The Unfinished Story of Quality-by-Design (QbD)

In the Pharmaceutical Industry

Bert T. Frohlich, Ph.D.
Principal & Owner
Biopharm Designs

Presentation to
ISPE Chapter Meeting
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Outline

The Unfinished Story of QbD

Origins: An Introduction to QbD
QbD and the Pharmaceutical Industry
FDA's/EMA's Joint QbD Pilot Program
Lessons Learned and Disillusionment
The Awakening
Challenges and the 'Holy Grail'!
What can you Do!?

Origins....
An Introduction to QbD

- Status of the Pharma Industry at the Turn of the Century
- Pharmaceutical Quality for the 21st Century Initiative
- Introduction to QbD
- PDA Workshop in 2007. Attendance by high-level FDA regulators
- The FDA's QbD Agenda

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The Pharma Industry at the Turn of the Century

The Good, the Bad, and the Ugly……..

The Good!

- Greater role of medicines in health care
- Advances in the pharmaceutical sciences and manufacturing technologies
- Advances in the science and management of quality
- Globalization

The Bad!

- Decreased frequency of FDA manufacturing inspections
  (limited funding = fewer resources available)
- Costs of drug development and commercialization continue to rise
- 'Stifled' innovation on manufacturing side
  (industry has not taken advantage of the same scientific methods and technologies that have benefited drug discovery and research in recent years.)

The Pharma industry at the Turn of the Century

FDA's Assessment:
*"Pharmaceutical manufacturing industry 'ossified' by prior environment."**

And the Ugly!

- "***Quality after design***" approach still being used
- Processes lack robustness
  - Processes are static
  - Measurement systems variable
  - Raw material characteristics not well understood
  - Out-of-specification values occur frequently
  - Data for continuous improvement segregated in different departments.
  - Stock outs and shortages on the rise
- Prices of drugs have not diminished
- Non-collaborative environment
- Global industry burdened by having to comply with multiple jurisdictions.

* **Janet Woodcock**, M.D., Currently: Director, Center for Drug Evaluation and Research
Ossified: rigidly conventional and opposed to change

Pharmaceutical Quality for the 21st Century!! Initiative

Objectives of the Initiative Announced by the FDA in 2002

Increase the accessibility of new drugs while maintaining their high quality…… by:

1. Early adoption of new technological advances
2. Application of modern quality management techniques
3. Implementation of risk-based approaches that focus both industry and Agency attention on critical areas
4. Ensure regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science
5. Enhance consistency and coordination of FDA's drug quality regulatory programs

Pharmaceutical Quality for the 21st Century Initiative

Qbd-relevant Publications over the past 25 years

Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach

Janet Woodcock

FDA / ICH Agreement

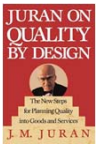
Pharmaceutical Quality for the 21st Century: A Risk-Based Approach. Final Report

J.M. Juran

Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations FDA, September 2006

1990 1995 2000 2005 2010 2015

QbD Pilot



Juran on Quality by Design: *The New Steps for Planning Quality Into Goods and Services*

Guidance for Industry, Process Validation. FDA, September 2011

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, guidance for industry, September 2004.

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Quality Systems Approach

New 2006 Guidance Solidified Concept of QbD

Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations. *U.S. Department of Health and Human Services, Food and Drug Administration, September 2006*

"The overarching philosophy articulated in both the CGMP regulations *and* in robust modern quality systems is:

Quality should be built into the product, and testing alone cannot be relied on to ensure product quality.

This guidance is intended to serve as a bridge between the 1978 regulations and our current understanding of quality systems."

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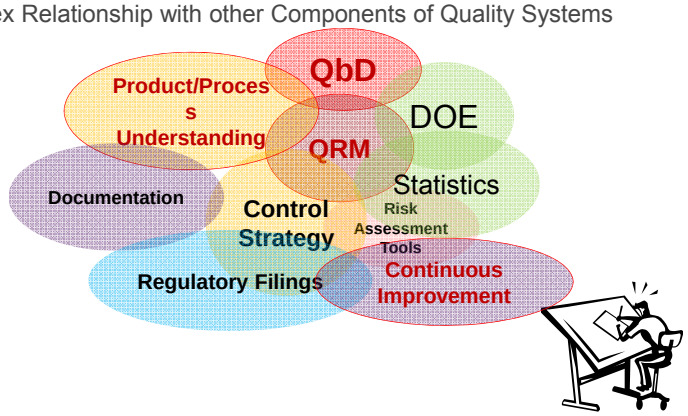
So What Really is QbD!?

A Complex Relationship with other Components of Quality Systems



So What Really is QbD!?

A Complex Relationship with other Components of Quality Systems

An approach to rational design. "Building in quality from the development phase and throughout a product's life cycle" …….. "Designing and developing a product and associated manufacturing processes that will be used during product development to ensure that the product consistently attains a predefined quality at the end of the manufacturing process." ***Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations ; U.S. Department of Health and Human Services, Food and Drug Administration, September 2006***

Quality by Design (QbD): [ICH Q8 (R2) Definition]
A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE. *This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.*

QbD and the Pharma Industry

- QbD Workshops
- The FDA's Agenda
- Factors Contributing to the Lack of Innovation
- The Blame Game!
- Getting 'Over the Hump' - Slow Adoption of QbD and Quality Risk Management

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PDA Workshop in 2007…

Attended by high-level FDA regulators

Conclusions of QbD Workshop

- "QbD is an Evolution, not a Revolution"
- QbD being implemented by some companies for small molecules
- Detailed guidance documents still not available
  - "No good definition of criticality".
  - "ICH Guidelines Q8, Q9 and Q10 are frustratingly vague"
  - Filing content? Level of detail?
- Not seeing any regulatory relief …..
- Greater willingness for collaboration on the part of the regulators

My Introduction to QbD!!

My subsequent publication in the PDA Journal ("QbD: Still in Design?") as summary and workshop conclusions.

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The FDA's Agenda….

We can't do this alone!.....

The FDA's Problem:

- The increasing number of different products
- The increasing number of submissions per year
- The increasing number of change requests
- Funding not keeping pace with the increasing work load….

