The Unfinished Story of Quality-by-Design (QbD)
In the Pharmaceutical Industry

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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

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**

*FDA / ICH Agreement*

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

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

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

*Guidance for Industry, Process Validation. FDA, September 2011*


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.
So What Really is QbD!? 
A Complex Relationship with other Components of Quality Systems

**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.

**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
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

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.
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!
Too many regulations!

You’re not investing enough in product/process understanding!
Global regulatory agencies are not aligned!

You need to share more data!
Drug development is already very expensive!

Your process IS your product!
The approvals process already takes so long, we can’t afford more delays!

We need to know if you change ANYTHING!
If it’s not (totally) broken, we are not going to fix it!

You need to improve your processes!
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 RegionalInspectors
- 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 ….

The QbD Work Flow
The Pilot focused on CMC filing content for a “QbD” Submission

- Development QbD
  - Design of Experiment (DOE), Process Characterization
  - Design Space definition, Scale-down Models
- Control Strategy
  - Risk Assessment, Failure mode identification, in-process tests and controls
- Validation
  - Process Performance Qualification (PPQ), Assay Validation, Design Space definition, Scale-down Model Qualification
- CMC Filing
  - Development History, Design Space Specification, Product Characterization and Comparability
- Approved!
- (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?

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

Leveraging Process Understanding for a QbD Filing….
Concerted collaborative effort by key industry players…
So….You Want to Make Change!......(?)
FDA Regional Inspectorate Disconnected from Central Office

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’!

Central Office Reviewers

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/ORM Makes Good Business Sense: the Potential Benefits of QbD
- ORM Enables Efficient Resource Utilization
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

(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 Critical 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!.....

- **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)

\[
\text{Risk to Patient} = S_{CQA} \times O_{CQA} \times D_{CQA}
\]
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

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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Ranking of Potency/Efficacy-Related Quality Attributes by Severity x Uncertainty (S * U)

- Safety-related attributes with high severity but also highly certainty
- Attributes indicated for further study (High combined severity and Uncertainty)

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
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 …. 

- “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 and 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 product’s 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.”**

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 DEVELOPMENT:**
- 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

**PRODUCT DEVELOPMENT**
- Discovery and Research; Preclinical Research
- Quality Target Product Profile (QTPP)
- Critical Quality Attributes

**PROCESS & ANALYTICAL DEVELOPMENT**
- Parameter Impact Assessments; Process Design (Stage 1 Process Validation); Analytical Development; Assay Performance Capability; Process Characterization; Parameter Classification; Process & Analytical Control Strategy
- Product Release Specification

**PROCESS & ASSAY IMPLEMENTATION**
- Process, Assay Transfer; Equipment Validation
- Overall Manufacturing Control Strategy
- Process Performance Qualification (Stage 2 Process Validation)

**COMMERCIAL MANUFACTURING & LIFE CYCLE MANAGEMENT**
- Instrument Calibration; Preventative Maintenance; Alarm System Management; Deviations Management; Process Monitoring;
- Continued Process Verification (Stage 3 Process Validation):
- Continuous Improvement

**Commercial Product**
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 intelligence

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.

SKILLS & SERVICES

Process & Technology Development
- Quality by 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 Training
- Business process design and governance
- Data & knowledge management and infrastructure

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

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Backup Slides
’Process Capability’ … What is it? 

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

A Parameter can influence the magnitude of Process Output Variability by both:

- The Slope of Process Performance Curve (i.e. the potential to impact the CQA or Performance Attribute) and ....
- The degree of the parameter’s variability (i.e. the ability to control the parameter)

Definitions:

- **Performance Parameter (PP) or Critical Quality Attribute (CQA)**
- **Upper Specification Limit (USL)**
- **Lower Specification Limit**
- **Operational Parameter (OP)**
- **Input (Parameter) Variability**
- **Output (Attribute) Variability**

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

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  
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.
Manufacturing Components and Control Systems
The Six M’s!

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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.”

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

**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

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<th>Disadvantages (Imbalance Indicators)</th>
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| Process failures, deviations and investigations  
- Variability in product quality  
- Resource drain on operations and quality personnel  
- Filing rejections or delays  
- Regulatory inspection observations | 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.