DRUG INFORMATION ASSOCIATION

42nd Annual Meeting

Implementation of Quality by Design

Designing Quality into Drug Products

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Philadelphia 2006

AMGEN 25 YEARS

Implementation of Quality by Design

- Amgen's Vision
- Motivating documents from Regulatory Agencies
- Brief History of Precursors to QbD
- Implementing QbD
- Tools and their value to QbD
- QbD Example Case
- Questions, answers and discussion

QbD = Quality by Design

Amgen's Vision for Commercialization

- World-class Commercialization means that we flawlessly execute the development, marketing, manufacturing and lifecycle management of products, based on breakthrough science and insightful marketing perspectives to fully address our customer's needs.

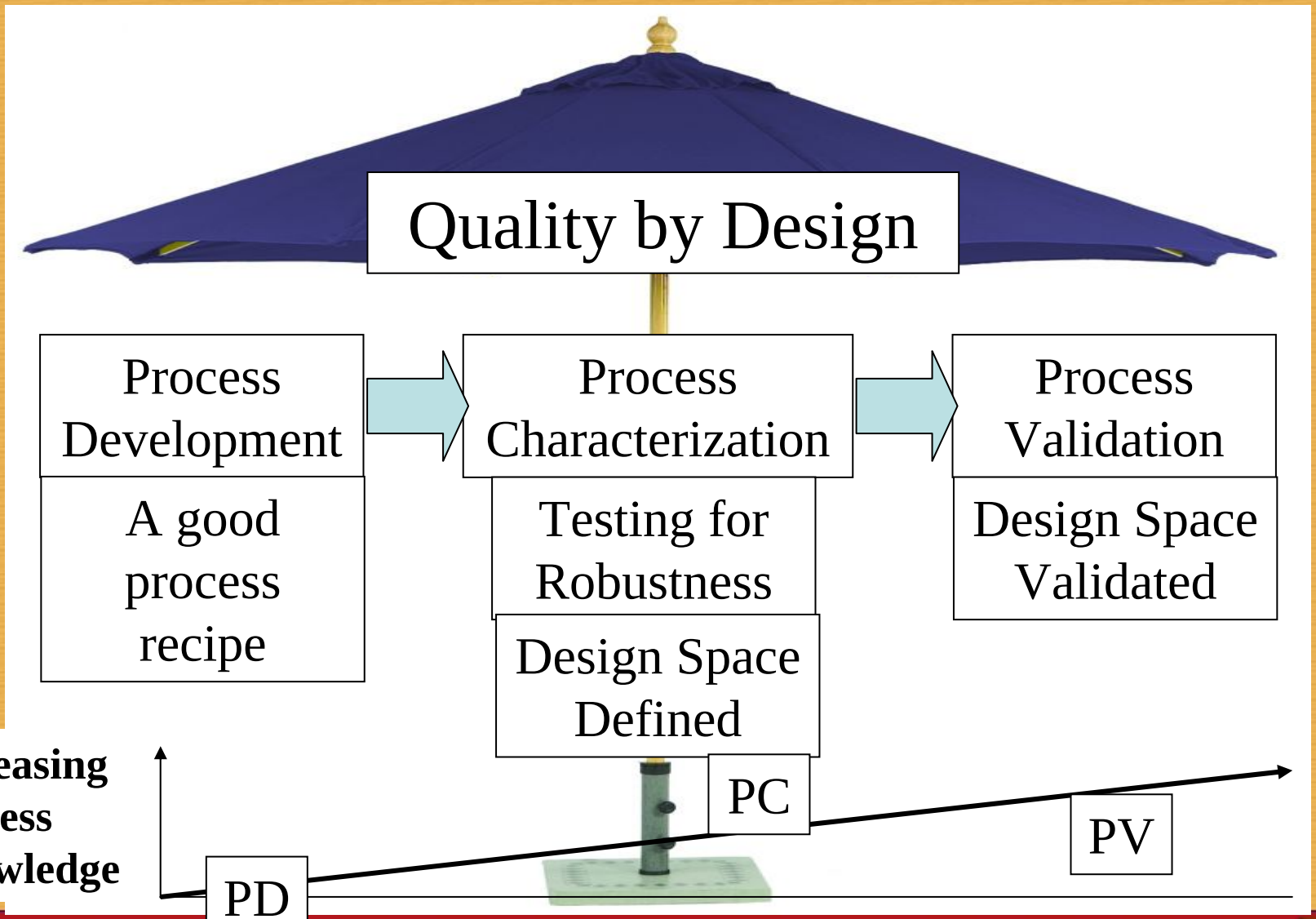
Emphasis added by presenter

Amgen's Vision for Commercialization -continued

- Our Commercial Product Development includes a clear connection between Process Development, Process Characterization and Process Validation. The umbrella over that connection is ***Quality by Design***.

