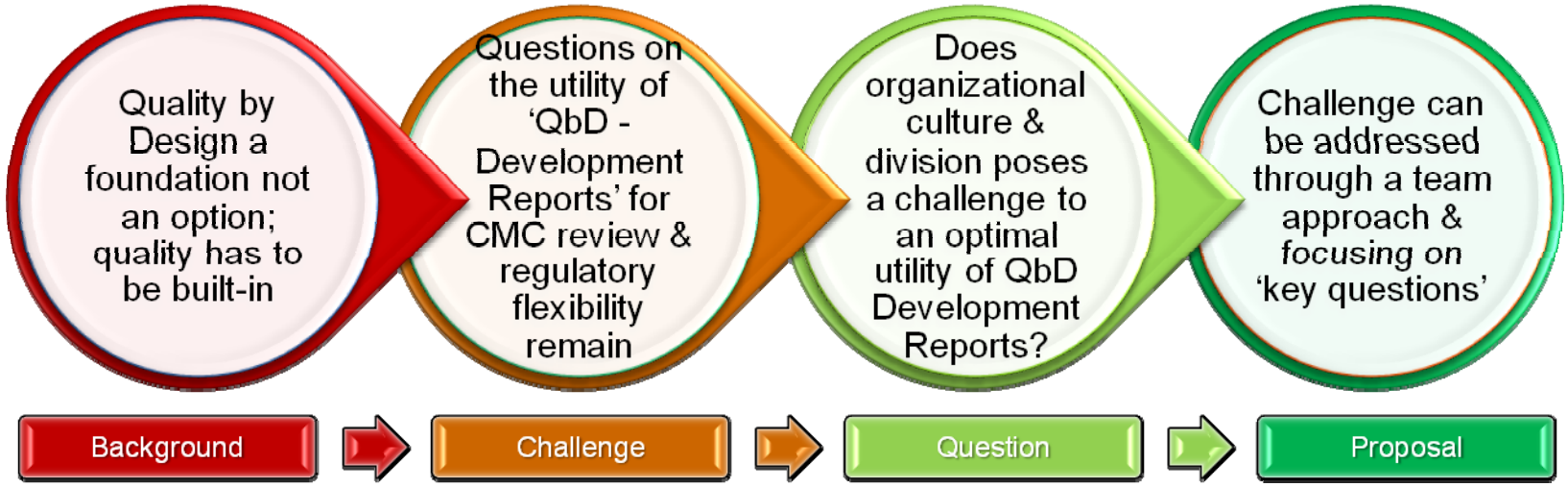
Presentation Outline

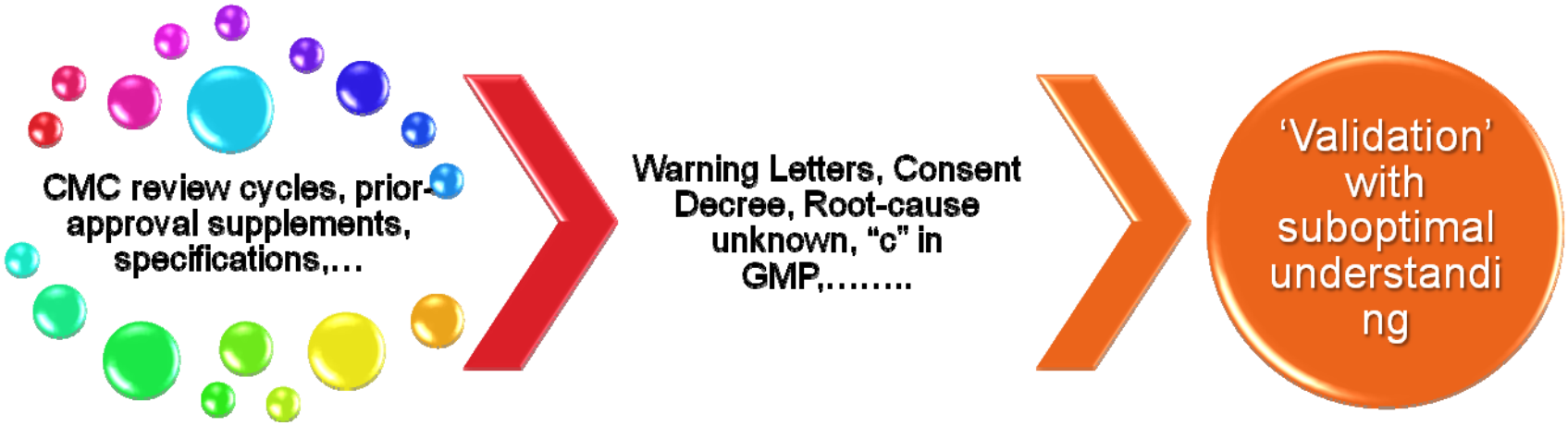


Quality has to built-in or be by Design

From 1987: FDA Guidance: General principles of process validation, May 1987

To 2004: "The goal of PAT is to enhance understanding and control the manufacturing process, which is consistent with … quality cannot be tested into products; it should be built-in or should be by design." (FDA's PAT Guidance, 2004)

What was not optimal?



