If Quality by Design, Supported by Process Analytical Chemistry, is the Solution, What was the Problem?

Stephen Wicks
The University of Greenwich

University of Heidelberg
European Compliance Academy - QbD/PAT Conference 2013
16-17 October, Crowne Plaza Hotel, Heidelberg, Germany

"The Desired State"

A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.

Janet Woodcock. Director CDER 2005

The Desired State

- Product quality and performance are ensured through the design of effective and efficient manufacturing processes
- Product and process specifications are based on a mechanistic understanding of how formulation and process factors affect product quality and performance
- Continuous quality assurance and process improvement
- Relevant regulatory policies and procedures are tailored to reflect current level of scientific knowledge
- Risk-based regulatory approaches recognize
  - the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance
  - the capability of process control strategies to prevent or mitigate the risk of producing a poor quality product

Moheb M. Nasr, Ph.D. Office of New Drug Chemistry (ONDC) 2004

New Quality Paradigm - Regulator view of benefits to Industry

- Ensures better design of products with fewer problems in manufacturing
- Reduces number of manufacturing supplements required for post market changes – rely on process and risk understanding and risk mitigation
- Allows for implementation of new technology to improve manufacturing without regulatory scrutiny
- Allows for possible reduction in overall costs of manufacturing –less waste
- Ensures less hassle during review –reduced deficiencies –quicker approvals
- Improves interaction with FDA –deal on a science level instead of on a process level
- Allows for continuous improvements in products and manufacturing process
- Allows for better understanding of how APIs and excipients affect manufacturing
- Relates manufacturing to clinical during design
- Provides a better overall business model!

Helen Winkle CDER 2007

What Appeared to be the Problem?

- Inefficiency
- Lack of agility
- Inflexibility
- Unreliability
- Unsatisfactory manufacturing
- The need for extensive regulatory scrutiny
- An inappropriate business model
- A lack of scientific understanding of products, materials and processes

Sigma	ppm Defects	Yield	Cost of Quality
2σ	308,537	69.2%	25-35%
3σ	66,807	93.3%	20-25%
4σ	6,210	99.4%	12-18%
5σ	233	99.98%	4-8%
6σ	3.4	99.99966%	1-3%

6 σ - World class
5 σ - Superior ⇦ Semiconductor Industry
4 σ - Healthy
3 σ - Average
2 σ - Not capable ⇦ Pharma Industry
1 σ - Not competitive

PWC, 2001,Productivity and the Economics of Regulatory Compliance in Pharmaceutical Production

Desirable Plant Metrics

Measure	Pharmaceutical Industry	A Winning Pharmaceutical Factory	A World Class Factory
Stock turn	3 to 5	14	50
OTIF	60% to 80%	97.4%	99.6%
RFT	85% to 95%	96.0%	99.4%
CpK	1 to 2	3.5	3.2
OEE	30.0%	74.0%	92.0%
Cycle time (hrs)	720	48	8
Safety/100,000 hrs	0.100	0.050	0.001

Source: Benson & McCabe Pharm. Eng. 2004

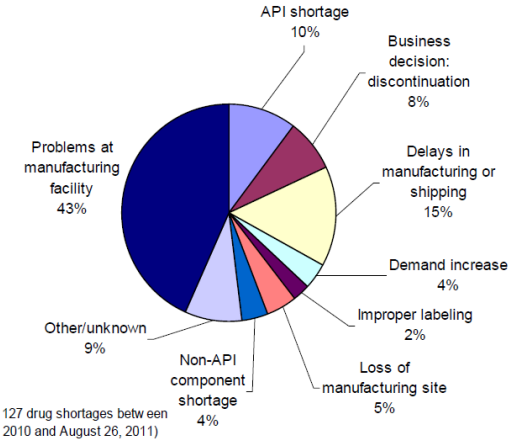
Stock Turn: total turnover divided by stock on site
OTIF: % of orders fulfilled On Time in Full with zero defects
RFT: % of product at point of manufacture delivered right first time with zero defects
CpK: Statistical process control measure of variability
OEE: Overall Equipment Effectiveness. Product rate x quality rate x plant availability
Cycle Time: Total time from manufacturing commencement to finished delivery
Safety: Reportable incidents (3 or more lost days) per 100,000 hrs

Metrics like these cannot be met with conventional or semi continuous processes or conventional control strategies – need new technologies such as continuous processes and newer control strategy paradigms such as RTRT

Key Facts about Drug Shortages

1. The number of drug shortages annually has tripled from 61 in 2005 to 178 in 2010.
2. Of the 127 studied* drug shortages in 2010-11, sterile injectables accounted for the majority (80%). The major therapeutic classes of drugs in shortage included oncology drugs (28%), antibiotics (13%), and electrolyte/nutrition drugs (11%).
3. The leading primary reasons for the shortages reported to FDA were problems at the manufacturing facility (43%), delays in manufacturing or shipping (15%), and active pharmaceutical ingredient shortages (10%).
4. Manufacturing quality problems that have resulted in shortages can be serious, including findings of glass shards, metal filings, and fungal or other contamination in products meant for injection into patients.

Figure 4: Drug Shortages by Primary Reason for Disruption in Production and Supply, 2010-2011



(Based on 127 drug shortages betw een January 1, 2010 and August 26, 2011)

** This represents a subset of drug shortages that occurred during 2010 and 2011. These shortages tended to be larger, of longer duration, and of greater public health impact than shortages not studied (see "Characteristics of Drug Shortages" in the text).*

U.S. Department Of Health And Human Services U.S. Food And Drug Administration *A Review of FDA's Approach to Medical Product Shortages* OCTOBER 31, 2011
www.fda.gov/DrugShortageReport

The Prescription for Change

Pharmaceutical Quality for the 21st Century A Risk-Based Approach (FDA 2002) with progress reports in 04 & 07

- Encourage the early adoption of new technological advances by the pharmaceutical industry
- Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance
- Encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas
- Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science
- Enhance the consistency and coordination of FDA's drug quality regulatory programs, in part, by further integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities

Implementing the New Prescription – A Major Role for PAT

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Key Progress (2007)

