From API to Formulated Product

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Objectives

- Truly robust analytical methods
- A knowledge management framework for API and DP product development
- What is process understanding and how can it be enhanced
- Understanding links between API and raw materials, to final product processing and performance
- Opportunities for facilitating a significantly improved continuum between R&D and manufacture

Narita Airport, April 11th, 2009

Airbus A380 Design Goals Clearly Defined Up Front (TPP)

Flying vs Developing Drugs: Similarities & Differences

- Always fly in air, pharma products usually are processed in air (usually) but sometimes not (lyophilization, N_2 blanketing, etc.)
- Water & wind are noise factors for airplanes, pharma uses them to process products
- Electricity (lightening) is a noise factor for airplanes, pharma sometimes creates its own electrostatics while processing drugs, leading to problems, or it is sometimes used for drug deposition
- The body of planes do not (chemically) react (quickly) to their environment, drugs typically degrade and water doesn't help
- Factors affecting flying are well understood; factors affecting drug product safety, efficacy, manufacturability, etc., are not well understood
- As a result, airplanes can be designed in silica, drugs have yet to be fully designed in silica

States of Pharma Manufacturing

Level of Understanding & Knowledge	σ Capability	Potential	Actual
First Principles & Mechanistic Modeling	≥6	Drying Blending Spray Drying Tablet Coating	
Empirical Modeling	3-5	Compression Roller Compaction	Drying Spray Drying Roller Compaction Tablet Coating
Correlative Understanding (Trial & Error)	2	Wet Granulation	Compression Blending Wet Granulation Tablet Coating
Descriptive Knowledge	<2		Wet Granulation

Performance Comparison for Various Industries

Operations in Pharmaceuticals Compare Poorly to Other Industries

The pharmaceutical industry lags similar industries in key measures of operations performance, most notably in overall equipment effectiveness, labor value-add time and direct/indirect labor ratio, McKinsey's Ted Fuhr told the recent CDER on CMC conference in Bethesda, Md. Many of the shortcomings reflect poor quality practices and represent cost savings opportunities for the quality by design paradigm. Estimates are from McKinsey Operations Practice.

Measure	Pharma	Automotive	Aerospace	Computer	Consumer Packaged Goods
Overall equipment effectiveness	10% to 60%	70% to 85%	50% to 70%	80% to 90%	70% to 90%
Annual productivity improvement	1% to 3%	5% to 15%	5% to 10%	1% to 3%	5% to 15%
First-pass yield – zero defects	60%	90% to 99%	70% to 90%	90% to 99%	90% to 99%
Production lead times in days	120 to 180	1 to 7	7 to 120	5 to 10	3 to 7
Finished goods inventory in days	60 to 90	3 to 30	3 to 30	5 to 50	10 to 40
Labor value-add time	20%	60% to 70%	60% to 70%	60% to 70%	60% to 90%
Direct/indirect labor ratio	1:1	10:1	10:1	10:1	10:1

Gold Sheet, Jan 2009

States of Product Capability by Industry

Level of Understanding & Knowledge	σ Capability	Industry
First Principles & Mechanistic Modeling	≥6	Aerospace Ch Semi-conductor Potato Chip Manufacturers (2004 WSJ)
Empirical Modeling	3-5	
Correlative Understanding (Trial & Error)	2-3	
Descriptive Knowledge	<2	

Goal for Pharmaceuticals

Pharmaceuticals w/ Inspection

Pharmaceuticals

Drivers for Change

Financial

- Decreased spending for development/redevelopment of products
- Decreased cost to maintain marketed products
- Reduced rework or scrap of product
- Prioritized spending for development and commercialized products
- Partner of Choice

Regulatory

- Regulatory relief
- Reduced submission review time
- Enhanced submission quality, with improved development focus
- Consistent with FDA & EU desired state
- Aligned with AAPS, ICH, ASTM, etc.