Emphasis added by presenter

Quality by Design=Umbrella



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Motivating Documents

- Quality by Design
- Design Space

Towards a Risk- and Science-Based Approach to Pharmaceutical Quality

"To make [the] link [between measurement and risk], we must turn to the science of manufacturing and the concept of quality by design (QbD), which means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches. To achieve QbD objectives, product and process characteristics important to desired performance must be derived from a combination of prior knowledge and experimental assessment during product development."

Woodcock, J. "The Concept of Pharmaceutical Quality" American Pharmaceutical Review, Nov/Dec 2004.

PQRI/FDA Report on the Workshop "A Drug Quality System for the 21st Century," April 22-24, Washington, D.C. (prepared June 16, 2003)

"Firms must continue to move from a compliance mindset to quality by design. FDA must understand that one size does not fit all for regulatory processes and quality by design will only be facilitated by increased flexibility." Sec.2

Motivation!!! From FDA!

http://www.fda.gov/cder/gmp/pqri-MfgSciWkshp.htm

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U.S. Department of Health and Human Services
Food and Drug Administration

http://www.fda.gov/ohrms/dockets/ac/03/slides/3980S1_09_Hussain_files/frame.htm#slide0335.htm

Quality by Design: Next Steps to Realize Opportunities?

Ajaz S. Hussain, Ph.D.
Office of Pharmaceutical Sciences
CDER, FDA
17 September 2003

Presentation to the Food and Drugs Administration Advisory Committee for Pharmaceutical Science: Manufacturing Science Subcommittee

Outline
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What is QbD?

- Design decisions based on thorough formulation and process understanding as these relate to the intended use
- What is the relationship between QbD and Risk?
  - Within a given quality system and for a product: inverse relationship between level of QbD and Risk

http://www.fda.gov/ohrms/dockets/ac/03/slides/3980S1_09_Hussain_files/frame.htm#slide0335.htm

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Implementation of Quality-by-Design Principles in CMC Review: Office Of New Drug Chemistry Approach

Chi-wan Chen, Ph.D.
Deputy Director
Office of New Drug Chemistry

Advisory Committee for Pharmaceutical Science (ACPS)
October 26, 2005

http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4187S2_04_Chen.ppt

(Implementing QbD)

PQAS - What does it mean?

Pharmaceutical Quality Assessment System

- In a QbD paradigm, process understanding links manufacturing controls to CQAs/specifications and hence to the desired performance of the DP
- In the desired state, quality control is moved upstream to critical process steps and CPPs rather than relying on end-product testing
- To achieve this desired state, relevant design information is necessary for quality assessment
- It is imperative to define CQAs through multi-disciplinary interactions, e.g., clinical, pharm/tox

http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4187S2_04_Chen.ppt

ICH Q8 Pharmaceutical Development: ICH Draft Guidance

DIA WEBINAR

MARCH 30, 2005 12:30 PM-1:30 PM ET

MODERATOR

LOIS Q. SEMMENS
Director, CMC Submissions
King Pharmaceuticals R&D

SPEAKER

AJAZ HUSSAIN, PhD
Deputy Director, Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Food and Drug Administration

Source: FDA website

Design Space

- 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.
- Working within the design space is not generally considered as a change of the approved ranges for process parameters and formulation attributes.
- Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

Source: FDA website (continued from last slide)

Guidance Q8
Pharmaceutical Development

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. Working within the design space is not generally considered as a change of the approved ranges for process parameters and formulation attributes. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process."

