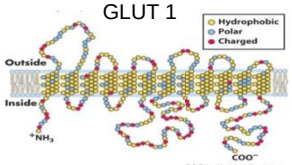
A Simple and Pragmatic Approach To Implementing QbD

The Inputs to the Process

Amy L Lachapelle
Founder
QBD Strategies LLC

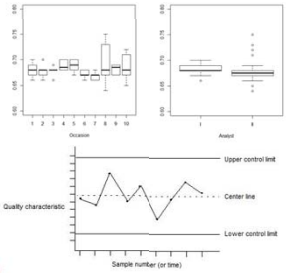
A Bit About Me

GLUT 1



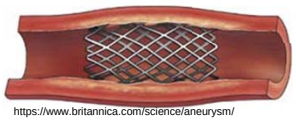
http://www.slideshare.net/AmitKumar325/cell-membrane-and-transport-52246921

Analytical Methods



QBD STRATEGIES

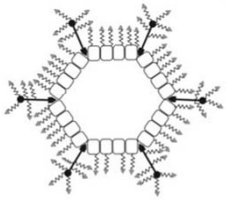
Flow in Stented Arteries



https://www.britannica.com/science/aneurysm/

$$\nabla^2 u = \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2}$$

Adenovirus-PEG-Fab



https://www.researchgate.net/figure/245029945_fig7

What is Quality?

QMS & QbD

- 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)

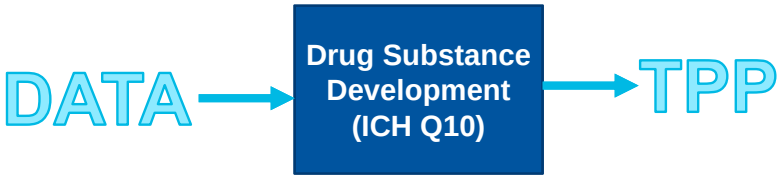
What is the FDA looking for in Drug Development?

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

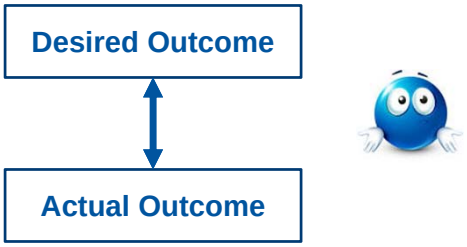


Do your strategic goals align with your company, your investors, and the FDA?

Drug Substance Development is a Process

A process needs:

- **Defined inputs**
- **Measurable outputs**



Troubleshooting or *ROOT-CAUSE ANALYSIS* requires **DATA**

"The process defines the product"

Design Quality into Your Product and Process

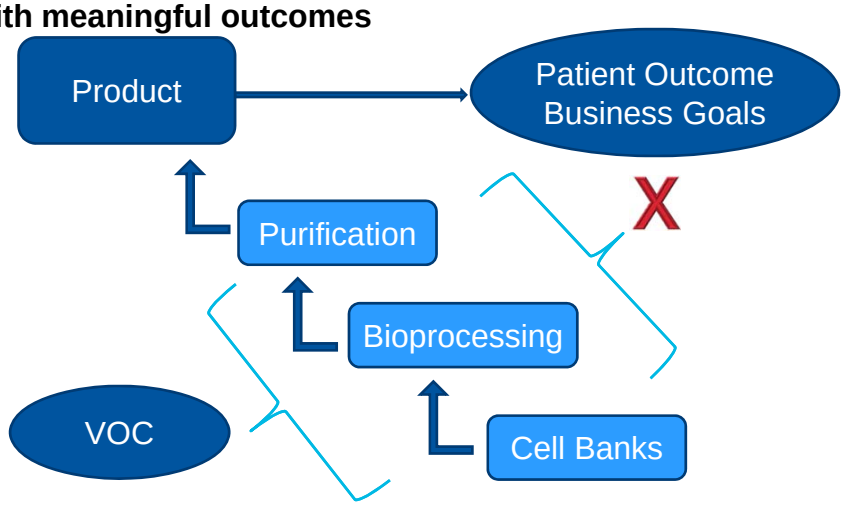
CQA = f(CMA) + f(CPP)