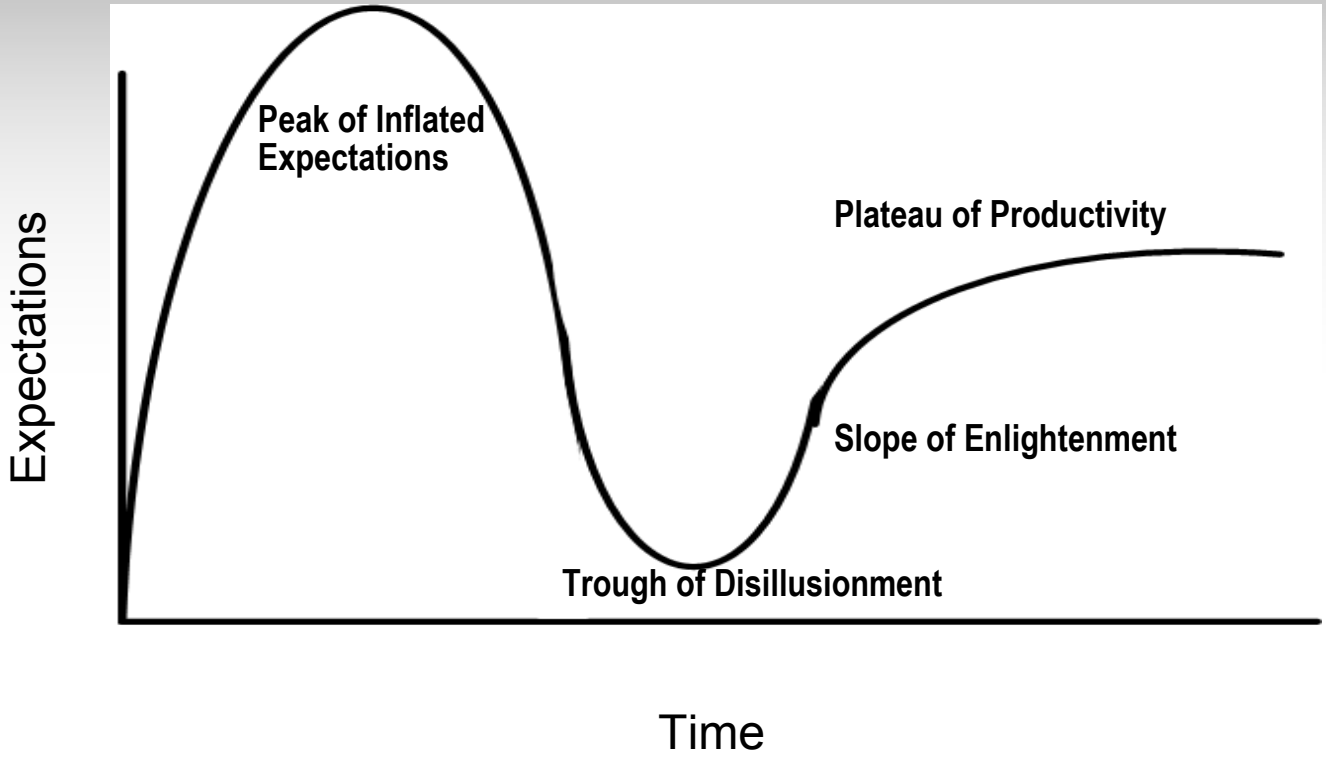
Quality

- Robust products and processes leading to reduced rework or scrap
- Predictive processes
- Prioritized continuous improvement
- Rapid troubleshooting
- Reduced, acceptable compliance risk

Product Development & Commercial Support

- Resources focused on key development tasks
- Efficient development processes
- Better definition of development & commercial risks

Status of Industry Relative to QbD



Martin Warman, 2009
Gartner Hype Model

Recent ICH/FDA Regulatory Trends & Guidance Changes

Item	Status
FDA Critical Path Initiative & Quality by Design	March 2004
ICH Q8 – Pharmaceutical Development (Science)	Effective May 2006
ICH Q9 – Quality Risk Management	Effective June 2006
ICH Q10 – Pharmaceutical Quality Systems	ICH Step 2

Achieving Quality by Design

Level of Understanding & Knowledge	Methodologies Risk Management
First Principles & Mechanistic Modeling	In Silica Development Using Theoretical/Predictive Models Characterization Of Raw Materials (Especially API) Predictive Manufacturing Processes Connecting Investigations On A Product Throughout Its Lifecycle Exploring Empirical Models For Potential Mechanistic/Theoretical Mechanisms
Empirical Modeling	Design of Experiments, Interactions Investigated & Understood EVOPS MVDA/MSPC Expert Systems
Correlative Understanding (Trial & Error)	One Factor at a Time Development, No Interaction Effects Detailed Flowcharts with Process Control Limits
Descriptive Knowledge	Observational High-level process flow charts Descriptive text/narration