The FDA's Agenda…. (Solution)

Transfer 'Ownership'…….

'Desired State' for the Pharmaceutical Sector

- Maximal efficient, agile, flexible pharmaceutical manufacturing sector that produces reliable high-quality products without extensive regulatory oversight.
- This state would encourage:
  - A regulatory process that is consistent, transparent and science-based
  - A regulatory process that allows for efficient and effective continuous improvement
  - A pharmaceutical sector that understands its products and the processes, uses risk assessment/mitigation tools and modern effective quality systems, and takes full ownership of the product

Industry Slow to Respond ... And Slow to Innovate!

Maybe we are Ossified!?...

Less investment in manufacturing technologies than in therapeutic technologies

- Product discovery and clinical development vs. process development

Biomanufacturers are risk averse

- The penalties are severe for delays and setbacks in drug commercialization
- Uncertainty around product comparability between scales and process changes
- New technology may not be adapted because of perceived risks to program
- Everyone wants to be a Fast Second!

Biomanufacturers and Suppliers tend to develop technologies in isolation

- Little Collaborative development
- Standardization usually occurs AFTER the technology is launched

Suppliers find it difficult to innovate

- Have to guess end user requirements
- Risk-reward balance is poor

The 'Blame Game'.

Complex Regulations vs. Risk Aversion

You need to follow ALL our regulations!

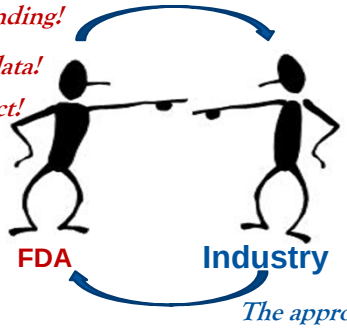
You're not investing enough in product/process understanding!

You need to share more data!

Your process IS your product!

We need to know if you change ANYTHING!

You need to improve your processes!



Too many regulations!

Global regulatory agencies are not aligned!

Drug development is already very expensive!

The approvals process already takes so long, we can't afford more delays!

If it's not (totally) broken, we are not going to fix it!

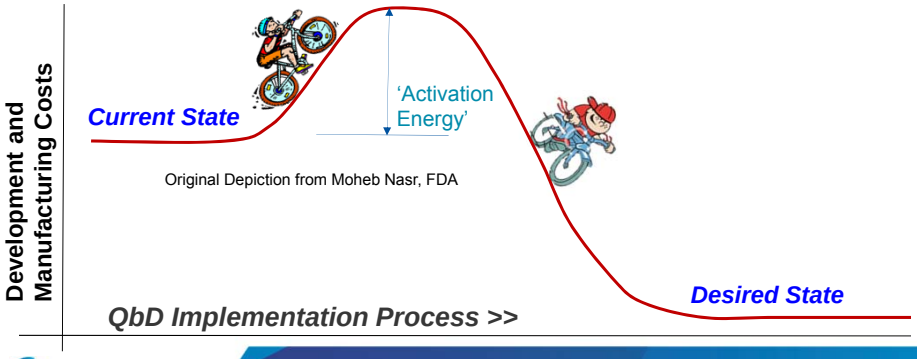
How do We Get Over the Hump!?

FDA's Admission…..

Actual deployment of QbD may well increase initial costs of commercialization

….. hoped that the long-term costs of manufacturing and regulation decrease…….

….Industry may have to take the first steps and further invest in their manufacturing facilities and process understanding…….



The QbD Pilot Program

- Announcement: an Opportunity for Collaboration
- Objectives of the Pilot
- The QbD Work Flow and CMC Filing
- The Disconnect between the Central Office and Regional Inspectors
- Aftermath and Disillusionment

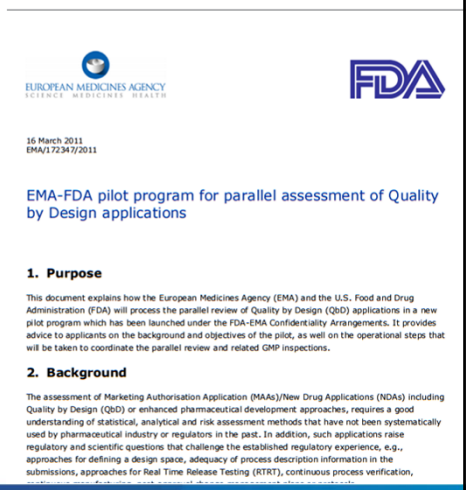
"As the number of applications that follow the QbD approach steadily increases, collaborative assessments will enhance understanding of QbD concepts. The tools used by FDA and EU reviewers will increase information sharing and reduce redundancy," said Janet Woodcock, M.D., director of FDA's Center for Drug Evaluation and Research. "To fully implement QbD, we need to further harmonize the implementation of the guidelines, work collaboratively, and provide scientific, risk-based regulatory decisions in a timely manner."

The FDA/EMA QbD Pilot Program

Announced on 2011 in an attempt to establish greater collaboration

Goals

1. Helping to ensuring consistent implementation of ICH guidelines for manufacturing quality in the application evaluation process
2. Increasing awareness of … concepts by staff that review marketing applications and inspect manufacturing facilities …….
3. Defining the reviewer and inspector interaction for QbD applications
4. ….. way for EMA and FDA assessors/ reviewers to share full knowledge ….
5. Developing and harmonizing regulatory decisions …..



EUROPEAN MEDICINES AGENCY

16 March 2011
EMA/172347/2011

EMA-FDA pilot program for parallel assessment of Quality by Design applications

1. Purpose

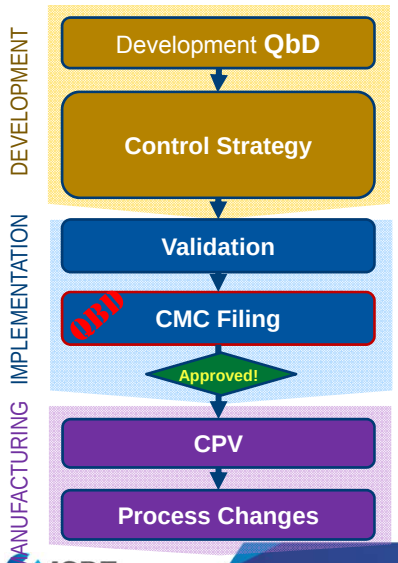
This document explains how the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) will process the parallel review of Quality by Design (QbD) applications in a new pilot program which has been launched under the FDA-EMA Confidentiality Arrangements. It provides advice to applicants on the background and objectives of the pilot, as well on the operational steps that will be taken to coordinate the parallel review and related GMP inspections.

