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Process Analytical Technology Initiative: An Overview

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5th EGA Symposium on Biosimilars, London

a Novartis company

Outline

- **A note about the EMEA Workshop on Process Analytical Technologies for Biologicals (15th March 2007, Room 3A, EMEA)**
- **An overview of the FDA's PAT Initiative and ICH "Desired State" for Pharmaceutical Quality**
- **Opportunities for complex generics and biosimilar development**
- **Summary**

Making Medicines Affordable

An Perspective on PAT and ICH Process: The Biosimilar Context

Workshop on Process Analytical Technologies for Biologicals

15th March 2007, Room 3A, EMEA

Ajaz S. Hussain, Ph.D.

Vice Chair, EGA B&B Committee

Quality by Design

- The comparability of a similar biological medicinal product to the reference product can only be successfully demonstrated if quality and similarity or equivalence have been designed into the product during development.
- Quality by Design includes the design of an independent cell line and manufacturing process to deliver all the relevant characteristics of a reference product
- A set of orthogonal characterization tools are essential and can help overcome the limitations of single methods to obtain a complete picture of the product
- Pre-clinical and clinical assessment utilized to address remaining uncertainty and to confirm similarity and equivalence

Opportunities for complex generic products and biosimilars

- **Regulatory utility of QbD and PAT principles can provide additional opportunities to**
  - Encourage technologies to help with the design of biosimilar processes and products
  - Utilize more effective approaches to demonstrate equivalence and/or comparability
  - Justify alternate pre-clinical and clinical assessment protocols to address residual uncertainty that minimize the need for certain clinical trials
  - Provide additional opportunities for scientific assessment and justification of interchangeability

Supporting Innovation

- Generic and Biosimilar industry are also investing in innovative technologies
- Regulatory policies and procedures should be flexible to accommodate innovative technologies
- ICH process often does not fully recognize the needs of the generic industry

EGA appretiates this opportunity to participate

- **Applauds EMEA's leadership to clarify the role of PAT for biologics**
  - Can help the biotech industry in their efforts to utilize new technologies to further improve their ability design high quality products and to demonstrate comparability
  - Further improve process control capabilities and improve manufactring efficiency
  - Ultimately, these efforts will potentially further enhance competition to best serve the patients by ensuring « affordable, high quality »

Historical Overview of FDA's PAT Initiative

- **Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach. Final Report - Fall 2004**
  - http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm
- **Innovation and Continuous Improvement in Pharmaceutical Manufacturing:**
  - **The PAT Team and Manufacturing Science Working Group Report: A Summary of Learning, Contributions and Proposed Next Steps for Moving towards the "Desired State" of Pharmaceutical Manufacturing in the 21st Century**
  - http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm#_Toc84065754
- **Guidance for Industry. PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance**
  - http://www.fda.gov/cder/guidance/6419fnl.htm

From 1990-2000: At FDA, the primary drivers for improving CMC/Biopharm regulatory policy

- Need for an efficient approach to *post approval* manufacturing changes (e.g., SUPAC Guidelines, Waiver of BE studies, etc.)
- Un-ending debates
  - In process controls/tests (e.g., blend uniformity)
  - Regulatory specifications (e.g., dissolution, impurities, etc); specifically for complex products such as MDI
  - Validation of new analytical methods
- Inability to efficiently approve generic versions of highly variable drugs, complex products, and “locally acting” generic products

Dr. Woodcock's Challenge: Starting in 2000

- **"Will this $ X00 million "consent decree" improve quality of the real product?**
  - **How effective is "process validation"? Is it not just a "well rehearsed demonstration…. 3 times"?**
  - **Is our system truly a "modern quality system"?**
  - **Are our "specifications" based on sound science and risk principles?**
  - **How is "c" in cGMP established?**
  - **Do current regulations support "continuous improvement"?**
  - **How efficient is pharmaceutical manufacturing?**

Need for a comprehensive solution!
PAT the door opener!

"….a little secret….."(WSJ)

THE WALL STREET JOURNAL.