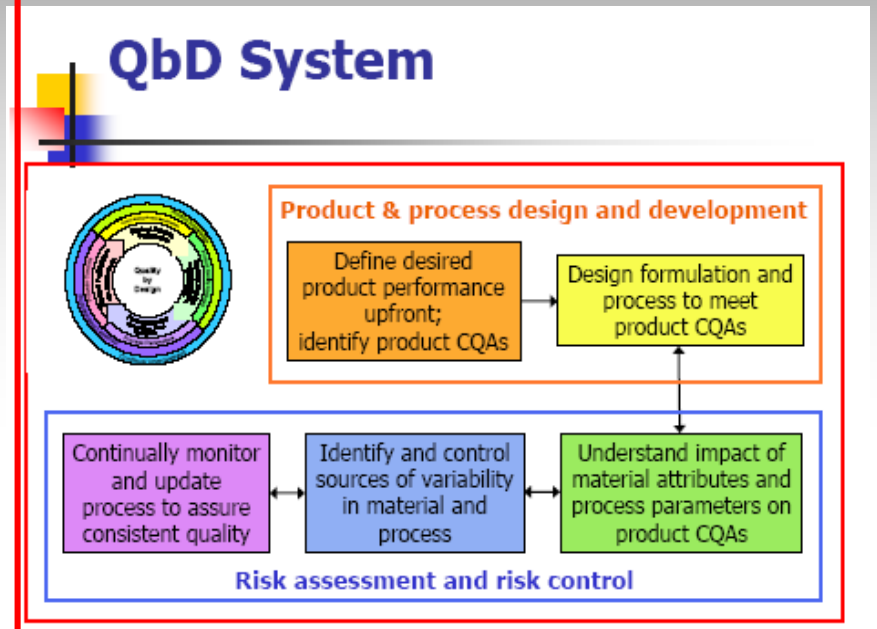
Comparing Traditional vs QbD Lifecycles

Aspects	Traditional	QbD
Pharma Development	Empirical, Univariate	Systematic, Multivariate
Manufacturing Process	Fixed Process & Raw Materials	Adjustable W/in Design Space
Process Control	Offline, Slow	Online, Fast
Specifications	To Achieve QC	Based On Desired Product Performance
Control Strategy	By Intermediate & End-Product Testing	Risk-based; Ctls Upstream, Real-time Release
Lifecycle Mgmt	Reactive, OOS, Post-Approval Changes	Proactive, Continuous Improvement

Helen Winkle, FDA
Sept 24, 2007

What Does QbD Look Like?