Plan ahead…

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

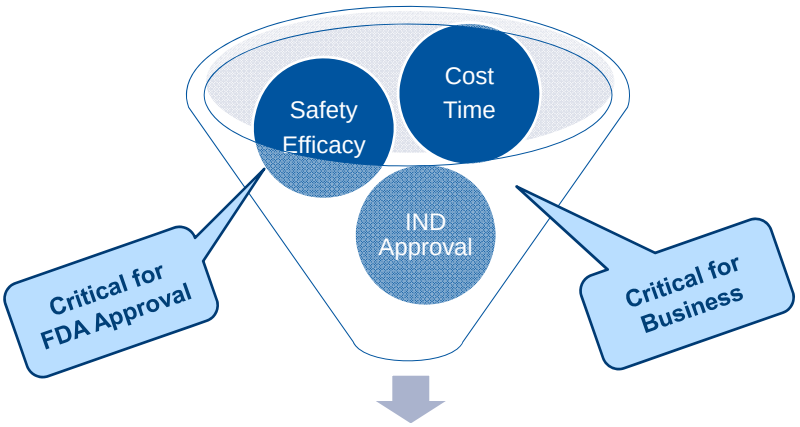
"The process defines the product"

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?



Phase I Clinical Trial

ISPE. Connecting Pharmaceutical Knowledge ispe.org

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

Who's up for crisis management?

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

Design It Right The First Time

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

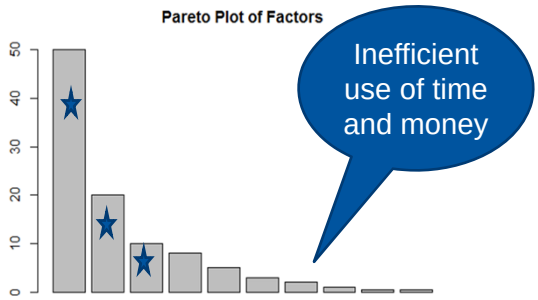
Variation is highest in R&D –

- *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?"

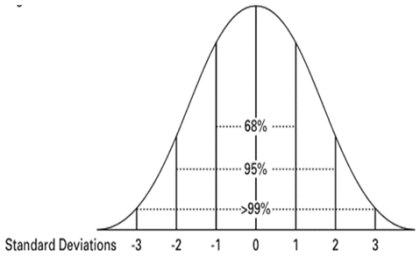
Only 20% of factors determine 80% of the main effects



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

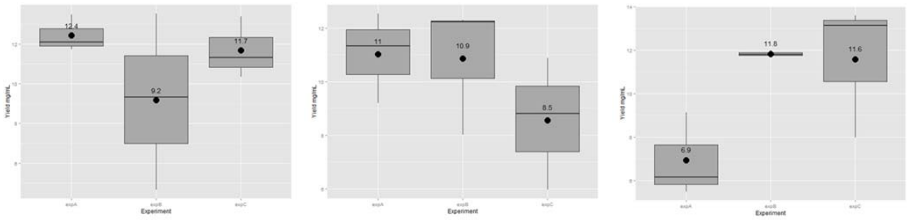


Inherent variation in early stage R&D can make it difficult to understand the significance of experimental changes

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)

Case Study: Development of an Impurity Analysis

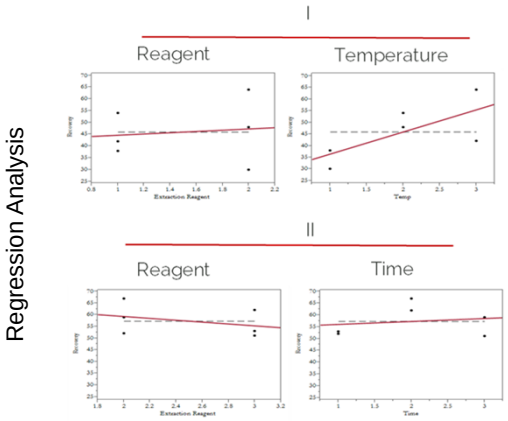
Data → **Knowledge** → **Information**

	Experimental Set 1				Experimental Set 2			
	Reagent	Temp	Time	Recovery	Reagent	Temp	Time	Recovery
Levels	1	1	2	38	2	3	1	52
	1	2	2	54	2	3	2	**67**
	1	3	2	42	2	3	3	42
	2	1	2	30	3	3	1	53
	2	2	2	48	3	3	2	**62**
	2	3	2	**64**	3	3	3	51