WEDNESDAY, SEPTEMBER 3, 2003 - VOL. CCXLII NO. 45 - ★★★★ $1.00

Factory Shift

New Prescription For Drug Makers: Update the Plants

After Years of Neglect, Industry Focuses on Manufacturing; FDA Acts as a Catalyst

The Three-Story Blender

By Leila Abboud And Scott Hensley

Main points from this:

- High tech in R & D
- Relatively low tech in Manufacturing
- It matters
  - Big Pharma manufacturing costs are $ 90 Bn
  - Significantly more than R&D

Quality by Design: A Challenge to the Pharma Industry

(CAMP, R. Scherzer. FDA Sci. Board. 4/9/02)

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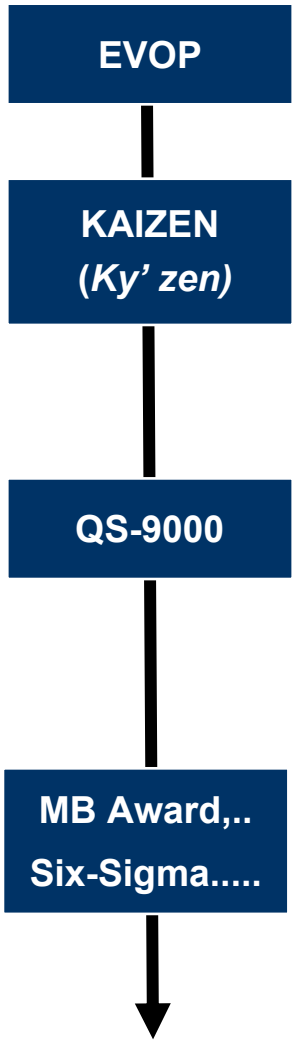
Continuous Improvement Process



Proposed in 1957 by G. E. P. Box

(Evolutionary operation: A method for increasing industrial productivity. Applied Statistics. 6: 81-101 (1957))

A Japanese word introduced in the West (~late 70's)

and translated as "Continuous Improvement"

- slow, incremental but constant.

"For those product characteristics and process parameters that can be evaluated using variable data, continuous improvement means optimizing the characteristics and parameter at a target value and reducing variation around the value.."

Quality System Requirement QS-9000, 3rd edition, element 4.2.5 – Continuous Improvement (1998)

- **Structured development then EVOP -**approach based on statisitical DOE's –EVOP protocol
- **Empowerment through training**
- **Specifications -** attribute data - continuous improvement is not possible until characteristics are conforming.
- **CAPA Vs Continuous Improvement Vs. Innovation -** If attribute data results do not equal zero defects, it is by definition a nonconforming product. Improvements made in these situations are by definition corrective actions, not continuous improvement.

No lurching from "fad to fad"- focus on solid foundation!

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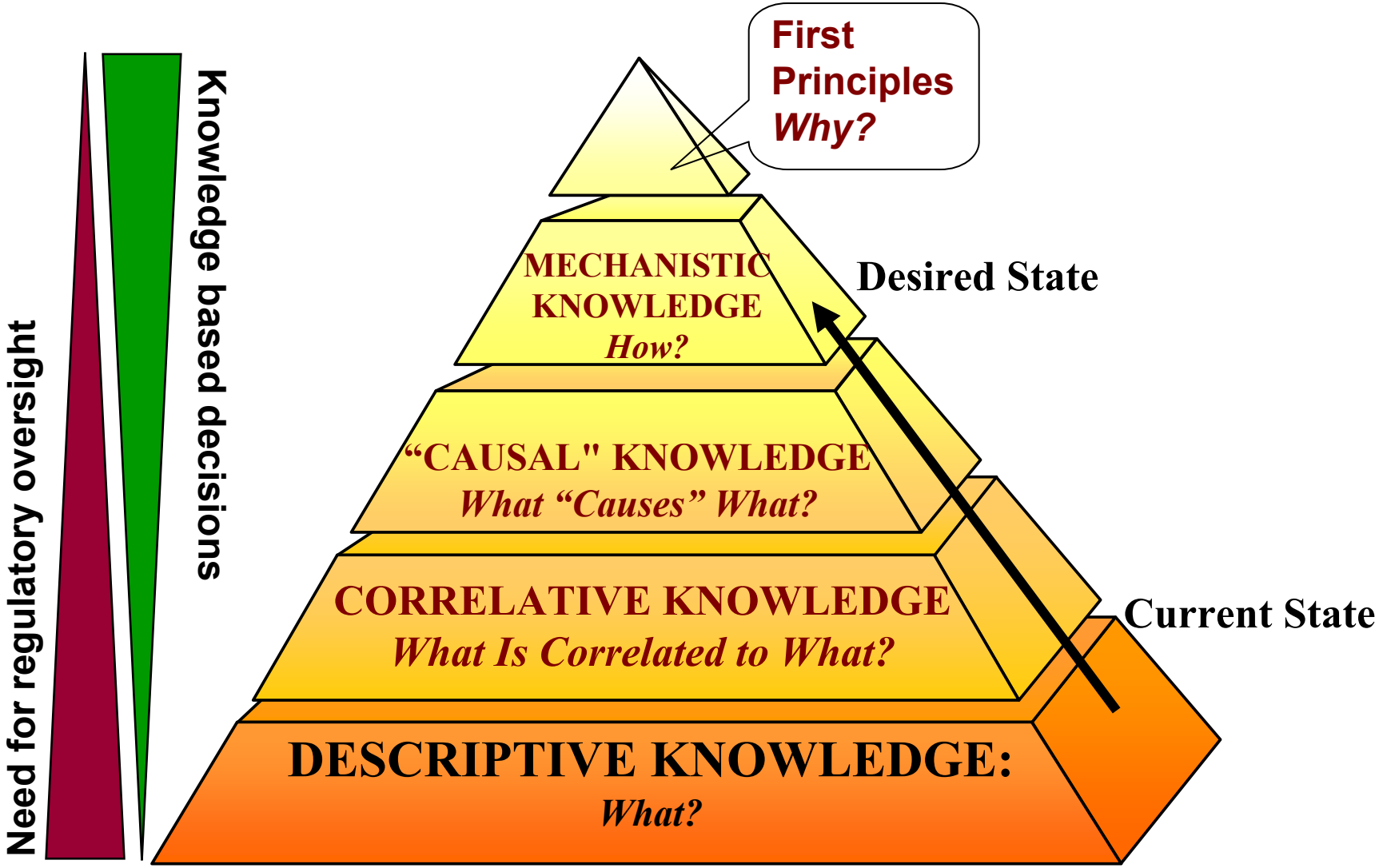
Regulatory oversight can be tailored to reflect scientific rigor demonstrated in an application when it is realized through company's robust quality system