- **External Quality Management Systems**
  - **Guidance for Industry -Quality Systems Approach to Pharmaceutical CGMP Regulations (2006)**
- **International Collaboration (with ICH, Q8, Q9, Q10 (Q11))**
- **Implementation of Quality by Design (QbD)**
- **Implementation of Process Analytical Technologies (PAT)**

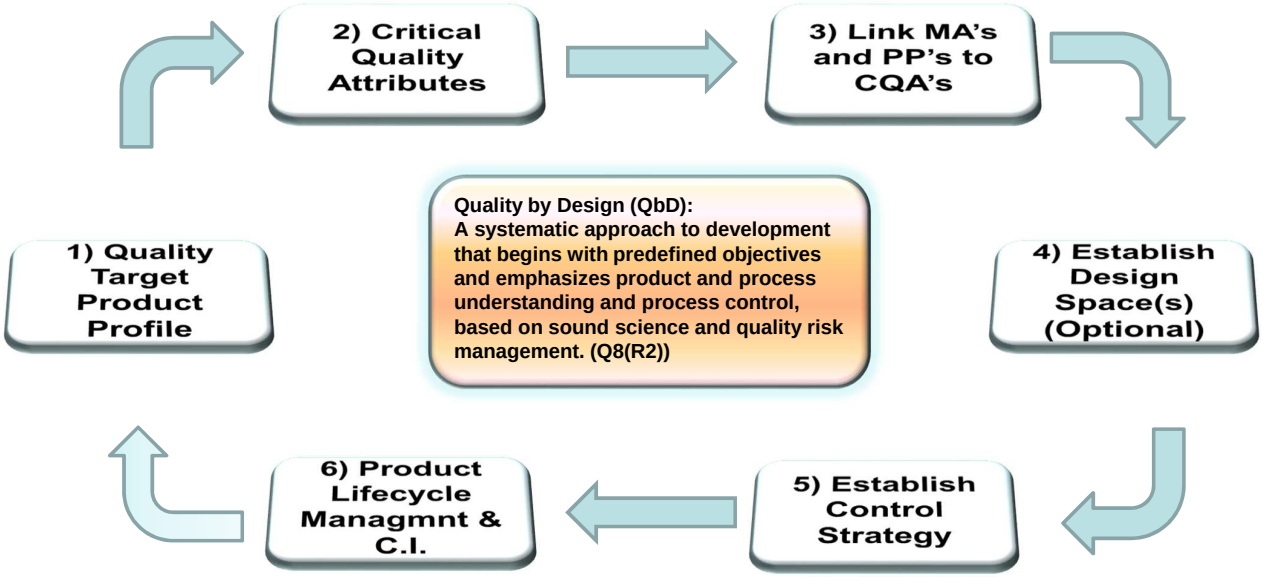
Quality by Design, Supported by PAT, the Solution to the Problem

Important Concepts

- Quality cannot be tested into products - should be built in by design
- Minimal & Enhanced Development Strategies
  - Links enhanced development to prior knowledge, formal experimental designs (DoE), PAT and use of quality risk management principles
- Introduces Design Space concept
- Regulatory Flexibility
  - Improvements within design space not considered a change
  - Real time quality control
  - Relates degree of flexibility to level of knowledge

Q8(R2) Pharmaceutical Development Part 1 The "Core" Document

A New Guideline: What Does It Say? How Do We Comply?



The QbD Framework can most simply be described by following the chapter headings in Q8(R2) Annexe II

What We Like; What We Are Used To; How We Control Uncertainty Within Our Organisations; What We Are Organised to deal With!

Example 1: **0.5 g Maximum Daily Dose**
Reporting threshold = 0.05%
Identification threshold = 0.10%
Qualification threshold = 0.15%

"Raw" Result (%)	Reported Result (%) Reporting threshold =0.05%	Calculated Total Daily Intake (TDI) (mg) of the impurity (rounded result in mg)	Action	
			Identification (Threshold 0.10% exceeded?)	Qualification (Threshold 0.15% exceeded?)
0.044	Not reported	0.2	None	None
0.0963	0.10	0.5	None	None
0.12	0.12[1)]	0.6	Yes	None[1]
0.1649	0.16[1)]	0.8	Yes	Yes[1]

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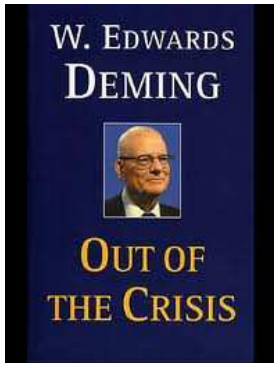
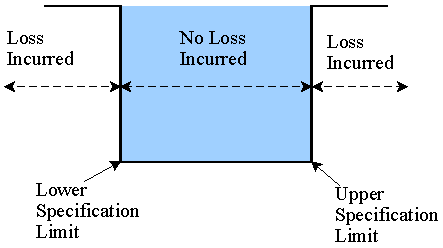
Before 'complying' with QbD as a regulatory mandate do we understand why these problems exist?

ARE OUR QUALITY FOUNDATIONS SECURE?

1. **Create constancy of purpose for improving products and services.**
2. **Adopt the new philosophy.**
3. **Cease dependence on inspection to achieve quality.**
4. End the practice of awarding business on price alone; instead, minimize total cost by working with a single supplier.
5. **Improve constantly and forever every process for planning, production and service.**
6. Institute training on the job.
7. **Adopt and institute leadership.**
8. Drive out fear.
9. **Break down barriers between staff areas.**
10. Eliminate slogans, exhortations and targets for the workforce.
11. Eliminate numerical quotas for the workforce and numerical goals for management.
12. Remove barriers that rob people of pride of workmanship, and eliminate the annual rating or merit system.
13. Institute a vigorous program of education and self-improvement for everyone.
14. **Put everybody in the company to work accomplishing the transformation.**



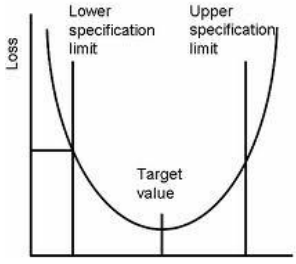
An Authentic Approach to Quality and Risk