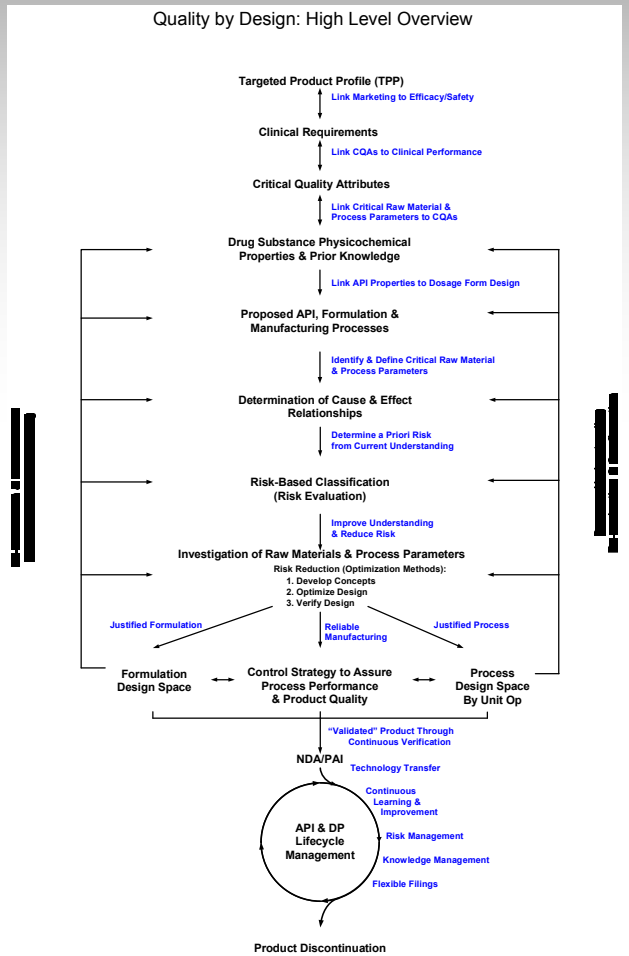
FDA High-Level View of Q-Trio



Helen Winkle, FDA
Sept 24, 2007

PDA/FDA Joint Regulatory Conference

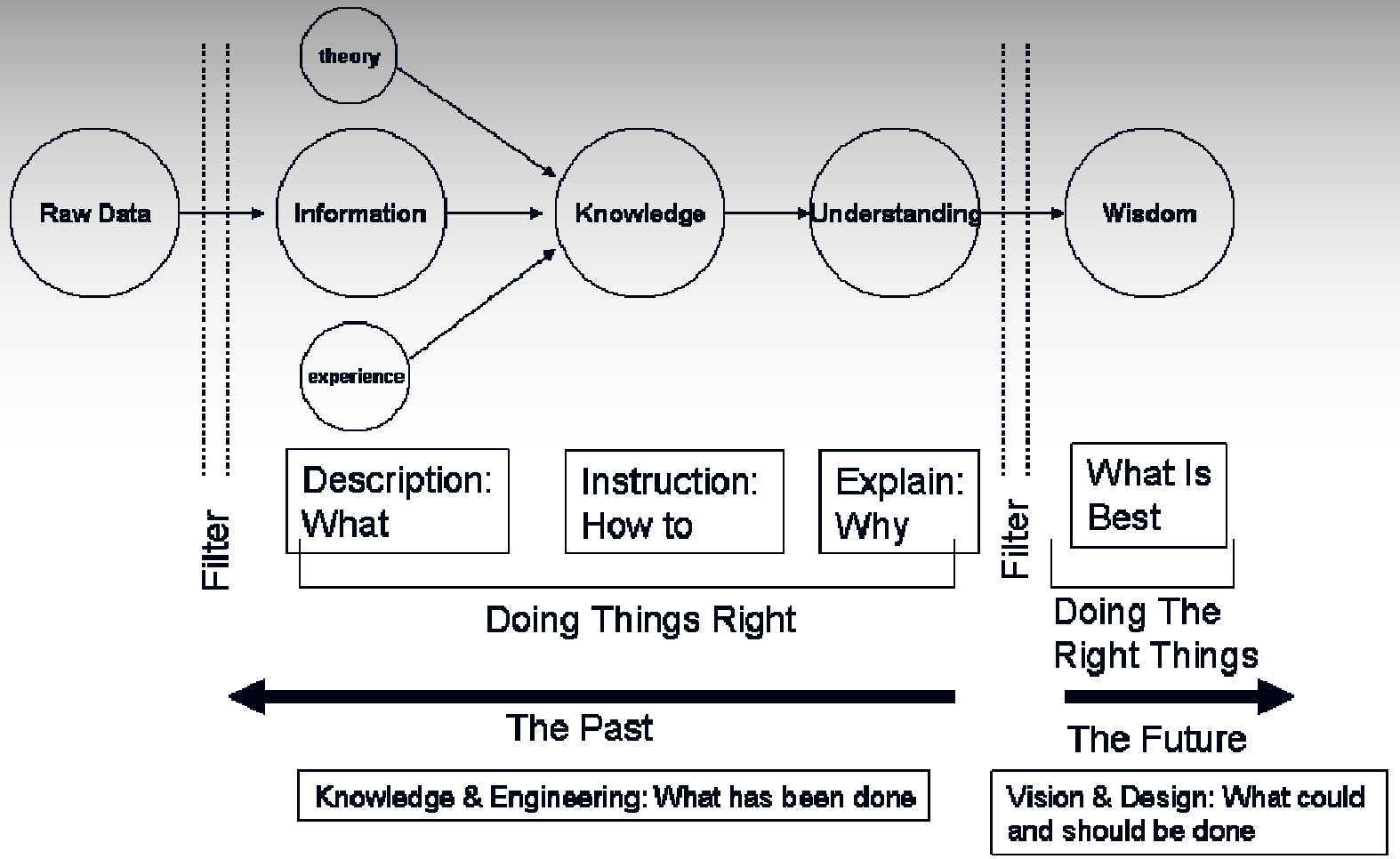
Alternate View of Q-Trio



Scope of Workshop

- A Potential Workflow for QbD
- Analytical Development
- API Development
- Drug Product Development
  - Linking API to DP Development
- Commercialization

DIKW Knowledge Management Model



Fourth Generation R&D: Managing Knowledge, Technology and Innovation, W.L. Miller and L. Morris, John Wiley & Sons, 1999. p 87.