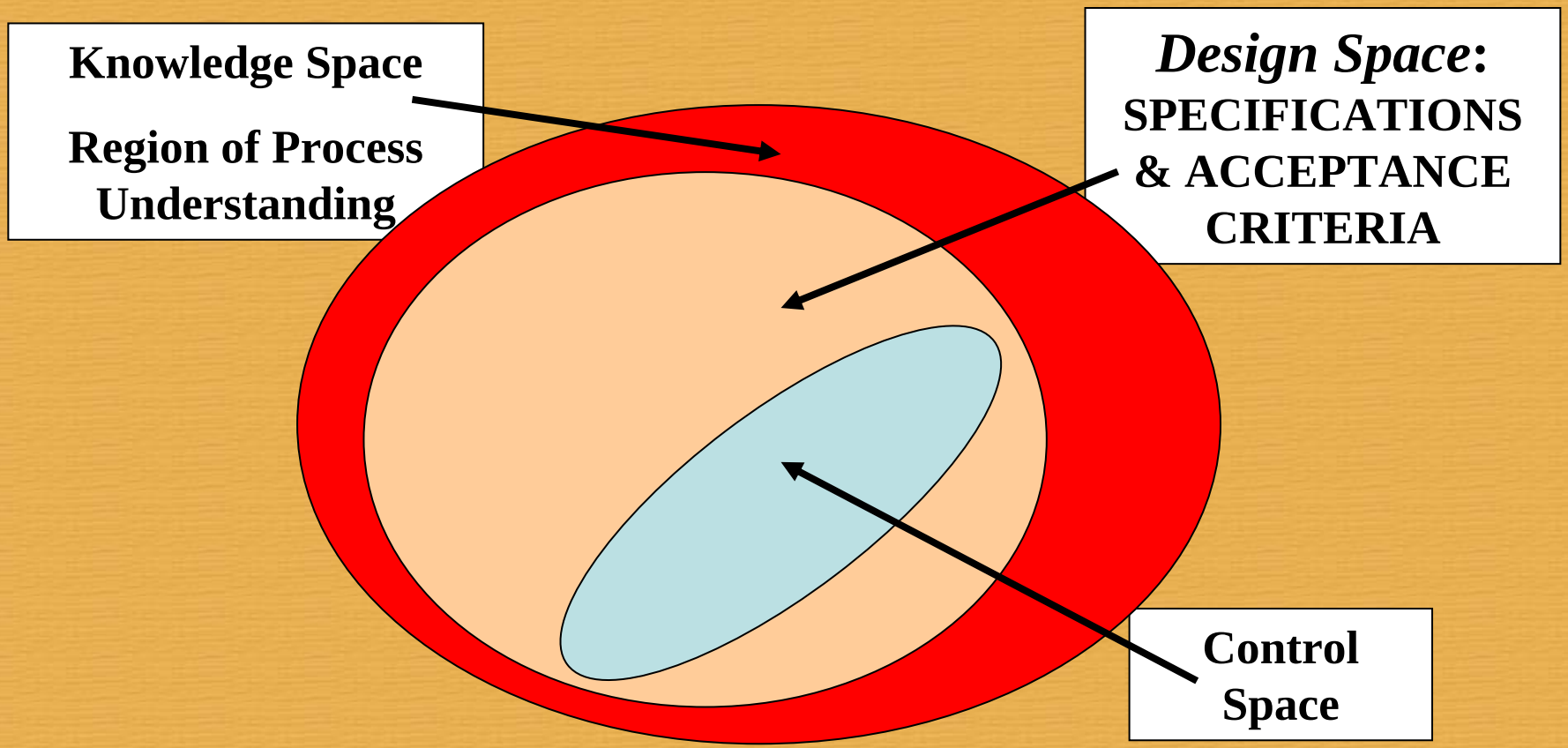
Source: Q8 Glossary

ASTM's Definition of Design Space

- Design space for the process …[is] the operating range for key process parameters which will deliver product that meets the key quality attributes of the product.
- CPP Critical (or Key) Process Parameters
- CQA Critical (or Key) Quality Attributes