FDA organizational culture & division

Does it poses a challenge to an optimal utility of QbD Development Reports?

Outside Pharma sector (in the 1990's)?

LEAN	SIX SIGMA	ISO to QS-9000	Baldridge Award, Deming Prize, etc.
Measure, analyze, and reduce • wait time • inventory • batch size • process time • rework	• Use specific metrics • Collect data • Analyze data • Collect control data	Monitor and measure process performance Continuous Improvement	Measure and improve • processes • business results • overall organizational performance
An important area of focus: Statistical analysis and Continuous Improvement (not just CAPA)			

Process Analytical Technology

- Understanding & controlling variability
- Removing fear of large samples & new analytics on old processes
- Opening the door to real-time release & 'Design for Six Sigma'

Process understanding

- Validation of new methods based on mechanistic understanding
- Improvements without "prior-approval supplement"
- Opening the door to 'Lean'; improvements managed within quality system

Continuous improvement

- Understanding technologies, functions & each other
- Finding lean solutions to facilitate improvement
- Ensuring quality in real-time from review, compliance and inspections perspectives

Review-Compliance-Investigator Team

Understanding via development reports?

Validation Times 1 May 2003

- a point of contention …. manufacturers are skeptical about how FDA will use the data,…. how much information to share with the agency

In 2003, "Development reports still a stumbling block"

- "What is needed is the knowledge .. captured within that report, ….. if companies can share that knowledge, the agency can …. set more meaningful specifications to manage those changes in less

Ajaz S. Hussain (CDER, FDA)

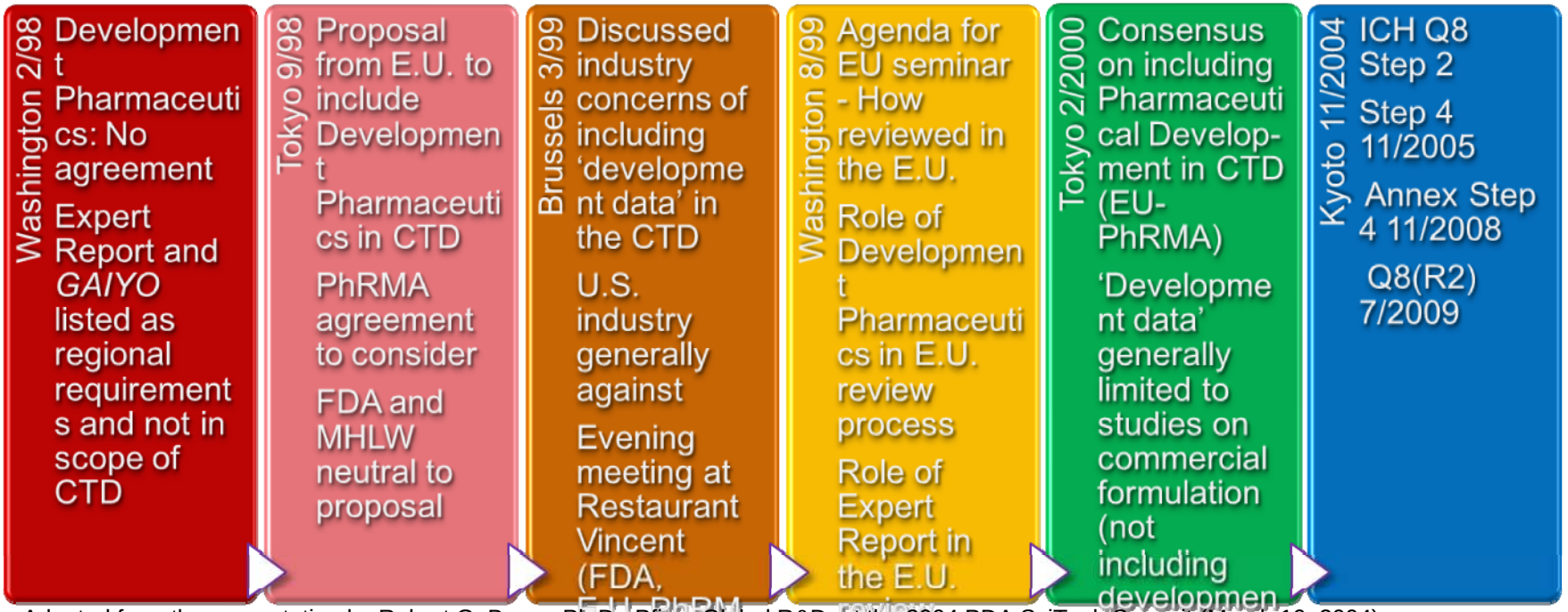
- "….spends a lot of time looking at deviations, failure investigations, things that are a result of a less- than- ideal product or process knowledge. …..how the product has been adequately validated,"