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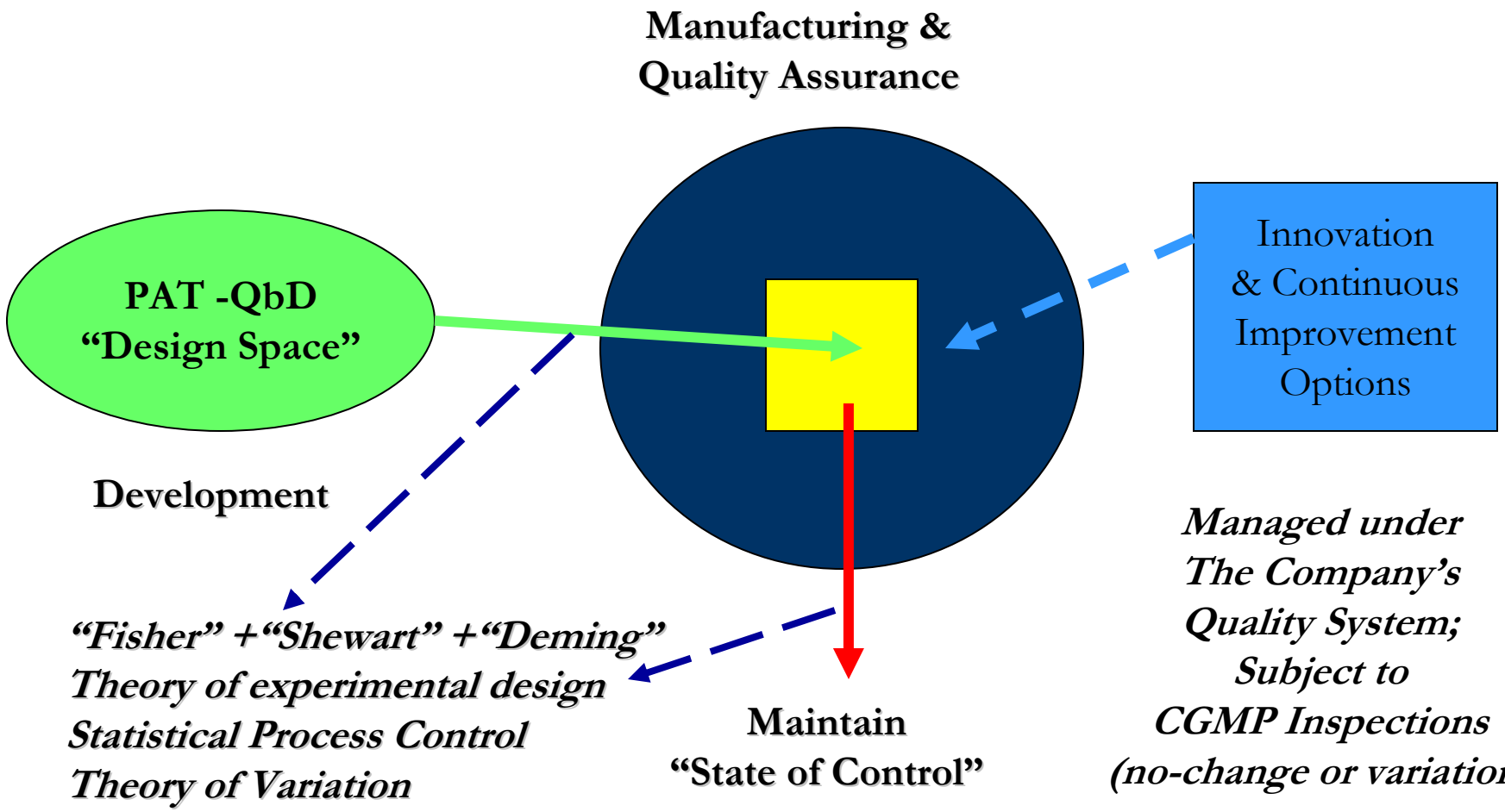
Opportunity Framework: “Right Specification” to “Continuous Improvement” to “Maximize Efficiency” to “Customer Satisfaction & Profit”