2. Background

The assessment of Marketing Authorisation Application (MAAs)/New Drug Applications (NDAs) including Quality by Design (QbD) or enhanced pharmaceutical development approaches, requires a good understanding of statistical, analytical and risk assessment methods that have not been systematically used by pharmaceutical industry or regulators in the past. In addition, such applications raise regulatory and scientific questions that challenge the established regulatory experience, e.g., approaches for defining a design space, adequacy of process description information in the submissions, approaches for Real Time Release Testing (RTRT), continuous process verification,

The QbD Work Flow

The Pilot focused on CMC filing content for a 'QbD' ***Submission***



Design of Experiment (DOE), Process Characterization Design Space definition, Scale-down Models

Risk Assessment, Failure mode identification, in-process tests and controls

Process Performance Qualification (PPQ), Assay Validation, Design Space definition, Scale-down Model Qualification

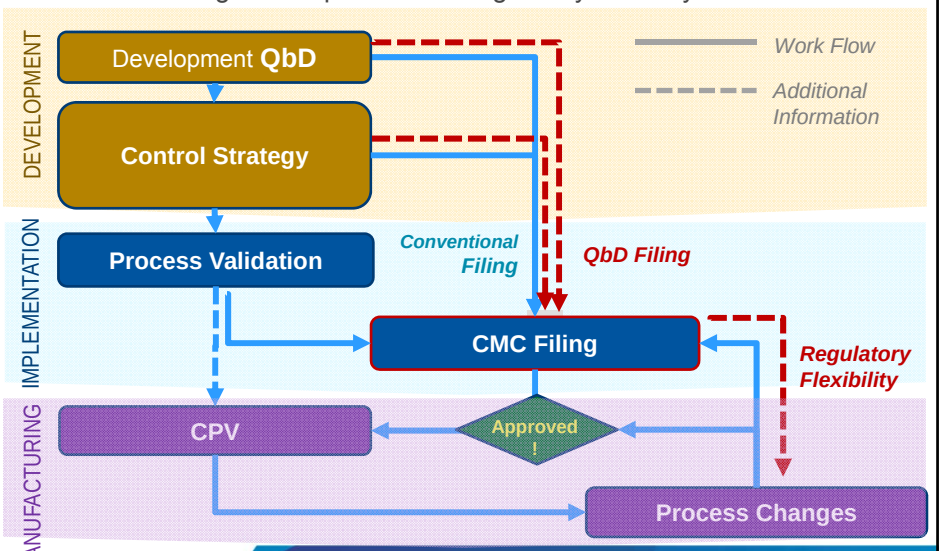
Development History, Design Space Specification, Product Characterization and Comparability

(Continued Process Verification), Process & Assay Monitoring, Trending, Variability Detection and Identification

Supporting Data, Risk Assessments, Product Comparability

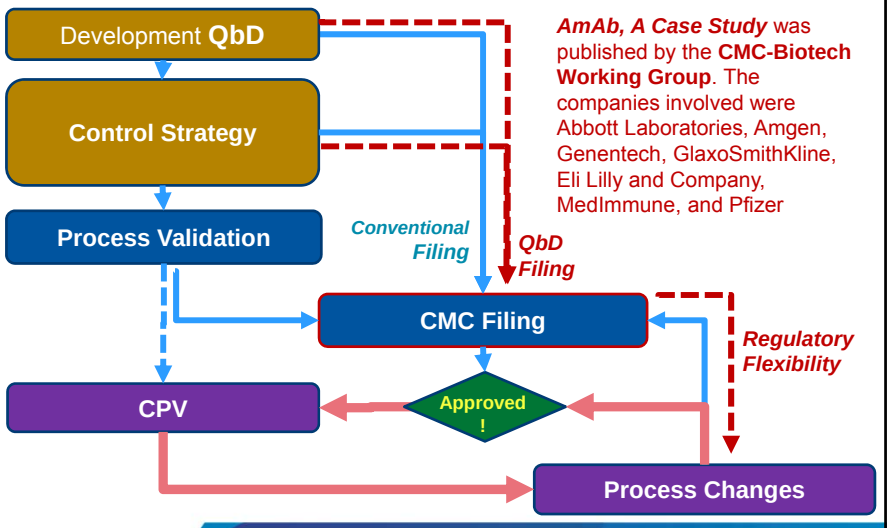
Leveraging Process Understanding for a QbD Filing….

Can a QbD Filing deliver post-launch regulatory flexibility?



Leveraging Process Understanding for a QbD Filing….

Concerted collaborative effort by key industry players…



AmAb, A Case Study was published by the **CMC-Biotech Working Group**. The companies involved were Abbott Laboratories, Amgen, Genentech, GlaxoSmithKline, Eli Lilly and Company, MedImmune, and Pfizer

So….You Want to Make Change!.....(?)

FDA Regional Inspectorate Disconnected from Central Office

Central Office Reviewers

Aspirational

- QbD and PAT are the solution…
- "A 'Quality Systems Approach' can handle many types of changes without the need for prior approval!"....?
- We want you to make 'improvements'!

Regional Inspectors

Compliance Focus

- Strict interpretation of the cGMP Guidelines
- We want to see everything you are changing.
- Make sure the product hasn't changed….Prove it!
- …and not before ALL your Quality Systems are solid..

Lessons learned…. And the 'Period of Disillusionment'

The old bait and switch!?!

Including elements of QbD….

- Can be the difficult, time consuming, and costly!
- Invites more questions from regulators as increased data is provided in filings!
- Still leads to different files in different jurisdictions if don't have global acceptance of QbD!
- Apparently no short-term relief from regulatory burden associated with QbD filings!
- Not clear that cost of manufacturing will be reduced with better process and product understanding…..