Taguchi's Loss Function (TLF) recognises that there is an economic loss (to the company & consumers) if products are not made exactly to their intended value

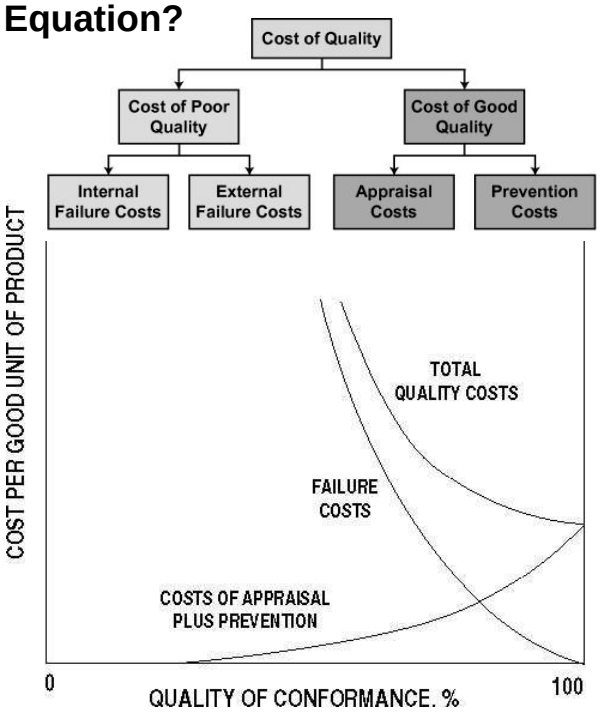
Taguchi says that the loss due to performance variation (away from the target value) is proportional to the square of the deviation of the performance characteristic from its target value:

$$L(y) = k(y - m)^2$$



If we consider the Taguchi model to be valid, it follows that continuous improvement and statistical process control can be used to lower cost by increasing quality. If we accept the "goalpost" model, neither of these things is true as long as we have product that consistently "meets spec"

Are We On The Wrong Side of the Equation?



Compliance vs. Creation

Whoosh; Business in the Fast Lane by Tom McGehee, 2001

Compliance cultures use systematic rules, policies, and procedures to produce **routine** responses.

Creation cultures tap into relationships and people's talents and initiative to produce **inventive** responses.

Think of the qualities on a continuum.

Where do you most need compliance?
Where would you benefit from creativity?

IS MANAGEMENT OF RISK A REGULATORY PROCESS OR PART OF OUR CULTURE?

Safety, NASA Family, Excellence, Integrity

The Strategy for Safety and Mission Assurance

- Known Knowns: *(Systems Engineering and Program Management)*
  - High quality program and mission management processes and people
  - "Listen to the hardware"
- Known ~~Un~~knowns: *(Continuous Risk Management)*
  - Reduce uncertainties with analysis, test and attention to flight results
  - Recertify to the real environment (has it changed over the years?)
  - Treat residual risk (including uncertainty) with conservative ground and flight procedures, quality assurance, operating margins, contingency plans
- ~~Un~~known Knowns: *(Continuous Process Improvement)*
  - Rigorous supplier quality programs
  - Continuously assess and improve program communications, documentation, workforce competence
  - Improve data analysis tools and techniques (e.g. trending)
- ~~Un~~known ~~Un~~knowns: *(Continuous Research, Test and Evaluation)*
  - Dedicate resources to better understand the limitations of the system in the real environment (*Curiosity saved the cat*)
  - Constantly challenge old assumptions, models and analyses

http://rmc.nasa.gov/archive/rmc_v/presentations/oconnor%20osma%20risk%20is%20part%20of%20nasa%20mission.pdf

26 October 04

An Authentic and Ethical Approach to Risk

Courtesy: www.washingtonspeakers.com

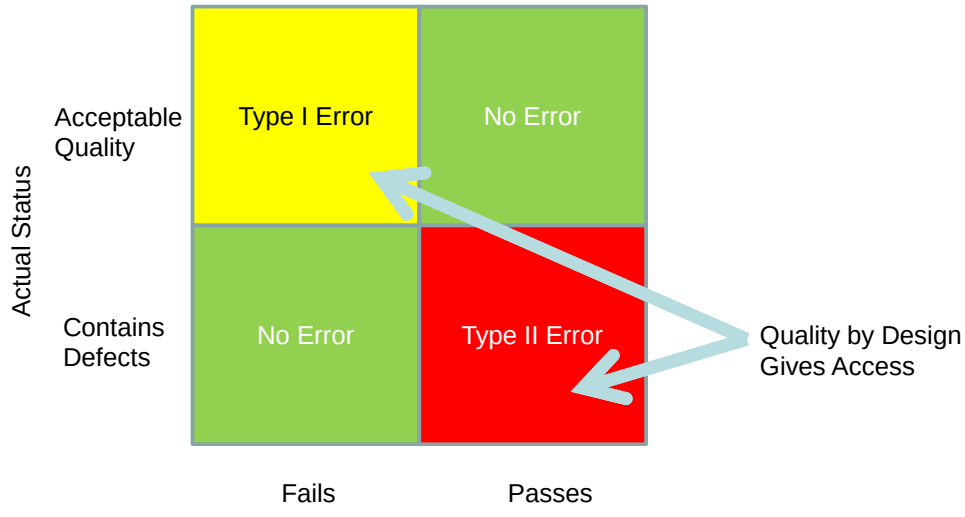
"There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know."