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First step in search for a comprehensive solution: Bridge the CMC-cGMP Divide

- **"Turf" battles >> Team Approach**
- **Vocabulary: Negative >> Collaborative ("process validation >> process understanding")**
- **"Process control": "Static" >> "Dynamic" concept (part of "design space")**
- **"Pharmaceutical Development" information kept at site >> shared with CMC reviewers (Quality by Design -ICHQ8)**
- **Risk-based decisions (ICH Q9)**
- **Minimize *Prior-Approval Supplements* >> Change Control within company Quality System ("ICH Q10")**
- **Reduce regulatory fear to promote continues learning**
- **CAPA >> Continues Improvement**

The CMC – cGMP Divide at FDA

The PAT Framework: Based on well established principles (Fisher + Shewart + Deming")

Guidance for Industry

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

Pharmaceutical CGMPs
September 2004

Regulatory strategy accommodating "process understanding" based regulatory flexibility for innovation and continuous improvement

The diverse and determined PAT team has good reason to smile.

Pharmaceutical Manufacturing • www.pharmamanufacturing.com

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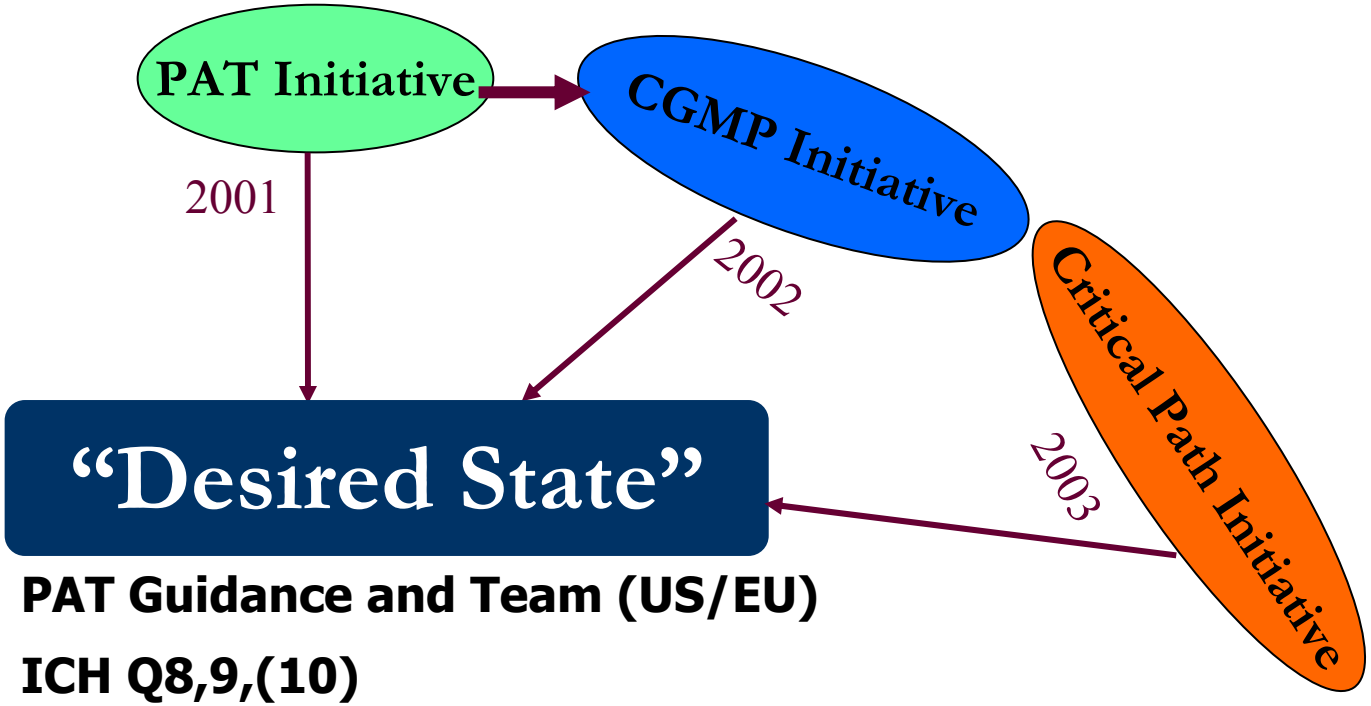
PAT: Opened the door for ICH Q8, Q9, Q10, FDA/OGD's Question based Review, etc.