Definition of 'Criticality' (e.g. Critical Process Parameter) has been resolved….

Back to Finger Pointing….

What's in it for us?!

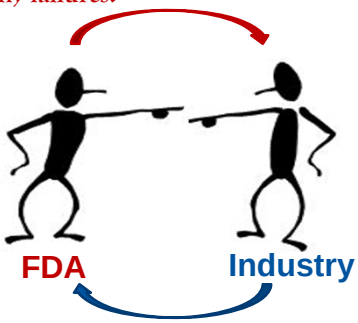
You need to share ALL your data!

You processes have too many failures!

You're still not investing enough in product/ process understanding!
You can't 'test in' quality!

We still need to know if you makes changes!

Are you controlling variability?



Still so many regulations!

This QbD thing is a lot more work and expense!

This could delay my program!

You're not giving us much credit for the extra work when we want to make changes!...

You still require the same filings and notifications for post-market changes!

The Awakening

- The Perfect Storm
- The Current Reality: Process Failures
- To QbD or Not to QbD?: Classic Dilemma Management
- The Critical Role of Control Strategy
- Why QbD/QRM Makes Good Business Sense: the Potential Benefits of QbD
- QRM Enables Efficient Resource Utilization

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U.S. Drug Shortages Frustrate Doctors, Patients

Drugs in short supply include cancer treatments and antibiotics; manufacturing snafus

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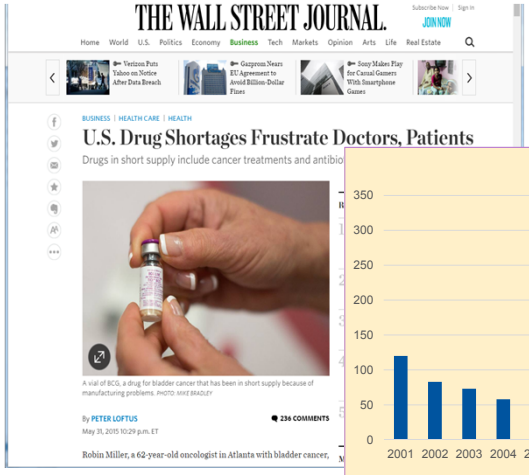
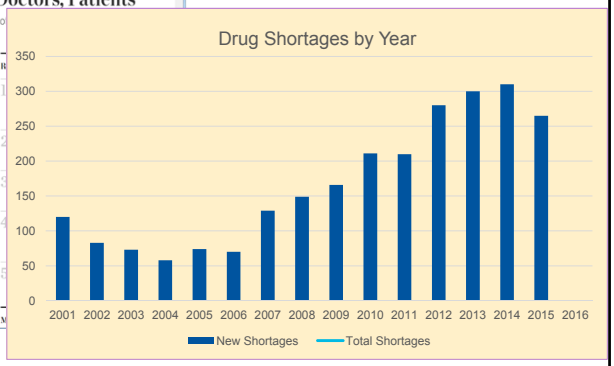
By PETER LOFTUS

Most Popular Articles

The Perfect Storm

Quality Issues, Drug Shortages, and Escalating Cost!!





The Current Reality

The Biopharmaceutical Paradox!!?

- Earlier proof of concept
- Lower-risk back-end expenditures
- Potential exclusivity
- Market capture

Speed to Market

vs.

(Poor) Process Robustness

- **Patients at Risk!!**
- Process failures, deviations and investigations
- Difficulty in meeting product demand
- Variability in product quality
- Resource drain on operations and quality personnel
- Filing rejections or delays
- Regulatory inspection observations

What's Missing?!! … The Critcal Role of Control Strategy

Translating QbD and Process Understanding into Real-time Control….

'Desired State' for the Pharmaceutical Sector

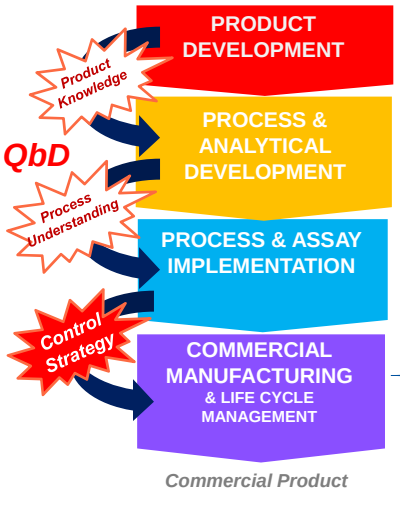
Maximal efficient, agile, flexible pharmaceutical manufacturing sector that produces reliable high-quality products without extensive regulatory oversight.

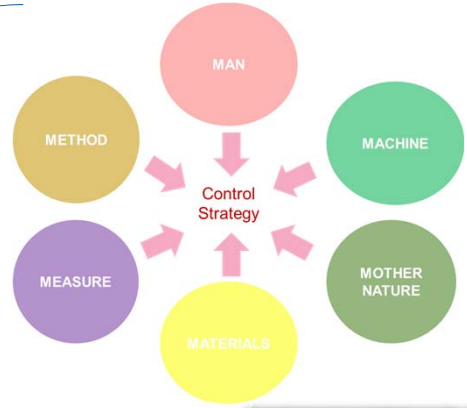
Control Strategy!!