Overview

- Concepts
  - Making connections from methods to API to Drug Product
  - Continuum
  - From R&D to commercialization
  - Traditional vs New Methods of Setting Specifications
  - Ansel Ford
    - Automatic transmissions

Process Understanding

- A process is well understood when:
  - all critical sources of variability are identified and explained
  - quality is designed into the process so that variability is managed by the process
  - product quality attributes can be accurately and reliably predicted
- Process understanding is inversely proportional to risk

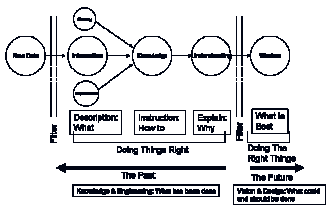
Workflow

Objectives	Deliverables
Target Product Profile	TPP Profile
Critical Quality Attributes	List of Potential CQAs
API Characterization & Prior Knowledge	Link API Properties to Dosage Form
Analytical Methods	Rugged/Robust Methods
Proposed API, Formulation & Manufacturing Processes	ID Potential Critical RMs and PPs
Determining Potential C&E Relationships	Det. A Priori Risk from Prior Knowledge
Risk Management	Risk Assessment
Investigation of Raw Materials & Process Parameters	Develop, Optimize, Verify Design
Design Space (API & DP)	Design Space Documents
Control Strategy (API & DP)	Control Strategy Documents
Validation	Continuous Verification Strategy
Commercialization & Continuous Improvement	Quality Systems working together, leading to Continuous Improvement