PAT Guidance and Team (US/EU)

ICH Q8,9,(10)

CPG 7132c.08

FDA QS Guidance

FDA in PICS

July 2003 *Informal discussions at ICH Brussels*
Nov. 2003 *Q8 and Q9 approved, Q10 unclear….*
Sept. 2005 *ICH Q10 Concept paper*
Nov. 2005 *Q8 and Q9 reach step 4*
Nov. 2005 *Q10 agreed as a formal ICH topic*

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The “desired state”- steps to get there

Product quality and performance achieved and assured by design of effective and efficient manufacturing processes

Product specifications based on mechanistic understanding of how formulation and process factors impact product performance

An ability to effect continuous improvement and continuous "real time" assurance of quality

Develop effective CAPA – eliminate “special cause” variability

Utilize Process capability analysis – reduce/control “common cause” variability

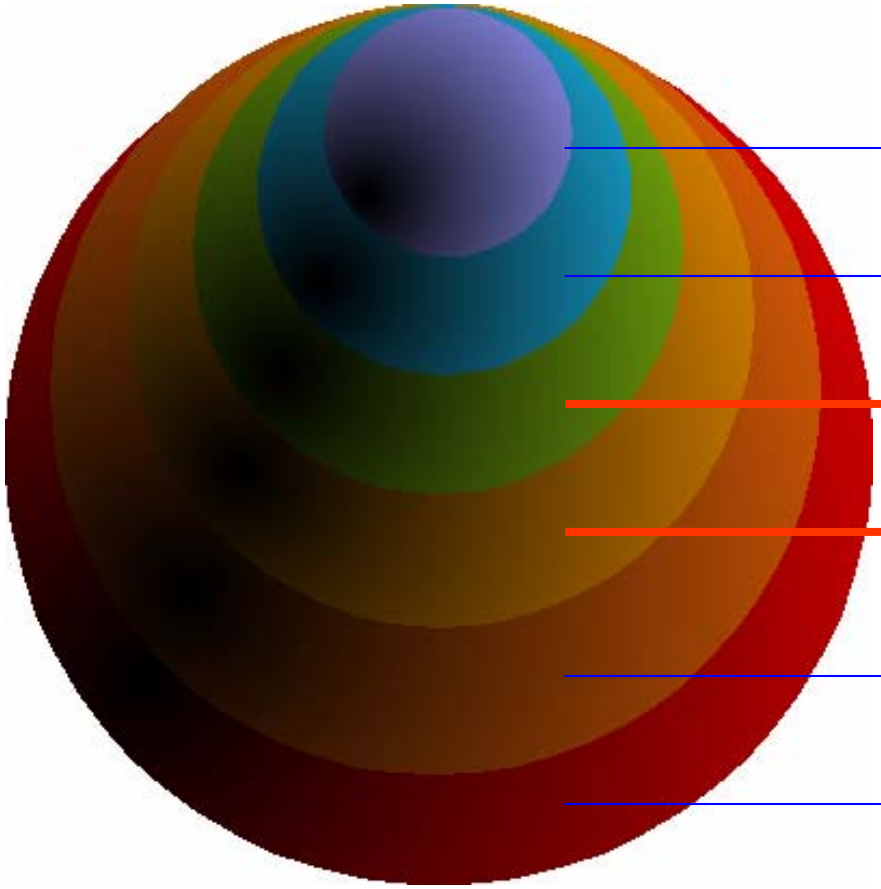
Identify, understand and acquire ability to predict critical to quality attributes of materials (CQA) (product/process/measurement)