Donald Rumsfeld

The Expectation Value of Unwanted Consequences

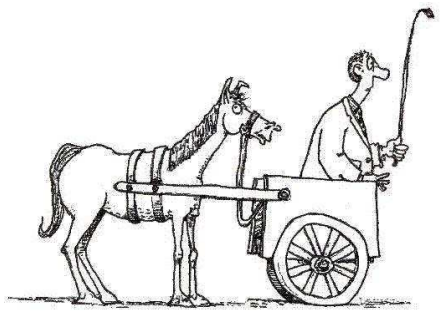
- An evaluation is carried out on a batch of injection vials to assess sterility
- A Type I error
  - The autoclave process works
  - The sterility test is unsuitable and the batch fails
  - The batch is considered to be non-sterile when it is
  - The batch fails when it should not
- A Type II error
  - The autoclave process fails
  - The sterility test is unsuitable and the batch passes
  - The batch is considered to be sterile when it is not
  - The batch passes when it should not
- It is better to quarantine/fail the batch and subsequently find that it is OK than release the batch with a problem

Risk and Uncertainty



The Expectation Value of Unwanted Consequences

- We tend to focus on type I errors because they arise in end product testing
- False positive errors are actually more problematic and can only be approached by a risk-based development approach
- Many industries give a higher priority to avoiding Type II errors – the pharmaceutical industry must do likewise
- Type II errors are prominent because the consequences are apparent



IS A PAT-BASED CONTROL STRATEGY OR PROCESS AND MATERIAL DESIGN THE STARTING POINT?

The PAT Opportunity Space

On-line GC
solvent reclamation

On-Line turbidity
crystallisation, liquid products

Mid-IR Probe
reaction progress

NIR Probe
Blending

FBRM Probe
Crystallisation / granulation

Acoustic Emission
Granulation

Fluid Bed Drying Stage in Examplain

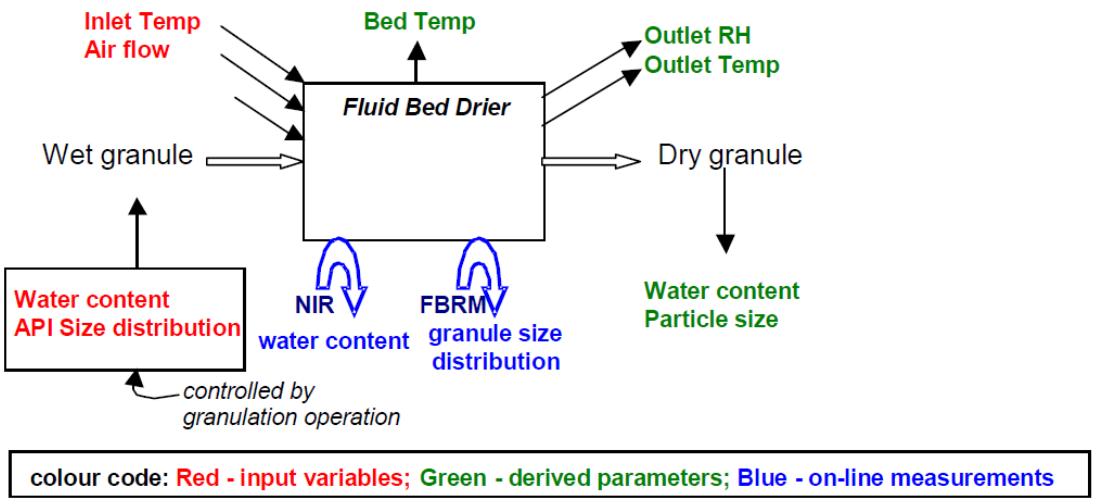
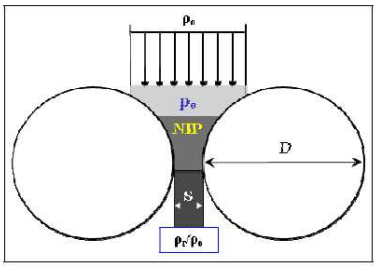


Figure 26: Description of Parameters associated with Roller Compactor



Ω = roll speed [1/T]
D = roll diameter [L]
s = roll gap width [L]
p_0 = feed pressure [$F/L^2 = M/LT^2$]
E = Young's modulus [$F/L^2 = M/LT^2$]
σ_y = yield stress [$F/L^2 = M/LT^2$]
ν = Poisson's ratio [-]
ε_0 = initial porosity [-]
μ_{pr} = friction between powder/roll [-]
μ_{pp} = internal powder friction [-]
ρ_0 = initial bulk density [M/L^3]
ρ_r = ribbon bulk density [M/L^3]

where the square brackets […] indicate the dimensions of a parameter, T refers to time, L is length, M is mass, and F is force (= ML/T^2).

The dimensional relation between the ribbon bulk density and the other parameters may be written as:

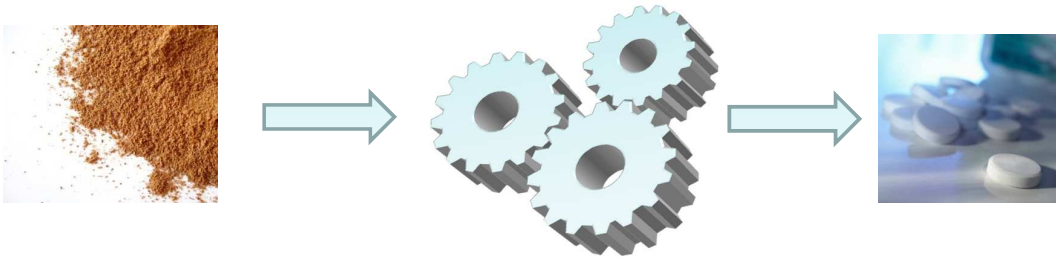
$$\rho_r = fcn_1\left(D, \Omega, s, p_0, E, \sigma_y, \nu, \varepsilon_0, \rho_0, \mu_{pr}, \mu_{pp}\right) \quad (1)$$

In dimensionless form, Eqn. (1) may be written as:

$$\frac{\rho_r}{\rho_0} = fcn_2\left(\frac{s}{D}, \frac{p_0}{\rho_0 \Omega^2 D^2}, \frac{E}{p_0}, \frac{\sigma_y}{E}, \nu, \varepsilon_0, \mu_{pr}, \mu_{pp}\right) \quad (2)$$

The dimensionless parameters in Eqn. (2) serve to establish truly scale and equipment independent metrics. Using the *relative density* of the ribbon (ρ_r/ρ_0) as the response, the range of s/D, $p_0/(\rho_0\Omega^2D^2)$, and E/p_0 were selected to give an acceptable ribbon density.