Design Space is but one part of QbD

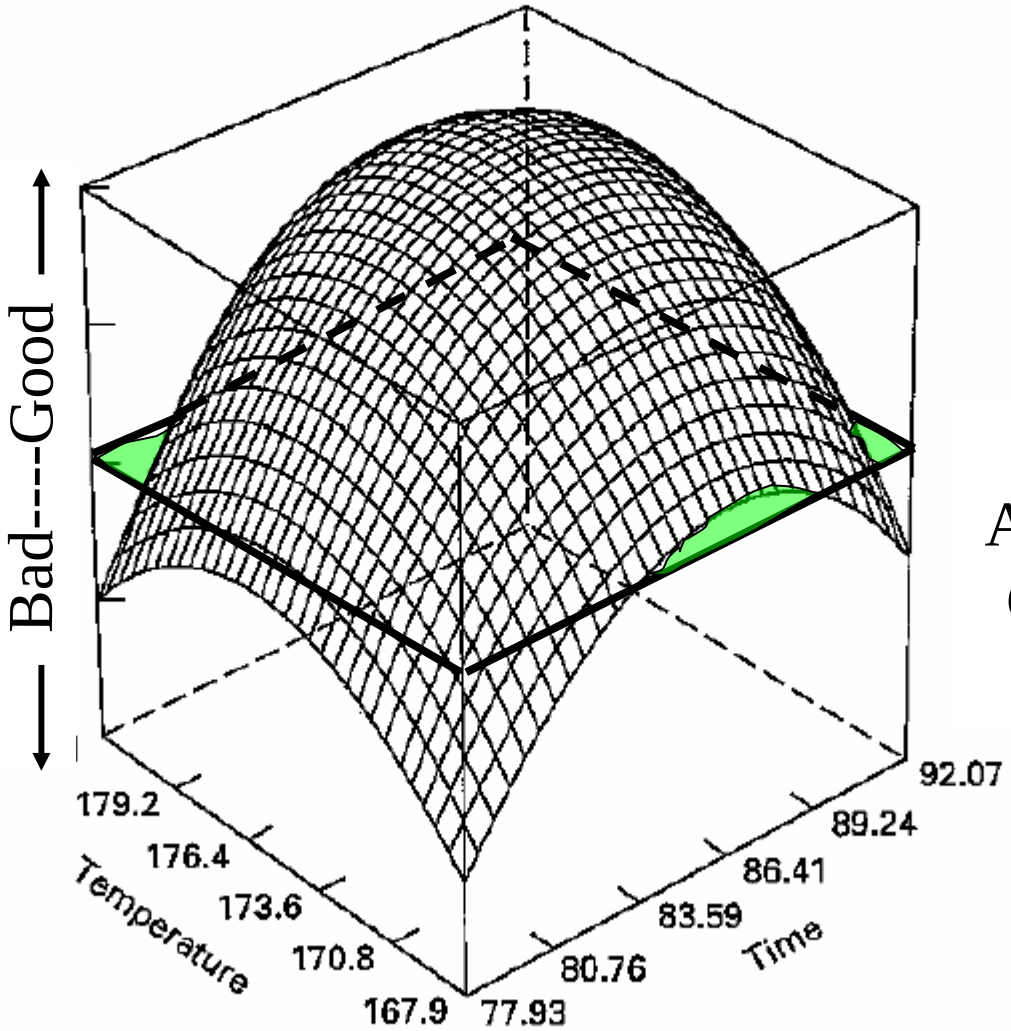
Establishing a Common Vernacular



Control space within *Design Space* i.e. control strategy allows control within DS: NOT CRITICAL- i.e. does not jeopardize specifications

Reference: Implementing Principles of ICH Q8 – industry perspective. PDA/FDA Joint Reg. Conf. Sep ’05. Presented by L. Coulson & R. Nosal (& J.Berridge) -Pfizer.

Response Surface Plot



Design Space:
Above the plain.
Control Space:
Yet higher up.

(Design Space added to Montgomery's figure.)

Montgomery, D.C. Design and Analysis of Experiments. J.Wiley & Sons. 1997. p592.

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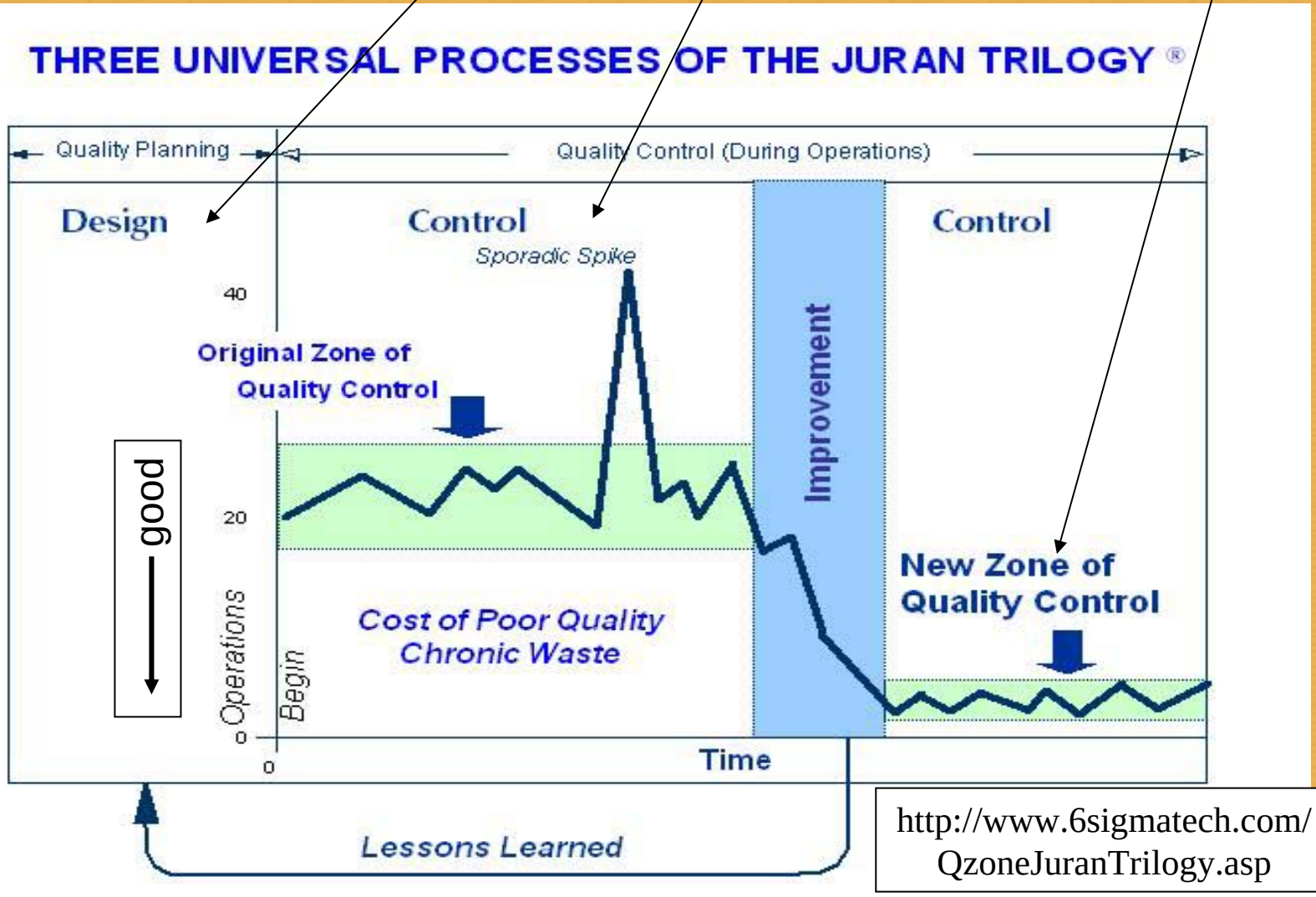
Pre-QbD History