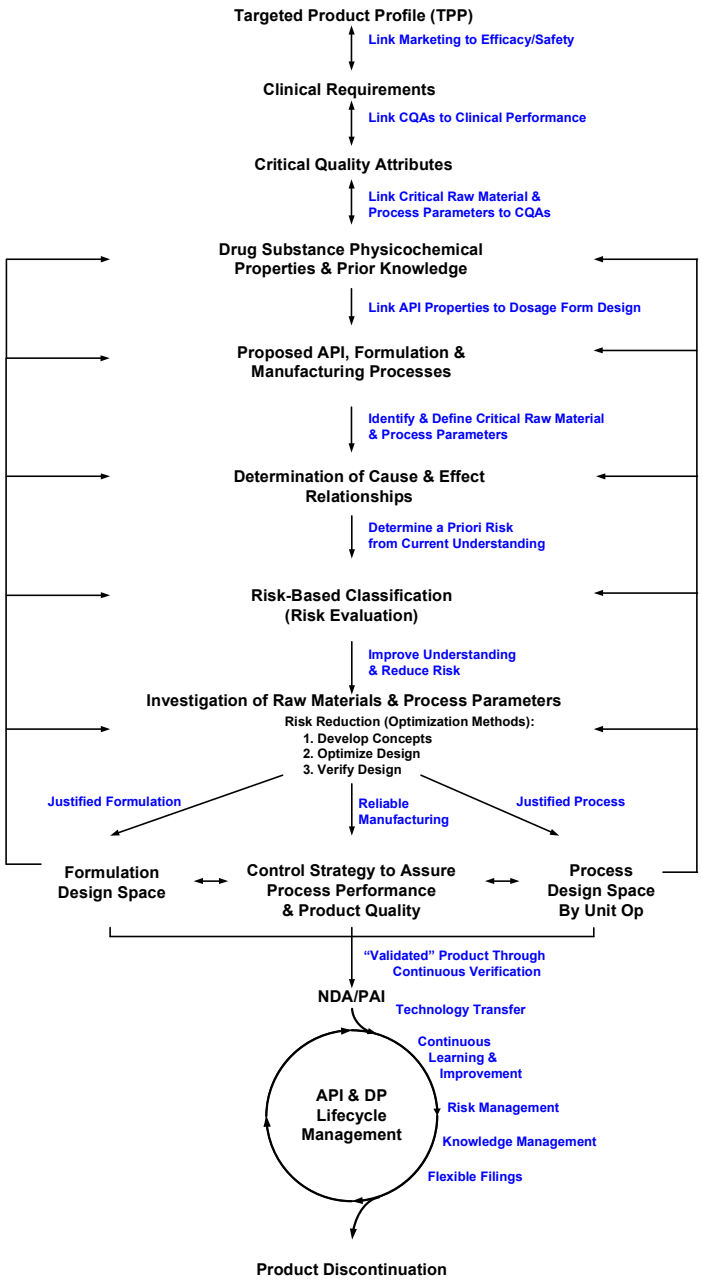
Bold Typeface: Covered in Detail

Summary of Workflow

- Science
- Risk Management
- Quality Systems

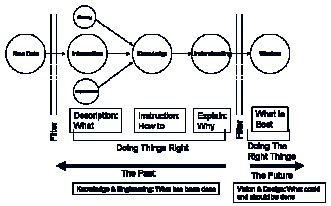


Quality by Design: High Level Overview



Analytical Methods

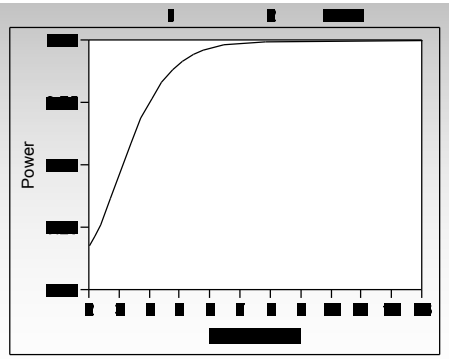
- Objectives
  - Stable, robust, rugged, reproducible methods
- Science
  - Analytical Method Development Strategy
    - Measurement Systems Analysis
      - Gage R&R
      - Taguchi Method
        - Addresses centering a process as well as minimizing impact of noise variables
        - One form of Measurement Systems Analysis (MSA)



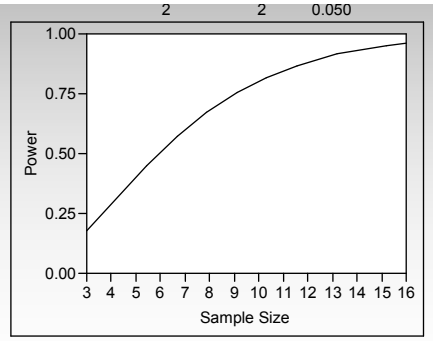
Future Sampling

- What is the right sampling frequency for development
- Impact of method bias & variability on confidence of measures

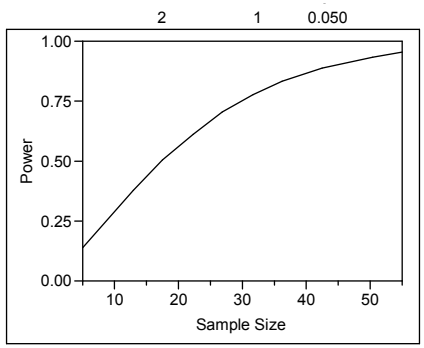
SD 1%
To detect 2% difference
N>6



SD 2%
To detect 2% difference
N>16

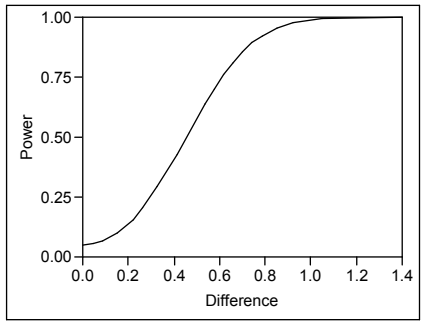


SD 1%
To detect 1% difference
N>50



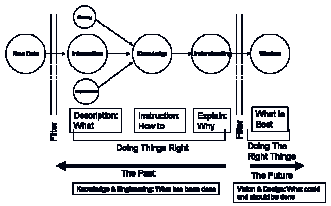
PAT

SD 4%
N=300
Detects <1% difference



Analytical Methods

- Link to presentation #2



API Development

- Link to presentation #3

Drug Product Development

- Link to presentation #4