Doug Ellsworth (ORA, FDA)

- … will improve our process, ..requirements are predictable and the process …streamlined, ..and very timely. .. a change …done without prior approval, where we've

Gerry Migliaccio (Pfizer)

Arduous path to Development Reports



Adapted from the presentation by Robert G. Baum, Ph.D., Pfizer Global R&D, at the 2004 PDA SciTech Summit (March 10, 2004)

Now, a option to submit …

- Is a option
- With the anticipation it will not delay approval process
- Not add new requirements

Development Reports for CMC review

- Demonstrate science-based development so that regulators can make risk-based decisions
- Reviewer to gain confidence to support continuous improvement without prior-approval supplements

Why?

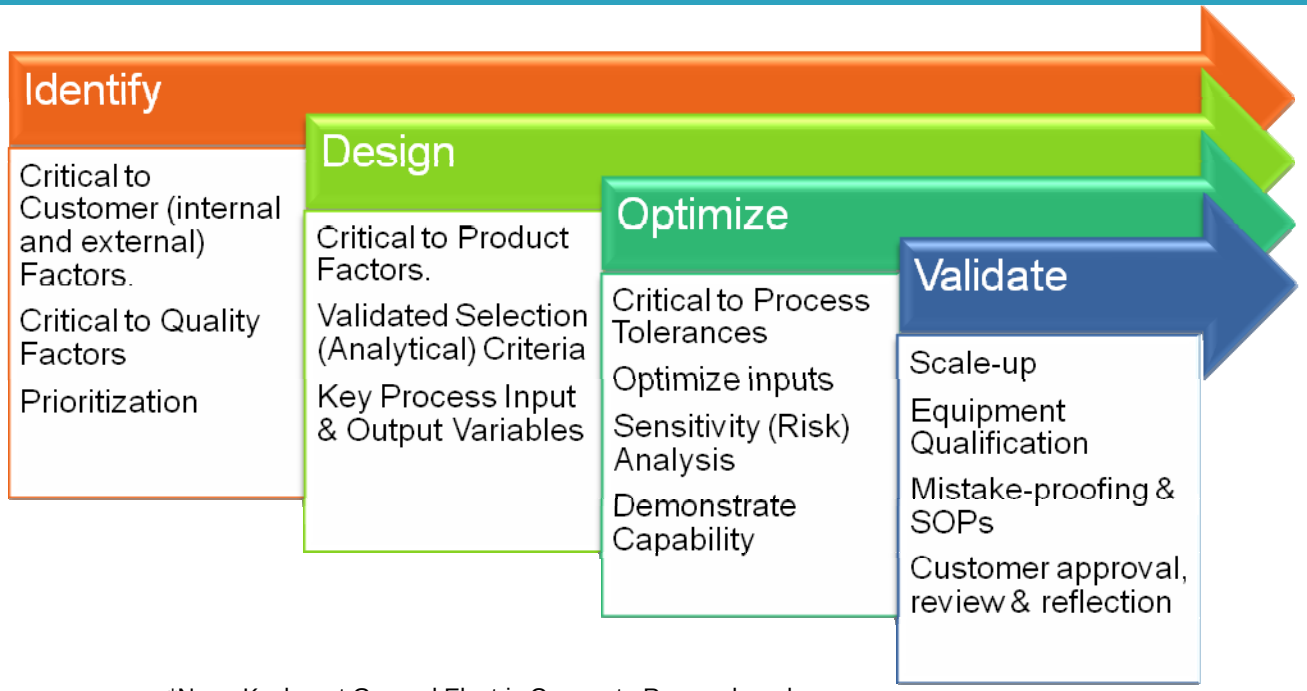
- Guidance per ICH Q8-10
- Design space?
- Review process?
- Role of compliance & investigators?
- Less burdensome approach to improvements?

How?

- Risk-based specifications?
- Less burdensome approaches for improvement?

What?