Pre-cursors to Quality by Design

- Quality Planning as part of Juran's Triology: Quality Planning; Quality Control; Quality Improvement
- Total Quality Management
- Six Sigma: i.e. Design for Six Sigma (DFSS)
- cGMPs FDA's Quality Initiative for the 21st Century including Process & Analytical Technologies (PAT)

Juran's Trilogy: Design, Control & Improve



http://www.6sigmatech.com/QzoneJuranTrilogy.asp

DESIGN: Create a process that will be able to meet established goals and do so under operating conditions.

Continuous Improvement Cycle

- Plan — Plan the steps
- Do — Perform the steps
- Check — Analyze the Results
- Act — Use the Results
- Cycle back and do it again
- May be called “PDCA cycle”

Six Sigma's Design Process (Design for 6Sigma)*

Define	•Define the project's goals and customer-deliverables (internal and external)
Measure	•Measure and determine customers' needs and specifications
Analyze	•Analyze the process options to meet the customers' needs
Design	•Design the process to meet the customers' needs
Verify	•Verify the design performance and ability to meet customers' needs

*DFSS is analogous to QbD.

Reference: isixsigma.com

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Implementing QbD

Top Down Implementation of QbD

- Commercialization Process includes QbD
- Awareness education is given broadly
- Quizzes, Surveys, Anonymous Q&A Sessions
- Road show presentation taken to each site
- Specific training in the tools to put them specifically into use is given "***in a timely manner***" prior to actual use
- Complimenting this is "Design for Six Sigma" education

Top Down Implementation of QbD

- Executives use the words and explain the concept and its value as part of our new Commercialization Process
- Operations Leaders' Meetings held at company sites
- One of 4 major lessons from Leader's Mtg given as:
  - "Practice **Quality by Design**, Risk Management and Continuous Improvement."
  - "Quality by Design is critical to ensuring a safe and reliable supply of products for our patients."

    -Stated by the VP for Quality
- QbD training delivered with hands-on exercises (instructors, mentors, team leaders are all defined)

Amgen Leadership Training

What is Quality by Design?

- Quality by Design - Is the activity of establishing customer needs and developing the process and products required to meet those needs.
  Quote from company communications.

Quality by Design is QUALITY PLANNING or PLANNING FOR QUALITY much like Juran's Trilogy

Excellence in Quality Award

The Quality by Design Team was Honored with Excellence in Quality Awards for 2005

Kent, Mike and Eric are being recognized for their vision, strategic leadership and key roles in the *Quality By Design* program. They developed training materials, which were tied to the business, and presented them in a compelling way that included interactive workshops. This program influenced many staff within ATO Quality, as well as select individuals from other organizations.

Kent, Mike and Eric are role models – they personally engaged in resolving underlying issues, persevering, and demonstrating commitment to create a lasting change to the organization. They significantly contributed to establishing a world-class culture of quality, which emphasizes Quality by Design, "Right the First Time," and knowledge sharing.

Graduates of the *Quality By Design* program have already applied the concepts they have learned to improve the quality of efforts in their areas.

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Sample Tools of QbD

Some of the Tools of QbD

- Plan for Quality
  - Establish Quality Goals. Develop Products & Processes to meet them
    - Juran's Quality Planning Roadmap
- Define Customer AND Product Needs
  - Risk Mgmt; FMEA; Quality Function Deployment
- Design the System to make the Product
  - Process Flow; Characterize; Validate; Monitor; Sample; Feedback Control; Cp; EVOP Experiments
- Design the System to deliver the Product
  - Bio; Chem; Physics; Ergonomics; Device Engineering

Planning for Quality (Juran)

Recognizing Gaps ("Mind the Gap"...London Underground)

Customer Expectations

Understanding Gap

Understanding Needs

Design Gap

Designing the Product

Quality Gap

Process Gap

Capability to Deliver

Operations Gap

Actual Delivery

Perception Gap

Customer Perceptions/Realities

Early,J.F. and O.Coletti. Section 3: "The Quality Planning Process." Juran's Quality Handbook. 5th Ed. 1999.