Meaningful Measurement



Raw Materials → **Manufacturing Process** → **Finished product**

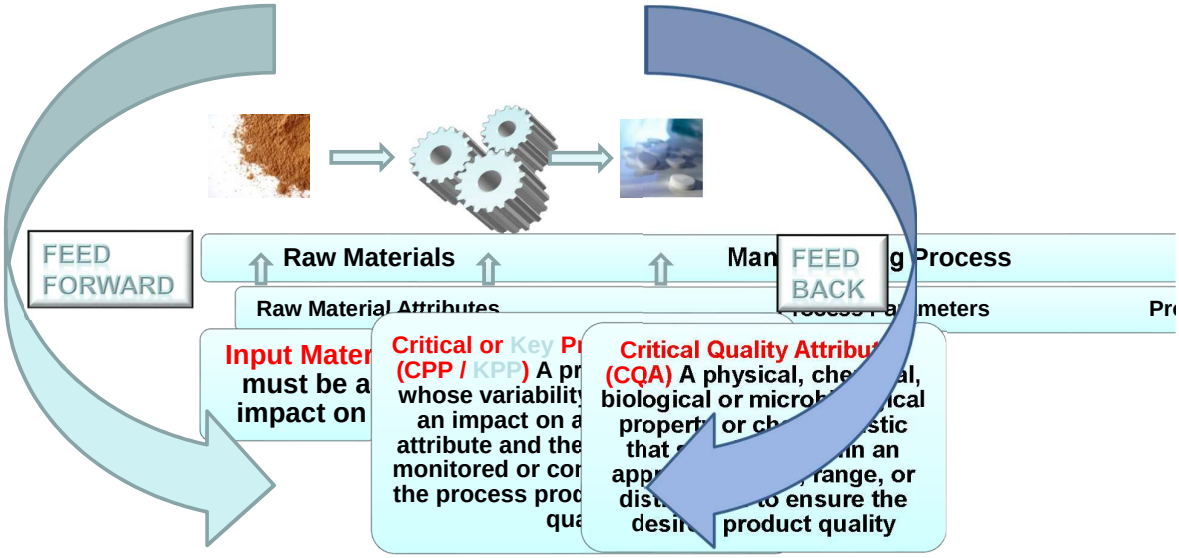
Raw Material Attributes | **Process Parameters** | **Product Quality Attributes**

Input Material Attributes must be assessed for impact on the process

Critical or Key Process Parameter (CPP/KPP) A process parameter whose variability has (may have) an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality

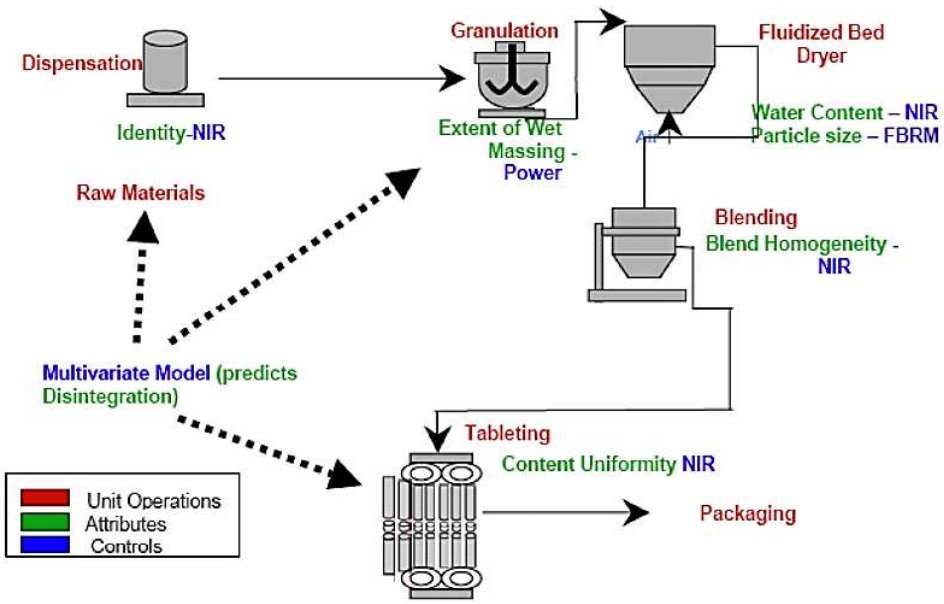
Critical Quality Attributes (CQA) A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality

Timely, Meaningful Measurements Can Put Us In Control

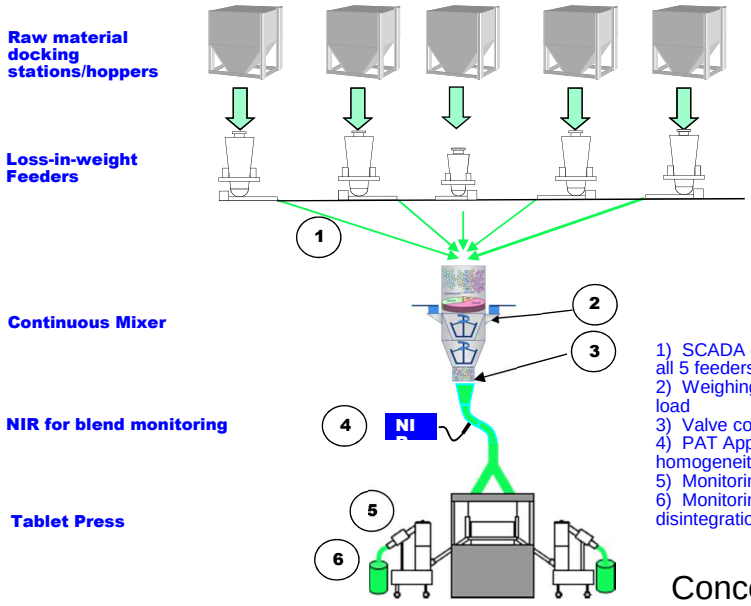


Process monitoring and control strategies are intended to monitor the state of a process and actively manipulate it to maintain a desired state. Strategies should accommodate the attributes of input materials, the ability and reliability of process analyzers to measure critical attributes, and the achievement of process end points to ensure consistent quality of the output materials and the final product. FDA PAT Guidance 2004

Rethinking Products and Processing in the Short Term



Continuous Process - Conventional



1) SCADA control and data acquisition – all 5 feeders
2) Weighing cells to monitor blender load
3) Valve control of blender load
4) PAT Application for blend potency & homogeneity
5) Monitoring of tablet weight, hardness
6) Monitoring of moisture content, disintegration

Concept ex Pfizer

WHAT IS THE RIGHT STRATEGY FOR PAT IMPLEMENTATION. TOOLBOX OR SYSTEM?

