A Simple and Pragmatic Approach To Implementing QbD

The Inputs to the Process

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A Bit About Me

GLUT 1

Flow in Stented Arteries

Analytical Methods

Adenovirus-PEG-Fab
What is Quality?

- Leadership
- Product Requirements for Business
- Product Requirements for Quality
- Proper Specifications
- Supply Chain Management - CXOs

The Regulatory Framework

“We don’t know what the FDA wants...”

“We don't need to worry about regulatory issues yet...” or “I don't understand how this applies to me”
Quality by Design – It’s a Mindset

**Leadership**

“Modern robust quality systems models call for management to play a key role in the design, implementation, and management of the quality system...management is responsible for establishing the quality system structure appropriate for the specific organization. Management has ultimate responsibility to provide the leadership needed for the successful functioning of a quality system.”

(from ICH Q8)

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What is the FDA looking for in Drug Development?

*Risks, knowledge, and understanding of your product and process*

**SUFFICIENT DATA TO EVALUATE DRUG SAFETY (CMC requirements)**

The data you generate during product and process research and development is the foundation of your knowledge and understanding.
**DEVELOPMENT is the FIRST STAGE IN THE LIFE-CYCLE and is part of your QMS**

**Drug Substance Development** (ICH Q10)

**DATA** → **Drug Substance Development** (ICH Q10) → **TPP**

*Do your strategic goals align with your company, your investors, and the FDA?*

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**Drug Substance Development is a Process**

**A process needs:**
- Defined inputs
- Measurable outputs

![Diagram](image)

**Desired Outcome**

**Actual Outcome**

“**The process defines the product**”

Troubleshooting or **ROOT-CAUSE ANALYSIS** requires **DATA**
Design Quality into Your Product and Process

CQA = f(CMA) + f(CPP)

Plan ahead...
- What does the product need to deliver?
- How will we achieve these deliverables?
- What is our timeline?
- What is our budget?

“The process defines the product”

Break down the deliverables into meaningful processes with meaningful outcomes

“If you can’t describe what you are doing as a process, you don’t know what you are doing.” - W. Edwards Deming
**Integration of FDA Requirements and Business Requirements: What Drives Your Corporate and Science Strategies?**

- Safety
- Efficacy
- Cost
- Time

**Critical for FDA Approval**

**Critical for Business**

**Phase I Clinical Trial**

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**Why Start Early: Early-Stage Data is the Input for the Development Process**

*Who’s up for crisis management?*

> “By failing to prepare, you are preparing to fail.”

*Benjamin Franklin*
What is the Right Data?
Statistical Terminology and Tools

“But we have no upfront time or SME to understand and put all this together…”

• DoE
• MVA
• FMEA
• Ishikawa
• Pareto
• SPC
• ANOVA
• Taguchi

Upstream Planning Affects the Final Results
Variability and Uncertainty

There is much more leverage in early stage
Costs get higher as you move through the pipeline
Variation is highest in R&D –

- Understand the variation that you see…this variation may show up at later stages
- Understand what variation has a significant effect on product quality.
- Document the knowledge…downstream teams will appreciate knowing what they may expect to see with scale-up
- Don’t try to control insignificant factors
Upstream Planning Affects the Final Results

- Pareto Effect or “80:20 Rule” – USE SCREENING DESIGNS
- “How likely does a factor effect outcome?”

Only 20% of factors determine 80% of the main effects

Most of the time, the factors are known…which is why we choose to change them one at a time

Upstream Planning Affects the Final Results

Variability and Uncertainty

Inherent variation in early stage R&D can make it difficult to understand the significance of experimental changes

Consider: If your process or experiment has 20% variation, 95% of your results will fall within ± 40% of the experimental mean.

Ask: How likely is it that a factor will have an effect on outcome?
What exactly does this mean?

- Potential for unnecessary restrictions on product/process
- Potential for unnecessary changes or off-target specifications

Randomly generated data simulating an experiment performed in triplicate on 3 independent occasions
Data was generated from a distribution with a mean of 10 ± 3 (30% variation)

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Case Study: Development of an Impurity Analysis

Data → Knowledge → Information

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DATA
Case Study: Development of an Impurity Analysis

Data → Information → Knowledge

Regression Analysis

- Reagent
- Temperature
- Reagent
- Time

Information

Variation and Regression Analysis

- Time
- Extraction Reagent
- Temperature

ROBUSTNESS

Decrease time
Decrease cost
Increase yield

Knowledge
**Case Study: Development of an Impurity Analysis**

Data → Information → Knowledge

- 12 experiments were performed…method not entirely optimized
- Not balanced…can’t determine significance

*AN 8 EXPERIMENT FULL FACTORIAL DoE WOULD HAVE RESULTED IN MORE KNOWLEDGE AND INFORMATION*

![Graph showing percent recovery over experiments](image)

**USE THE LEVERAGE YOU HAVE IN R&D**

Variability and Uncertainty

QbD

Understand Variation

Target Product Profile
The QbD Thought Process and Supply Chain Management

Quality Agreements

Deliverables, Costs, and Timelines
QbD and DoE

- **Target Product Profile** – helps define your deliverables
- **QbD** – helps define the quality of your deliverables and the quality of materials and services (contract organizations)
- **DoE** – helps define timelines, cost, and specifications

*Enables strategic planning for your business needs and your science*
Target Product Profiles <> Quality Agreements

What specifications do your suppliers’ products meet?

Manufacturers
CROs
Analytical APIs
Materials
Sterilization
Internal

What specifications do you need for product success?

Target Product Profile and Quality Agreements
What deliverables are required to achieve your goals?

Stakeholders
CXOs
Quality Agreements
Communication

Critical Material Manufacturers
Leadership, People, and Knowledge Transfer

http://s949.photobucket.com/user/seraiwallpapers/media/daily/Trafficjam.jpg.html

Quality by Design – It’s a Mindset

“Quality managers will be losing their staff…”
From “Trending in the Future of Quality”, Joseph Defeo, CEO of Juran Global

ISO
ANSI
ASTM
EMA
FDA

MANAGEMENT IS ULTIMATELY RESPONSIBLE
Questions?
Please use the microphone indicated so
our recording includes audio of your
question

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