Focus on the “critical few”

Establish CQA target values and acceptable variability around the target value

Utilize a monitoring system that demonstrates “state of control” preferably based on critical material attributes (not just end product testing)

What is the ICH Q8 Opportunity?



ICH Q6A
Decision Characteristics

- Specifications
- In process controls
- Development
- Design
- Process validation
- GMP Controls

"…where the provision of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches."

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ICH Q8: The Design Space

- **Is the established range of process parameters that has been demonstrated to provide assurance of quality. In some cases design space can also be applicable to formulation attributes.**
- Provide confidence to regulators that certain changes can be managed within a company's quality system, which is subject to CGMP Inspections, so that CMC Supplement approval process can be eliminated – incentive for continuous improvement!
- **Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.**

Realizing the benefits of “Design Space”

- Define product specifications based on prior knowledge; iteratively refine using development data
- Experimental product - Utilize a structured development approach to identify and control sources of variability to reliably deliver a product of desired specifications
- Clinical trial product - Within an established control system, measure and record intra- and inter-batch variability in critical attributes (raw, in-process, and product) – adequacy of the design reflected in state of statistical process control; establish in-house alert and control limits (well within the desired specifications – proposed regulatory specifications)
- Justify regulatory in-process and final product specifications, on relevant material attributes, in the form of “variable data” – avoid the erroneously termed “zero tolerance” limits

Realizing the benefits of “Design Space”

- **Provide justification to regulators that application commitments should be limited to specified material attributes for the established control strategy**
- **Transfer knowledge to regulators, TechOps, QA,….**
- **Acceptable product transfer from R&D to TechOps based on demonstration of equivalent *process capability* (intra- and inter-batch)**
- **Establish Continuous Improvement Protocol to incorporate quality and business needs**
- **Empower TechOps & QA with effective knowledge transfer and training to execute continuous improvement program**
- **Maintenance of established statistical process control alert limits document the effectiveness of continuous improvement activities**
- **Special cause variability within the control limits investigated and removed – knowledge transfer back to R&D**

QbD: Complex Generics and Biosimilars

- **The Quality-by-Design framework provides an scientific basis for developing therapeutically equivalent generic and biosimilar products and establishing appropriate regulatory requirements**

Sandoz Presentation at EMEA PAT Workshop

Illustrate an integrated *quality by design* approach for development of a therapeutically equivalent XYZ product

- **Establishment of design specifications based on originator product design space**
- **Design and control of XYZ manufacturing process and starting materials to reliably deliver a product within the target product design space**
- **Establishing manufacturing process design space**

Sandoz Presentation at EMEA PAT Workshop

- **Through characterization of originator XYZ products and lot-to-lot variability to yield the *target product design space***
- **Validate the established target product design space**
- **Design a manufacturing process and its control strategy within defined constraints on starting material to reliably produce a product within the target design space**
- **Establish process design space to demonstrate adequacy of controls on starting materials and manufacturing process to justify regulatory flexibility with respect to:**
  - **Pre-clinical and clinical requirements**
  - **Regulatory specifications for raw material and in-process controls**
  - **Anticipated scale-up and post-approval changes.**

Summary: Manage variability, uncertainty and science & technology

Mode of Response	Key Focus Areas	System Modification	
		QbD	Flexibility
Operational	CAPA, Efficiency, etc. – Learning to R&D	Control of excipients and other sources of "common cause" variability	Reduce CGMP Risk Classification – Continuous Improvement of Quality System
Tactical	Statistical Process Control (Technology & Knowledge Transfer)	Critical Control Points - Robust process end-point Reg. Spec – material attributes	"Design Space" Real –Time Release, Modular Validation Reg. CMC Approval
Strategic	Science of Design Technology Management Business Case	Sci. & Tech. Integration – Continuous Learning & Improvement Regulatory Communication	Integrate Sci - Enabling Technology Platform – "Plug & Play" "Time to Market" + "Production Efficiency"