PAT: .....a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality

The goal of PAT is to enhance understanding and control the manufacturing process

- the tools and principles…. **should be used** for gaining **process understanding**
  - *Note – its quite likely that you have first been introduced to PAT in exactly the opposite context – something is bought (NIR?) to measure something before it is realised what is critical to be controlled*
- **can also be used** to meet the regulatory requirements for **validating** and **controlling** the manufacturing process.
- the term *analytical* in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner.

 FDA PAT Guidance for Industry 2004

PAT Tools

Multivariate tools for design, data acquisition and analysis

- **statistical design of experiments, response surface methodologies, process simulation, and pattern recognition tools**

Process analysers

- **at-line: Measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream.**
- **on-line: Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.**
- **in-line: Measurement where the sample is not removed from the process stream and can be invasive or non-invasive**

Process control tools

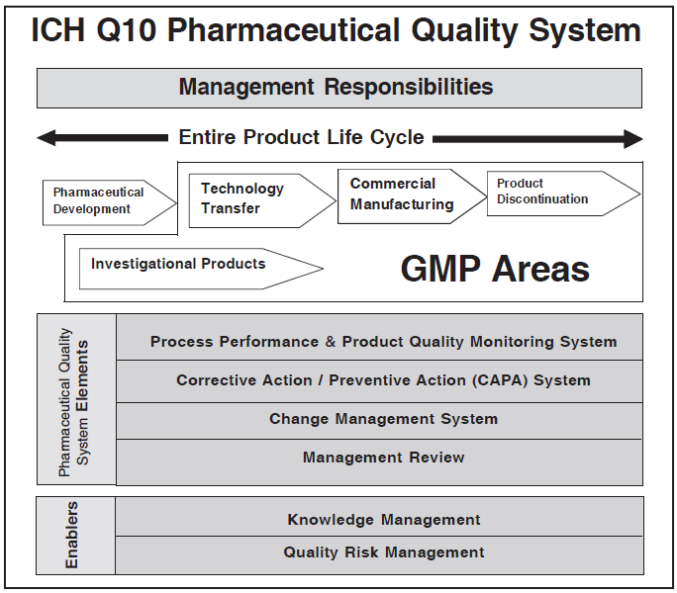
- **Identify and measure critical material and process attributes relating to product quality**
- **Design a process measurement system to allow real time or near real time (e.g., on-, in-, or at-line) monitoring of all critical attributes**
- **Design process controls that provide adjustments to ensure control of all critical attributes**
- **Develop mathematical relationships between product quality attributes and measurements of critical material and process attributes**

Continuous improvement and knowledge management tools

- **Continuous learning through data collection and analysis over the life cycle of a product**
- **A knowledge base…. consists of scientific understanding of the relevant multi-factorial relationships (e.g., between formulation, process, and quality attributes)**

The Challenge to Conventional Structure for the Pharmaceutical Industry

A Modified Diagram of the ICH Q10 Pharmaceutical Quality System Model



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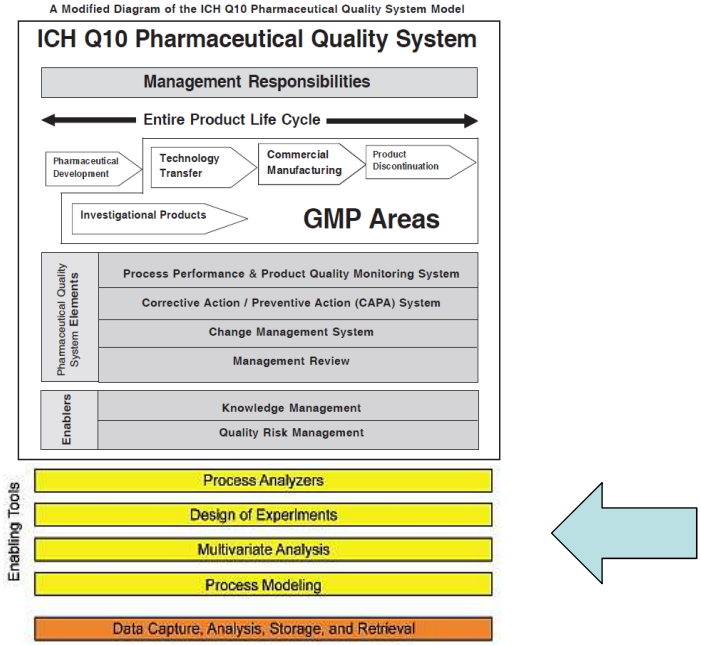

Challenges in Developing a PAT Strategy

QbD and PAT are inextricably linked

- A QbD Development strategy must include a strong PAT element

Developing a PAT Strategy requires investment in:

- People (statisticians, chemometricians, equipment experts)
- Technology (Analyzers – NIR, Raman, Particle size monitoring etc.)
- IT Infrastructure (Data "Warehousing", ability to integrate with existing systems (LIMS, SCADA, Process Historian Databases etc.)
- Quality Infrastructure

Integrating the whole PAT strategy within the QbD (Process) development paradigm is likely to be challenging

- PAT Development may already be underway with a process control focus
- Will require a much greater cross departmental strategy