Planning for Quality

Close these Gaps

1. **Customer Expectations**
2. **Understanding Needs**
3. **Designing the Product**
4. **Capability to Deliver**
5. **Actual Delivery**
6. **Customer Perceptions**

Use these Quality Tools

1. **Voice of the Customer**
2. **Establish What is Critical to Quality***
3. ***CTQs become Product Attributes**
4. **Voice of the Process (How to make it)**
5. **Crit. Qualities Deployed to Functions Experiment, Measure, Control (Quality Function Deployment)**
6. **Complaints & Adverse Rxn Tracking**

*CTQ = Critical to Quality

Quality by Design – Training Objectives

Identify Customers and Needs

- Define Scope
- Id Customers
- Identify Critical to Quality Customer Requirements (CTQ's)
- Agree on Specific Measures

Develop Product Features

- Priortize CTQ's
- Identify Product Features
- Set Product Feature Specifications
- Analyze Product Features against Regulations and Standards

Develop Process Features

- Review Product Specifications
- Identify Operating Conditions
- Identify Process Features
- Prioritize and set Process Feature Specifications
- Build/Confirm Design Space

Create Process Map & Assess Risk

- Create Process Map
- Define Roles and Resp.
- Use Process Map to Assess Risk
- Know Risks at Edges of the Design Space

Identify Process Controls & Monitoring

- Id controls to Mitigate Risk
- Design Feedback Loop
- Establish Audit
- Id key In-Process and Output Measures to Monitor System Health

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QbD Example:

Instrument Calibration

Quality System: Equipment Calibration

Identify Customers and Needs (CTQs) → Develop Product Features → Develop Process Features → Create Process Map & Assess Risk → Identify Process Controls & Monitoring

Suppliers	Inputs	Process	Outputs	Customers
Provide input to process	*Resources required by the process*	*Top level description of activity*	*Deliverables from the process*	*Anyone who receives a deliverable from the process*
Work Order System	Work Order	Equipment needing Calibration	Instrument with Calibration Status Assigned (Pass/Fail) **CTQ**	System Owner
System Owner	Instrument			Reg Affairs / Agencies
Calibration Staff	Standards	**Instrument Calibration**	Closed Work Order	QA
Document Management	SOPs			Mfg/Labs
Manufacturing	Parameters			F&E / End User
HR	Trained Staff	Calibration Status Defined		

Quality System: Equipment Calibration

Identify Customers and Needs (CTQs) → **Develop Product Features** → Develop Process Features → Create Process Map & Assess Risk → Identify Process Controls & Monitoring

QBD Worksheet - Product Design

Quality System:

Calibration			Product Features					
			Electronic System (Mgmt)	Defined & Aligned Acceptance Criteria	Scheduling Capability	Label Generation Feature	Scalable	Use of training Program
CUSTOMER	VOC	CTQ						
System Owner	Tolerance Cal / Process Align	Fit for use	O	X				
Quality	In Calib	Accurate Reliable		O				
End User	Availability	On Time / Schedule*	#		X			
	Fully Documented	Traceable	OX			O		
	Status Check ID	Legible / Accurate Current	O		X	OX		
	Trained Cal Staff	Ease of Use	O					O
		Notification / Investigation of Failure	X		#	#		
	Efficiency of Cal Process	Cost Effective			#		X	#
			Amgen IS system with Controled Access and Audit Trail	100% Accuracy of Acceptance Criteria	Real Time Notification/update (within 1 hour) * No Delays	100% Accurate Legible Lables (Specified Font, Color)	Modular Infrastructure 10-10x (?) Current Capacity	< 8 Hours Training Annually < 2 Help Desk Calls Per Month
			Product Feature Specifications					

Priority

X Very Strong
O Strong
Weak

Quality System: Equipment Calibration

QbD Worksheet - Process Design

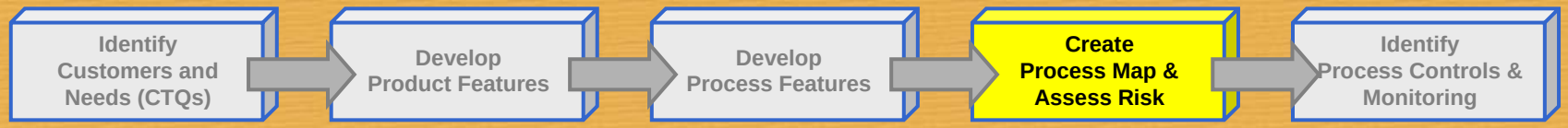
Quality System:

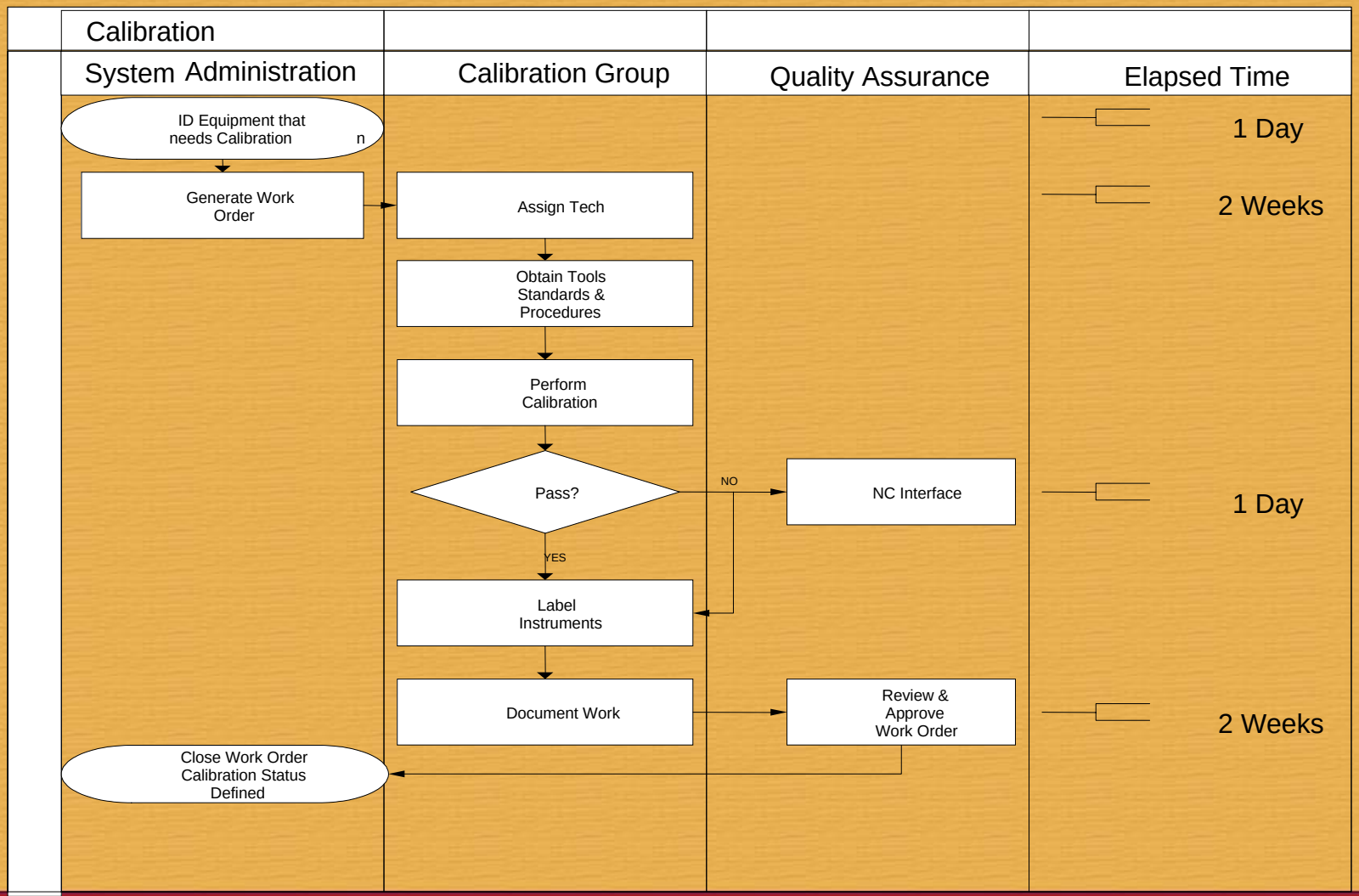
Calibration		**Process Features / Specifications**					
		Online Calibration Management System	**Defined Roles & Responsibilities with Respect to Process**	**Defined Procedures & Specs for Calibration Equip**	**Bar Code Equipment & Procedures**	**Calib. Staff Training / End User Training**	**Technical Support**
Product Features	**Product Feature Spec.**						
Electronic System (Mgmt)	**Amgen System with controlled access & audit trail**	X			X		
Defined / Aligned Acceptance Criteria	**100% Accuracy of Acceptance Criteria**	X	OX				X
Scheduling / Capability	**Real Time Update Notification within 1 hour no delays**	O		X			
Label Generation Ease of ID of Cal Status	**100% Accurate, Legible Lables (Specified font, color)**	X					O
Scalable	**Modular Infrastructure (10x current capacity)**	O			X		O
Training Program	**< 8 Hours Training Annually < 2 Help Desk calls per month**	X			O		O
Interface with existing Systems	**Capability with Key Systems**	O	X			X	O
Failure Notification	**100% Notification within 24 hours to appropriate people**	X					X
		R & D in Place before Implementation	R/R Defined in SOP prior to Implementation	Procedures / Specs Defined & in place prior to equipment entry	Bar Code Scanners, Printers qualified - Prog in place	Training Modules in place and assigned to appropriate people	System in place prior to implementation
		Process Feature Requirements					

Priority

X Very Strong
O Strong
Weak

Quality System: Equipment Calibration





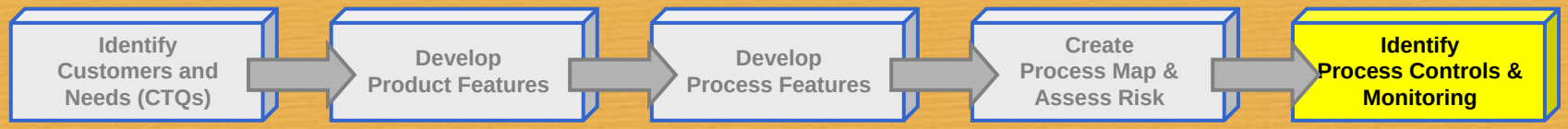
Quality System: Equipment Calibration

Identify Customers and Needs (CTQs) → Develop Product Features → Develop Process Features → **Create Process Map & Assess Risk** → Identify Process Controls & Monitoring