A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. *The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)*

Comprehensive and Integrated Control Strategy Needed

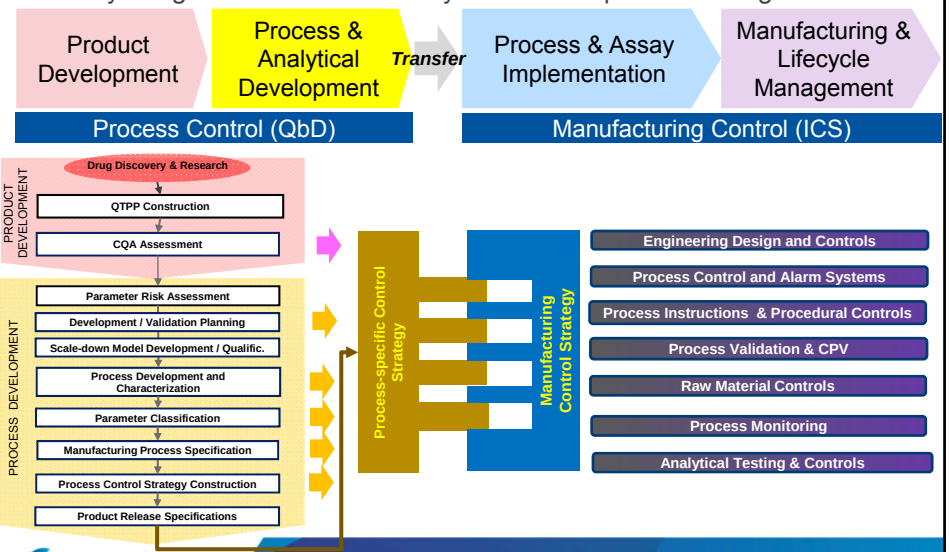
Addressing All the M's…..





Using QbD Outputs to Build the Control Strategy

A Truly Integrated Set of Control Systems is Required Leverage QbD



The Role of QRM

Embracing Quality Risk Management… a Different Mindset…..

Making decisions from the Patient's perspective!.....

QRM

- ***Total Risk is a function of:***
  - Severity of the event if it were to occur (**S**)
  - Probability or Frequency of Occurrence (**O**)
  - Probability of Detection (**D**) — CQA Detection Risk
  - Process Risk (Capability)
  - Medical Severity

$$\textit{Risk to Patient} = S_{CQA} \times O_{CQA} \times D_{CQA}$$

Why QbD/QRM Makes Good Business Sense

Streamlining process development, design, technology transfer and implementation.

Potential Benefits …. With or without a QbD Filing….

For Development Organization

- *Clarifies and Standardizes…. to improve consistency of approach*
  - ***Business processes*** *for development and tech transfer*
  - ***Documentation*** *(promotes consistency between project teams and functions)*
  - ***Demonstrating*** *product and process* ***knowledge*** *and understanding*
  - ***Risk assessment*** *methods*
  - *Concept of '****Criticality****'*
- *Efficient allocation of resources*
- *Logical and risk-based construction of control strategy*

Why QbD/QRM Makes Good Business Sense

Potential benefits continued ….. . *With or without a QbD Filing….*

For Engineering Organization

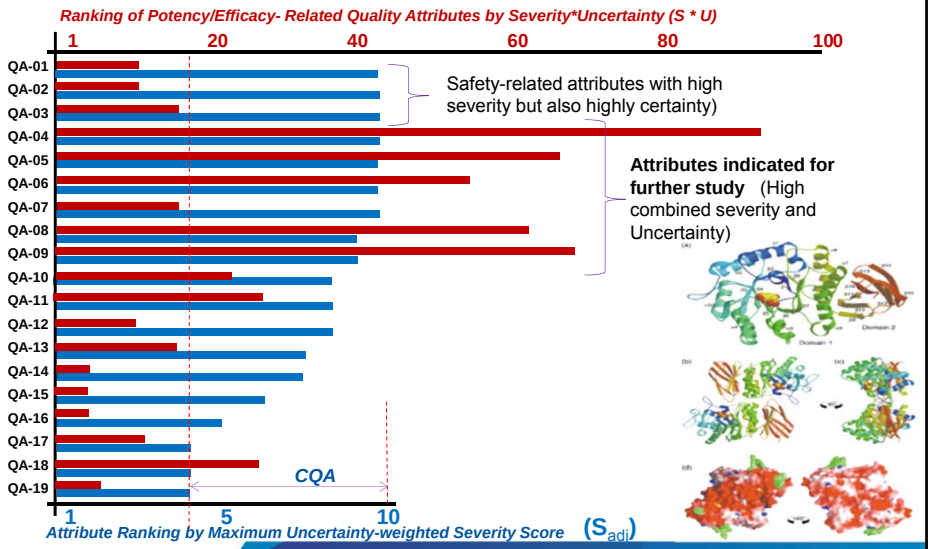
- *Translates process requirements into engineering design specifications*
- *Indication of 'Critical Controls' and 'Critical Aspects'*
- *Direct input into design FMEA's*

For Manufacturing and Quality Organizations

- *Increased product and process understanding*
- *Focus on truly 'Critical' events*
- *Fewer failures and more consistent product quality*
- *Lower burden / resource requirement on Quality organization*
- *Leverage knowledge to support manufacturing investigations*

QRM Good for Efficient Resource Management and Utilization

Example: Using Quality Attribute Assessment Data to Prioritize Further Study



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Challenges

- The 'Holy Grail(s)' of QbD: Real-time Release and Regulatory Relief
- Lifecycle Approach to Process Validation
- The Role of Continued Process Verification (CPV)
- Data intensive nature of QbD and Knowledge Management
- Fully integrated Business Process
- What Can You do!?: Opportunities for the Manufacturing and Supplier Community

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The Future of QbD !!?

The Holy Grail! ……..

Regulatory relief for post-launch changes….

- Faster implementation of improvements and
- Faster realization of benefits
- Reduced filing requirements

Real-time release

- Faster response to changes in demand; Reduced cycle times
- Reduced inventory and associated costs
- Leverage full shelf life

……but, we are not there yet…….

- Greater product and process understanding required for self regulation
- Robust monitoring and CPV for detection of variability
- Still lack regulatory harmonization

Lifecycle Approach to Process Validation

QbD principles extend beyond development in the product lifecycle ….