QBD – THE 'WRONG' COST OF QUALITY CURVE

Q8(R2) Appendix 1. Differing Approaches to Pharmaceutical Development

Document provides a table listing examples of a minimal approach and an enhanced QbD approach	Note from the Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers
• "The comparisons are shown merely to aid in the understanding of a range of potential approaches to pharmaceutical development and should not be considered to be all-encompassing."	• **Question:** Is the minimal approach accepted by regulators? • **Answer:** Yes. The minimal approach as defined in Q8(R2) (sometime also called 'baseline' or 'traditional' approach) is the expectation which is to be achieved for a fully acceptable submission. However the 'enhanced' approach as described in ICH Q8(R2) is encouraged

Q8(R2) Appendix 1

Aspect	Minimal Approaches	Enhanced QbD Approaches
Overall Pharmaceutical Development	• Mainly empirical • Developmental research often conducted one variable at a time	• Systematic, relating mechanistic understanding of material attributes and process parameters to drug product CQAs • Multivariate experiments to understand product and process • Establishment of design space • PAT tools utilised

Q8(R2) Appendix 1

Aspect	Minimal Approaches	Enhanced QbD Approaches
Process Controls	• In-process tests primarily for go/no go decisions • Off-line analysis	• PAT tools utilised with appropriate feed forward and feedback controls • Process operations tracked and trended to support continual improvement efforts post-approval

Q8(R2) Appendix 1

Aspect	Minimal Approaches	Enhanced QbD Approaches
Product Specifications	• Primary means of control • Based on batch data available at time of registration	• Part of the overall quality control strategy • Based on desired product performance with relevant supportive data

Q8(R2) Appendix 1

Aspect	Minimal Approaches	Enhanced QbD Approaches
Control Strategy	• Drug product quality controlled primarily by intermediates (in-process materials) and end product testing	• Drug product quality ensured by risk-based control strategy for well understood product and process • Quality controls shifted upstream, with the possibility of real-time release testing or reduced end-product testing

Process Validation – 3 Stages

Step 1: Process Design

- The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Step 2: Process Qualification

- During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Step 3: Continued Process Verification

- Ongoing assurance is gained during routine production that the process remains in a state of control

Step 1: Process Design

- **The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.**

Provides further expansion of FDA intentions regarding QbD Development
Contains concepts from Q8,9,10 – Split into 2 parts:

- *1) Building and Capturing Process Knowledge and Understanding*
  - **Design of Experiment (DOE) studies can help develop process knowledge by revealing relationships, including multivariate interactions, between the variable inputs (e.g., component characteristics 13 or process parameters) and the resulting outputs (e.g., in-process material, intermediates, or the final product).**
  - **Risk analysis tools can be used to screen potential variables for DOE studies to minimize the total number of experiments conducted while maximizing knowledge gained.**
  - **The results of DOE studies can provide justification for establishing ranges of incoming component quality, equipment parameters, and in-process material quality attributes.**

Step 1: Process Design

- **The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.**

Provides further expansion of FDA intentions regarding QbD Development – Split into 2 parts:

- 2) *Establishing a Strategy for Process Control*
  - Process controls address variability to assure quality of the product. Controls can consist of material analysis and equipment monitoring at significant processing points (§ 211.110(c)). **Decisions regarding the type and extent of process controls can be aided by earlier risk assessments**, then enhanced and improved as process experience is gained.
  - More advanced strategies, which may involve the use of **process analytical technology (PAT),** can include timely analysis and control loops to adjust the processing conditions so that the output remains constant.

Step 2: Process Qualification

- During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Split into 4 Sections

- *Design of a Facility and Qualification of Utilities and Equipment*
- *Process Performance Qualification (The new term for what we USED to call Process Validation)*
- *PPQ Protocol*
- *PPQ Protocol Execution and Report*

The amount and type of work done at this stage is dependant on the amount and type of work done in Stage 1. If a design space has been established, PPQ will challenge the NOR (or Control Space)

The PPQ should contain "criteria and process performance indicators that allow for a science- and risk-based decision about the ability of the process to consistently produce quality products

- **In other words, we can no longer do 3 batches at appropriate scale and say we are done. The PPQ Protocol will be produced considering the amount of knowledge about the process gained in Stage 1.**

THE BRIGHT FUTURE OF PAT-ENABLED QBD

Rethinking Pharmaceutical Manufacture in the Long Term

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(54) **APPARATUS AND METHOD FOR PRODUCING A PHARMACEUTICAL PRODUCT**

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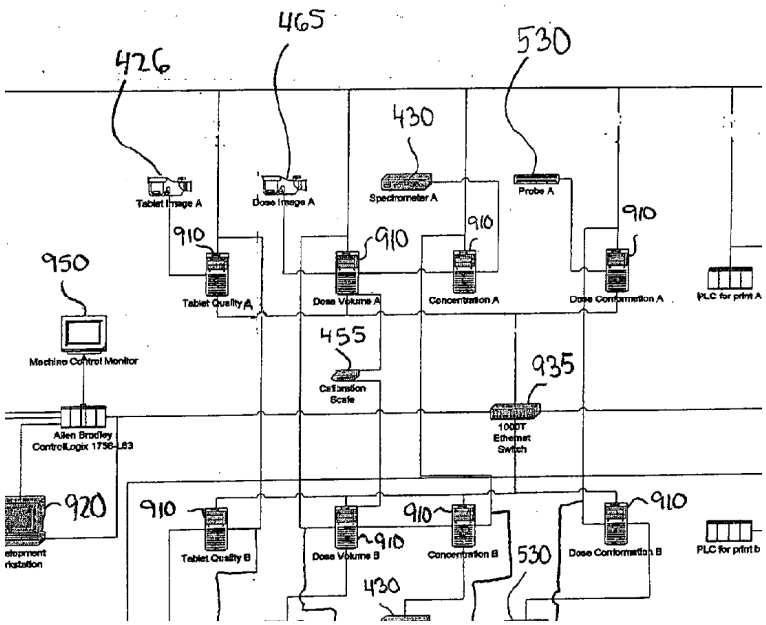
A61M 11/00 (2006.01)