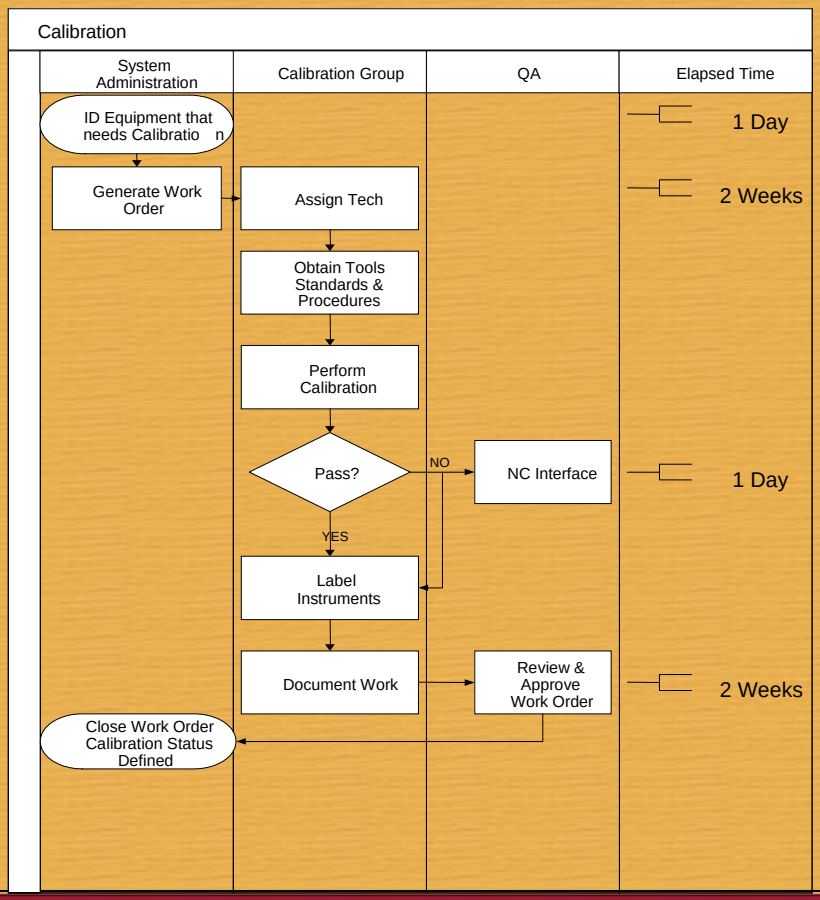
Process or Product Name:	Calibration **Failure Mode and Effects Analysis Tool (FMEA)**
Responsible:	

Process Function or Step	Potential Failure Mode	Potential Effects of Failure	SEV	OCC	DET	RPN
ID Equipment	Not In System	Decay in Disposition of Product	5	2	1	10
	Mislabeled	Decay in Disposition of Product	5	3	3	45
	System Crash	Production Delay	3	2	1	6
Assign Tech	Wrong, Untrained Overtasked Tech	Product Impact	3	2	2	12
Tools, STD & Procedures Perform Calib	Human Error Wrong STDs	Product Impact	5	3	3	45
PASS / FAIL	Incorrectly assigned status	Product Impact	5	2	5	50
	Can't Read Label	Production Delay	3	1	1	3
NonConf. Notification	Fails to Notify	Production Delay or ??	3	1	2	6

Quality System: Equipment Calibration



The **Plan** for **Do** ing The Work	**Check** ing the Work	**Act**: Respond to the Results
Flowchart	Key Process Indicators	Corrective Actions



This example showed 5 major steps in a general QbD process.

Pharmaceutical Product Applications

- Lypholization to optimize reconstitution
- Blend uniformity to minimize dose variation
- Delivery device designed to allow self-injection by elderly & by weak/handicapped
- Systems to improve dose delivery accuracy
- Systems to eliminate drug identification mistakes
- Molecular modifications to extend bioavailability of drugs
- Improved drug and device product robustness in distribution and use
- New drug designs to interact with specific genotypes
- Automated drug delivery
- Simplified diagnostics based on drug - biology reactions

Questions to help you recognize QbD in action

Do you use a step-by-step approach to product design?

How do you incorporate feedback into your product design?

How do you choose product attributes to incorporate?

How do you choose process attributes to incorporate?

How do you assign (distribute) responsibilities for the design to be put into action?

How do you rate and compare design options?

How do you make design choices?

How are customers' needs incorporated?

How do you build your understanding of the production process?

How do you ensure process control to meet the design?

Questions, Answers and Discussion

- Questions
- Answers
- Discussion

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