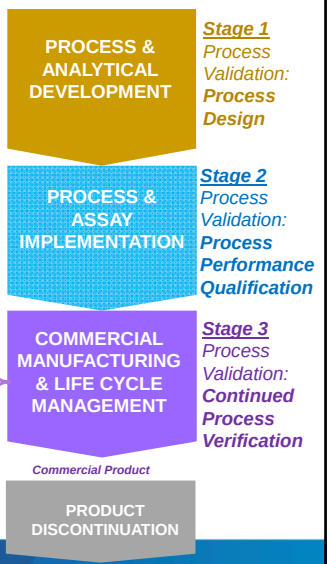
FDA: Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations. U.S. Department of Health and Human Services, Food and Drug Administration, September 2006

- *"Building in quality from the development phase and **throughout a product's life cycle**"*
- *"QbD in conjunction with a quality system, provides a sound **framework for the transfer of product knowledge** and process understanding from drug development to the **commercial manufacturing processes and for post-development changes and optimization**."*

***FDA: Guidance for Industry, Process Validation*…….**

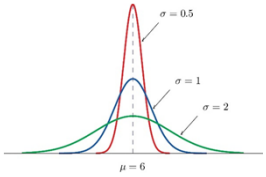
U.S. Department of Health and Human Services, Food and Drug Administration, September 2011

- *"The goal of the third validation stage is continual **assurance that the process remains in a state of control** (the validated state) during commercial manufacture. "*
- *"A system or systems for **detecting unplanned departures** from the process as designed is essential to accomplish this goal."*



Continued Process Verification (CPV)

Controlling (Long-term) Variability……

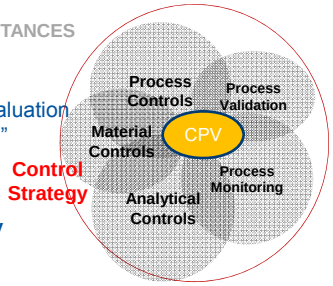


ICH Q8(R2): PHARMACEUTICAL DEVELOPMENT; Current Step 4 version; August 2009

"A comprehensive pharmaceutical development approach will generate process and product understanding and ***identify sources of variability***."

ICH Q11: DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES (CHEMICAL ENTITIES AND BIOTECHNOLOGICAL/ BIOLOGICAL ENTITIES): Current Step 4 version dated 1 May 2012

"…….use of upstream controls should be based on an evaluation and ***understanding of the sources of variability*** of a CQA."



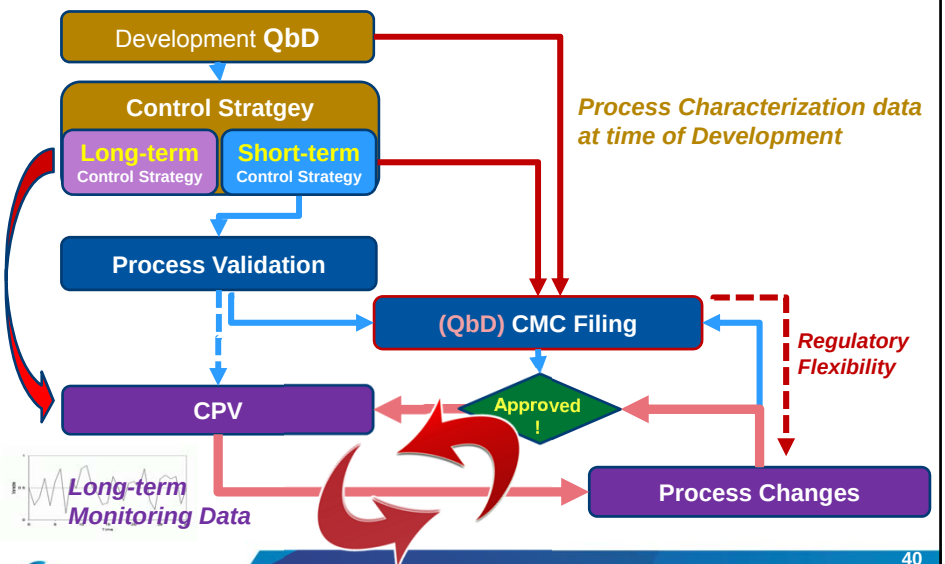
CPV an integral part of Control Strategy

ICH Q10: Pharmaceutical Quality Systems (Sect. 3.2.i)

- "…….execute a system for the monitoring of process performance and product quality to ensure a state of control is maintained. An **effective monitoring system provides assurance of the continued capability of processes and controls** to meet product quality and to identify areas for continual improvement."

A Robust Long-term Control Strategy Required……

Process Characterization during Development can not guarantee long-term Control…..



The Data Challenge:

QbD is Data Intensive !!

- Biological products are complex have many 'Critical Quality Attributes' (CQAs)
- Multiple high-resolution methods are typically required to analyze product quality
- Bioprocesses are also complex with many unit operations.
- Each unit operation can have multiple 'Critical Process Parameters' (CPPs)
- Relationships and interactions between process parameters and raw material attributes can be complex and difficult to measure
- Raw materials can be complex and can vary long term over the course of a products manufacturing lifecycle.

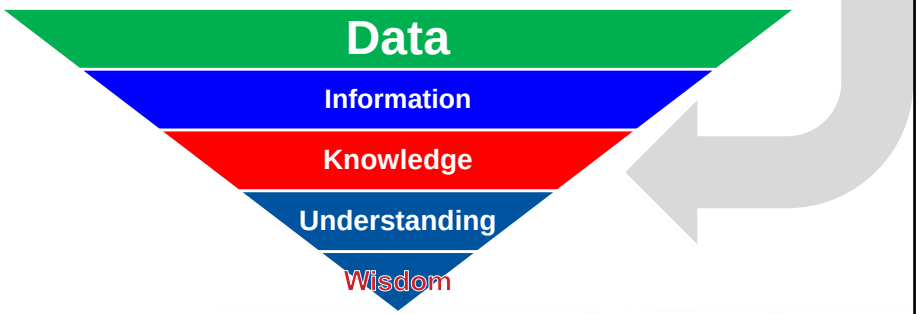
Knowledge Management Seen as a Key Enabler for QbD

Leveraging what was learned from QbD studies……

*"Knowledge Management is arguably the biggest challenge for QbD"**

*"…it is knowledge and not the volume of data that supports science-based submissions and their evaluation."**

* *Knowledge management in the QbD paradigm: manufacturing of biotech therapeutics.* Herwig, Garcia-Aponte, Rathore. Trends in Biotechnology, July 2015, Vol33, No.7



The Complete Picture ….. of Future State

Organizational Commitment to Systematic Approach throughout Product Development and Commercialization

PRODUCT DEVELOPMENT:

- Key focus on product's critical quality attributes (CQA) as the primary process performance target.
- Use of structure / function and pre-formulation studies for rational development
- Use of advanced high-throughput analytical methods

PROCESS & ANALYTICAL DEVELOPEMNT:

- Well documented use of risk assessments (QRM!!)
- Use of qualified Scale-down models
- Design of Experiments (DOE) and statistical data analysis
- Identification of Critical Process Parameters (CPPs)
- Process understanding used to build control strategy.