(52) **U.S. Cl.** **128/200.23**; 382/120

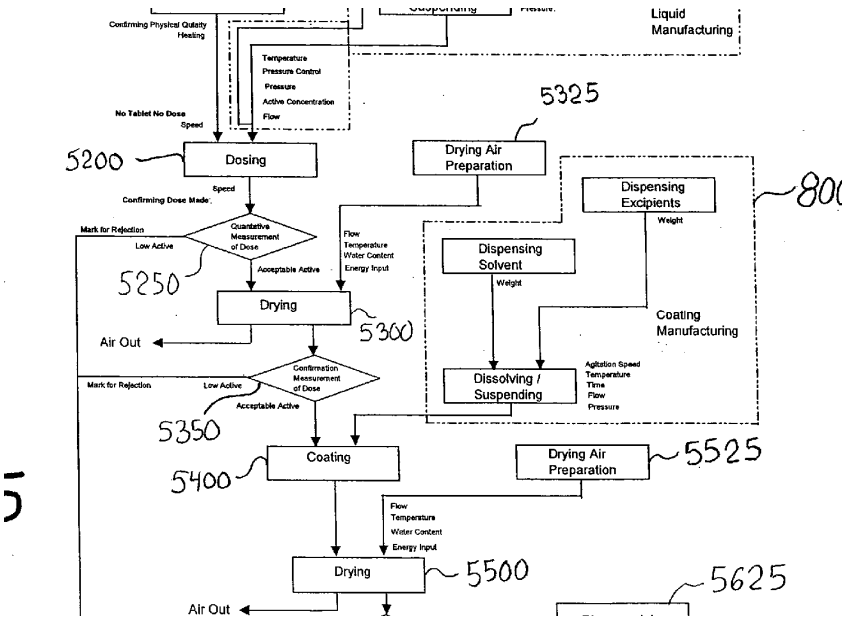
(57) **ABSTRACT**

An apparatus and method are provided for producing pharmaceutical and pharmaceutical-like products. The apparatus and method provide real-time monitoring of the pharmaceutical product and can provide real-time control. The apparatus and method can monitor the dosage both before and after it has been added to a carrier substrate. The apparatus and method can provide monitoring of each pharmaceutical product that is processed.

The Integration of Process and PAT Design – Mixing Skill Sets



The Integration of Process and PAT Design – Mixing Skill Sets



How Do We Ever Implement This In An Old-Fashioned Pharma Culture?

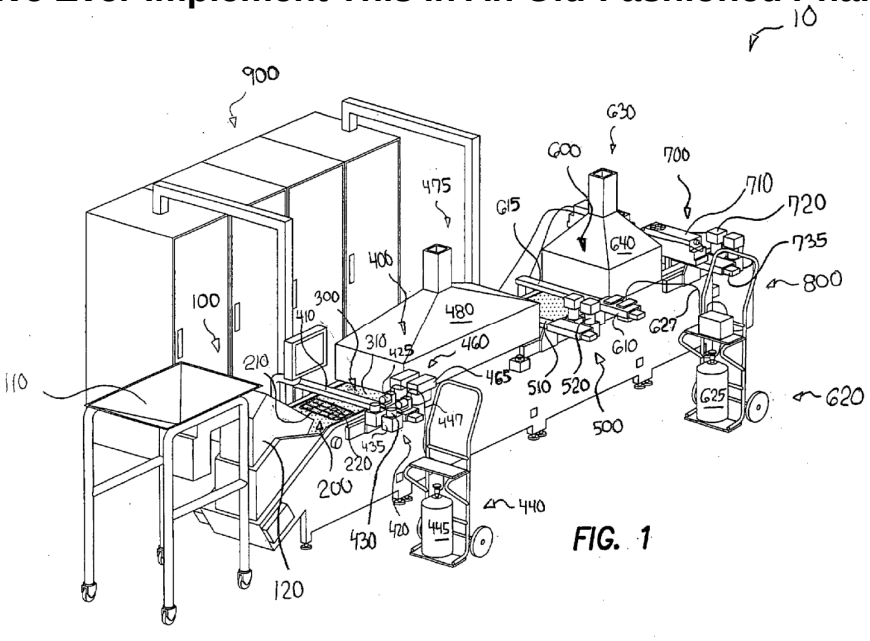


FIG. 1

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- To you for listening and keeping 'The Faith'
- Let the discussion and debate begin

At the End of the Day, Who Really Pays For Our Being on the Wrong Cost of Quality Curve?

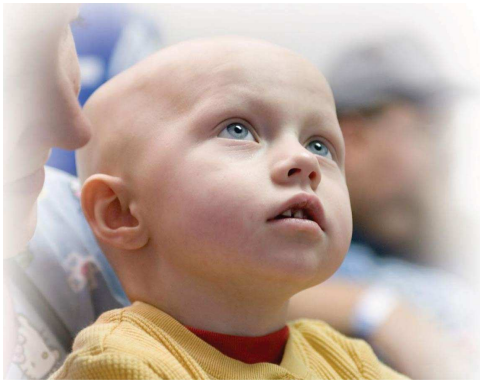
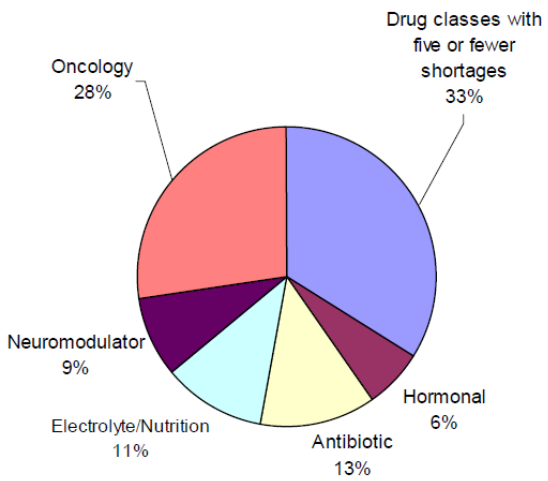


Figure 3: Drug Shortages by Drug Class, 2010-2011



(Based on 127 drug shortages between January 1, 2010 and August 26, 2011)

U.S. Department Of Health And Human Services U.S. Food And Drug Administration *A Review of FDA's Approach to Medical Product Shortages* OCTOBER 31, 2011
www.fda.gov/DrugShortageReport