Non-pharmaceutical Design for Six Sigma*

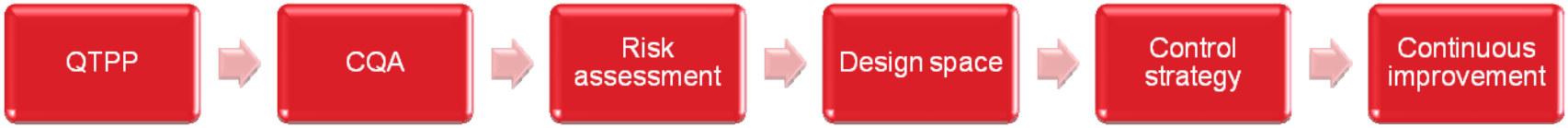


*Norm Kuchar at General Electric Corporate Research and Development. Other approaches - Define, Measure, Analyze, Design, Verify (parallel to the DMAIC process and is advocated by American Society for Quality)

Design for Six Sigma & Pharma QbD

Design for Six Sigma

Pharma QbD as currently implemented: Advisory Committee for Pharmaceutical Science and Clinical Pharmacology July 27, 2011



Some observations

Design for Six Sigma

- Seamless alignment across functions that are compartmentalized in pharmaceutical regulatory review, compliance & inspection
- Prioritization of critical factors over the development process
- Optimization includes considerations for ‘process capability’
- Validation includes a notion of ‘design’ of SOP’s

Current Pharma QbD

- Outlined to reflect CMC review; possibly carving out compliance & inspection functions
- Conceptual compartmentalization of QTPP, CQA’s, etc.
- Design space substituted for “optimization”?; if so, this was not the original intent
- Validation not considered; possibly carving out compliance & inspection functions

Design-space substituted for “optimization”?

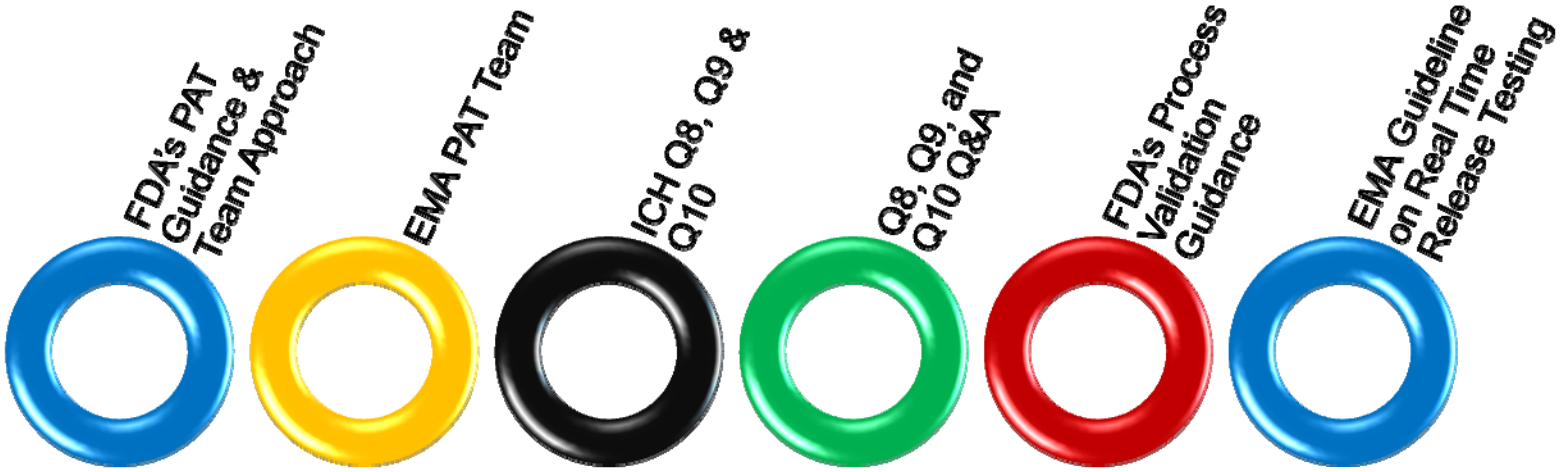
Would make optimization based on ‘response surface’ methodologies a “new review requirement”

- Too narrow in scope to be an effective means for realizing ‘less burdensome approaches for continuous improvement’
- Focuses review staff to seek large amount of empirical data which previously was not submitted

Challenge can be addressed

Through a CMC-cGMP team approach & focusing on ‘key questions’

Guidance documents & practices



Additional guidance is not a solution!