PROCESS & ASSAY IMPLEMENTATION:

- Technology Transfer and
- Integration of process-specific controls and Manufacturing and Quality Systems to create comprehensive control strategy.

CLINICAL /COMMERCIAL MANUFACTURING:

- Continuous monitoring and process verification (CPV)
- Identification of performance trends and opportunities for improvement.

The Complete Picture ….. of Future State

Organizational Commitment to Systematic Approach throughout Product Development and Commercialization

What can you Do!?

Implications and Opportunities for the Manufacturing and Supplier Community…..

Retrospective QbD …. An oxy moron!?
Data mining, multivariate analysis and identification of interactions
Efficient experiment design, First-principles modeling
Rapid, high-throughput analytical methods

Characterization of raw materials and their variability
Single greatest impact on process performance and variability!!
Detailed sourcing information and change notification
Raw material manufacturing data (can be blinded)

Data sharing
Supplier databases
Leveraging data/experience from other operating companies

Filing support
Submission ready documents and data sheets
Links to pre-characterization work

Standardization of equipment and components
Allowing interchangeability without extensive characterization, Validation ready
Failure rate estimation
Integration of instrumentation and controls with process equipment, Pre-qualification

Knowledge and Data Management Systems
Data collection efficiency, standards, sampling systems, cross-platform inteligence

Questions?

Please use the microphone indicated so our recording includes audio of your question

BioPharm Designs

Consulting and Technical Services

Bert Frohlich, Ph.D. Biochemical Engineering

Helping clients set strategic direction in process and manufacturing technology and infrastructure and in the design and implementation of high-level business processes towards improving work efficiency, costs, timelines, and product quality.

bert@biopharmdesigns.com

+1-978-496-0182

www.biopharmdesigns.com
(under construction)

BACKGROUND & EXPERIENCE

PhD biochemical engineer with 25+ years of experience in the biotechnology, pharmaceutical, and chemical industries. Bert has held director-level positions at Shire, Amgen, EMD and Acambis (now Sanofi) and worked as a senior engineer at Genzyme, Biometics and Roche in process/facility design, bioprocess development and manufacturing technical services.

Bert received his B.S and M. Eng. Degrees at Cornell University in Chemical Engineering and his Ph.D. at Tufts University in Biochemical Engineering

SKILLS & SERVICES

Process & Technology Development

- Quality be Design (QbD)
- Bioprocess development and characterization
- Bioprocess design and modeling
- Process & analytical control strategy and design
- Validation and CPV
- Process documentation including CTD filing sections

Engineering

- Conceptual design
- Cost modeling
- Design documentation
- Capital project management and commissioning
- Facility and process validation

Technical Management

- Technical organizational design
- Coaching and Trainng
- Business process design and governance
- Data & knowledge management and infrastructure

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Backup Slides

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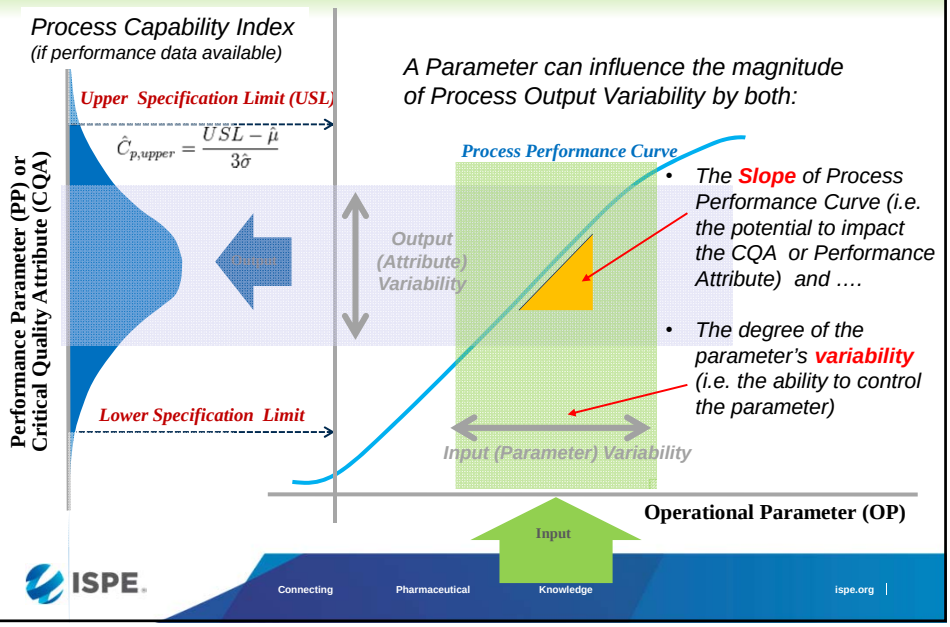
'Process Capability' … What is it?

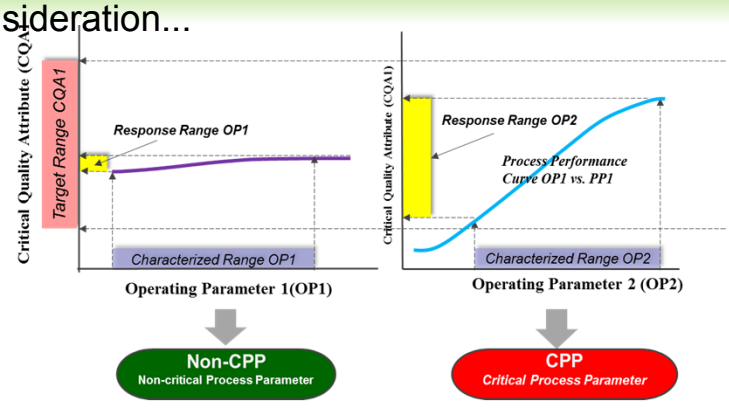
Process Capability O_{CQA}

Process capability is a measure of the process' ability to maintain performance within specified limits



Definition of '*Critical Process Parameter*' (CPP) …Should not take controllability into consideration...