Seamless alignment across functions

Pictures from PAT Team-building event in early 2000

The CMC – cGMP Divide at FDA

- Necessary for common understanding & confidence
- Would allow for an aligned and logical Pharma QbD process
- Facilitate prioritization of critical factors that would be addressed over the development process
- Improve scientific communication within FDA and with sponsors
- Build confidence in risk-based decisions and to identify opportunities for 'less burdensome approaches for continuous improvement'

CMC review, cGMP compliance and investigations team approach (e.g., the previous FDA's PAT Team)

Examples of less burdensome approaches for continuous improvement?

Specifications based on criticality & acceptable variability (e.g., lots used in pivotal clinical trials); and avoiding debates such as need for 'USP Specifications'

Limit on the types of (Prior Approval) CMC Supplements; information kept at site for cGMP Inspection

Confidence (e.g., process capability) based decisions on number of batches needed for process qualification; and other examples such as 'real time release'

Effective risk-assessment

Can occur when both CMC and cGMP functions have a common understanding, and confidence in, the scientific understanding communicated (in development reports) and established at a manufacturing facility where a new product will be manufactured

- Acceptable product variability over the intended shelf-life; prior-knowledge, development data and characterization of clinical trial lots - including process capability (Cpk) assessment
- CMC to cGMP knowledge sharing meeting - specific considerations relevant to a novel product and its implications for technology transfer
- Multi-functional FMEA; considering manufacturing facility data (Cpk of similar products, reject rate, effectiveness of root-cause investigations); also can serve as a structured approach to guide definition of “c” in GMP

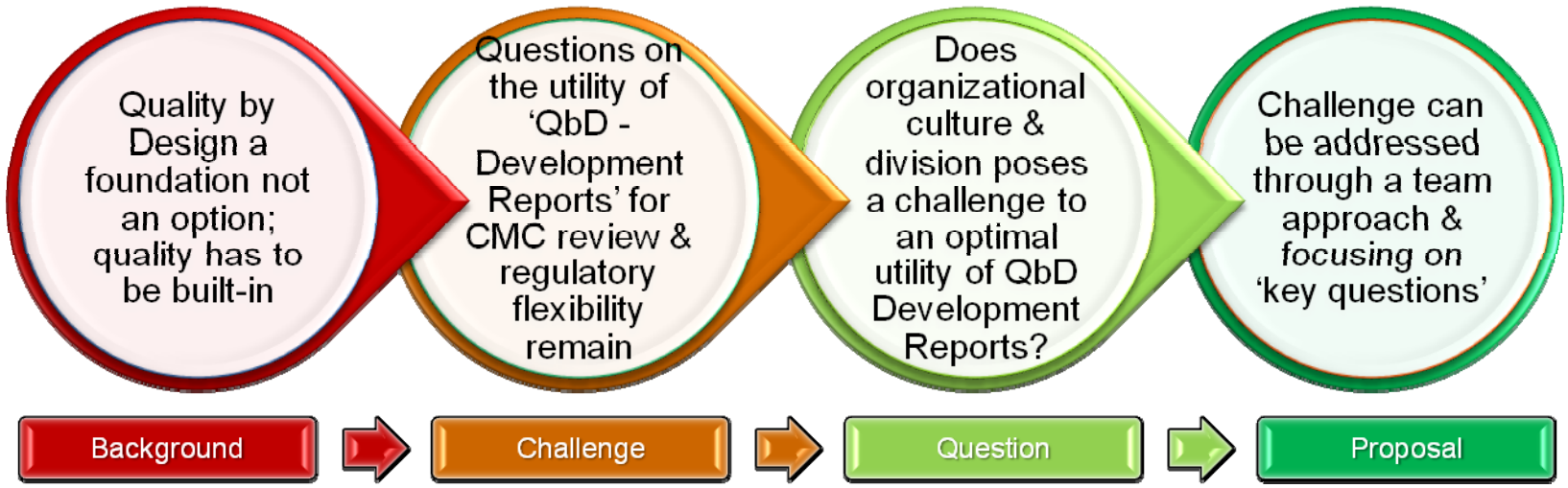
Proposed changes in CDER, FDA

Announced on September 06, 2012

Exploring the creation of a new Office of Pharmaceutical Quality (OPQ)

- Overseeing quality throughout the life cycle of a drug
- CMC review functions (New Drugs, Biotech., Generics) and cGMP compliance (Office of Manufacturing and Product Quality)

Summary


Quality by Design a foundation not an option; quality has to be built-in
Questions on the utility of 'QbD - Development Reports' for CMC review & regulatory flexibility remain
Does organizational culture & division poses a challenge to an optimal utility of QbD Development Reports?
Challenge can be addressed through a team approach & focusing on 'key questions'
Background
Challenge
Question
Proposal