$O_{CQA} = \sum [IP_i \times PC_i \times DF_i]$



Human Medicines Development and Evaluation ***EMA/430501/2013*** ***20 August 2013***

EMA-FDA pilot program for parallel assessment of Quality-by-Design applications: lessons learnt and Q&A resulting from the first parallel assessment

In accordance with ICH Q8(R2) a critical process parameter is one whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality……. **The fact that a risk of failure is mitigated by applying a robust proactive control strategy should not allow for the underestimation of assigning criticality.** …….. in the… "Description of the Manufacturing Process and Process Controls" and …. "Control of Critical Steps and Intermediates" sections, the description of all parameters that have an impact on a CQA should be classified as critical.

Human Medicines Development and Evaluation
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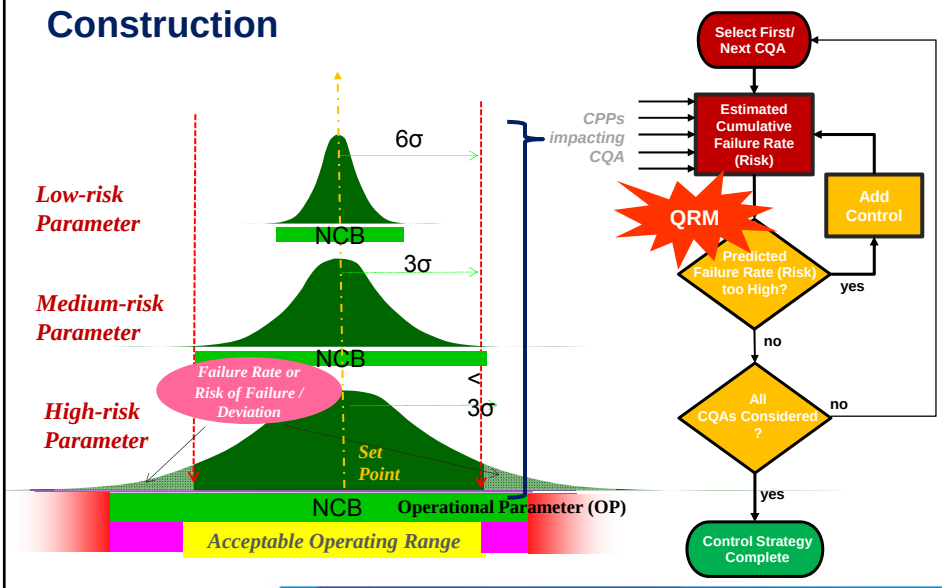
Process & Analytical Control Strategy Construction



Manufacturing Components and Control Systems

The Six M's!

MAN	METHOD	MACHINE	MATERIAL	MEASURE	MOTHER NATURE
Training Qualification Job Descriptions Alarm Response Communication Escalation	Process Description Process Instructions Master Batch Record Design Batch Records SOPs Form Preps Deviations	Engineering Design Automation and Controls Alarm System Equipment Validation Calibration Maintenance Utilities L&E	Raw Materials Testing Vendor Management Component Testing Raw Materials Monitoring	In-process Assays Release Assays Stability Testing Assay Controls Assay Performance Monitoring Process Monitoring	Biological contamination controls Chemical Contamination Controls Environmental Monitoring Pest Control

The Promise of PAT….?

Process Analytical Technologies to the Rescue!?

"This guidance is intended to describe a regulatory framework (Process Analytical Technology, PAT) that will encourage the voluntary development and implementation of innovative pharmaceutical development, manufacturing, and quality assurance."

"Unfortunately, the pharmaceutical industry generally has been hesitant to introduce innovative systems into the manufacturing sector for a number of reasons. …..."

"The goal of PAT is to enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design."

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

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
and/or
Communications Staff, HFV-12
Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Place,
Rockville, MD 20855
(Tel) 301-827-3800
http://www.fda.gov/cvm/guidance/published.html

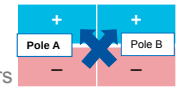
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)
September 2004
Pharmaceutical CGMPs

PAT seen as an enabler of QbD but…..

- Considerable investment required
- Limited analytical methods available for complex biological molecules
- Insufficient product and process understanding to know what to measure much less what to control
- Limited on-line and even at-line sensors available

To QbD or Not to QbD!?

Classic Dilemma Management - Requires monitoring of leading indicators



Advantages

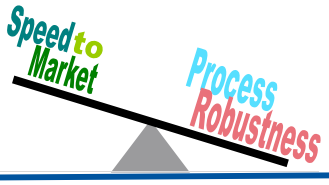
- Market Capture
- Potential exclusivity
- Earlier proof of concept
- Lower-risk back-end expenditures

Disadvantages (Imbalance Indicators)

- Process failures, deviations and investigations
- Variability in product quality
- Resource drain on operations and quality personnel
- Filing rejections or delays
- Regulatory inspection observations

Advantages

- Well understood process with less upsets or deviations
- Smoother tech transfer
- More complete filing and better chance of approval
- Ability to meet product demand



Disadvantages (Imbalance Indicators)

- High up-front expenditures
- High resource loads
- Program delays
- Loss of market advantage

Product / Process Development & Lifecycle Management

is an Iterative Process!

- The development work flow is iterative by virtue of the phases of clinical development through human trials. Phase appropriateness.
- Clinical data feed back into product development and ultimate definition of product's design space
- Knowledge gained from clinical manufacturing of the clinical lots can be leveraged for subsequent rounds of process development.
- As the development progresses, the total quality risk is reduced until acceptable for commercial licensure and manufacturing.
- Continuous process monitoring and verification enables process improvement over time.