DATA

Case Study: Development of an Impurity Analysis

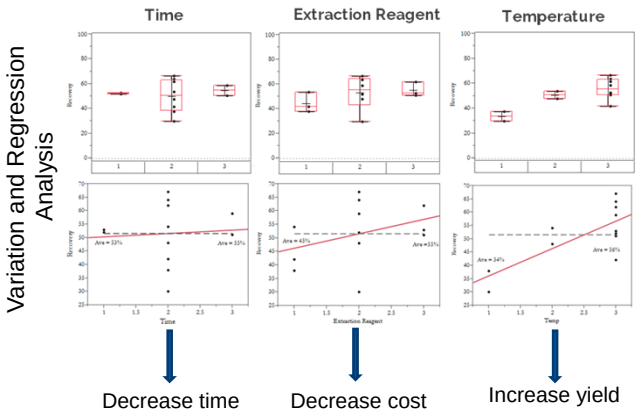
Data → Information → Knowledge



Information

Case Study: Development of an Impurity Analysis

Data → Information → Knowledge



ROBUSTNESS

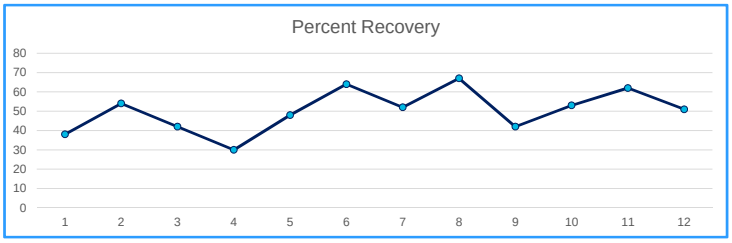
Knowledge

Case Study: Development of an Impurity Analysis

Data → Information → Knowledge

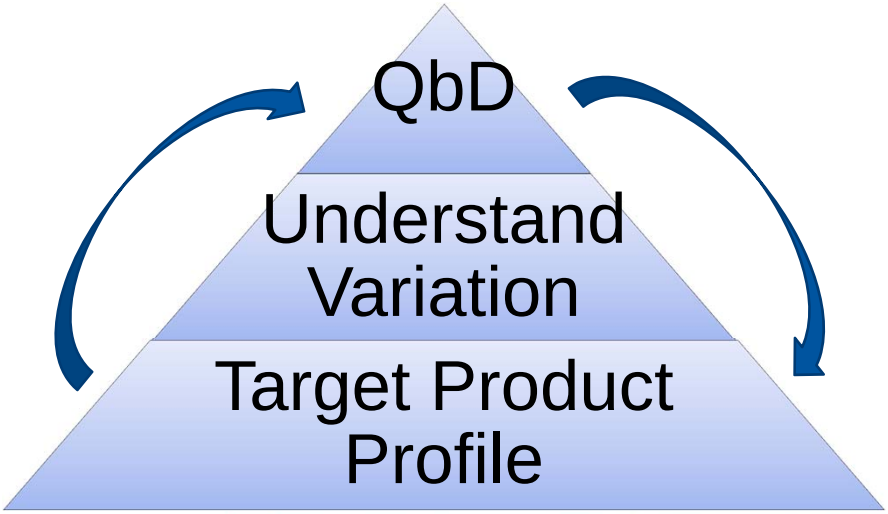
- 12 experiments were performed…method not entirely optimized
- Not balanced…can't determine significance

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



USE THE LEVERAGE YOU HAVE IN R&D

Variability and Uncertainty



The QbD Thought Process and Supply Chain Management

Quality Agreements

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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

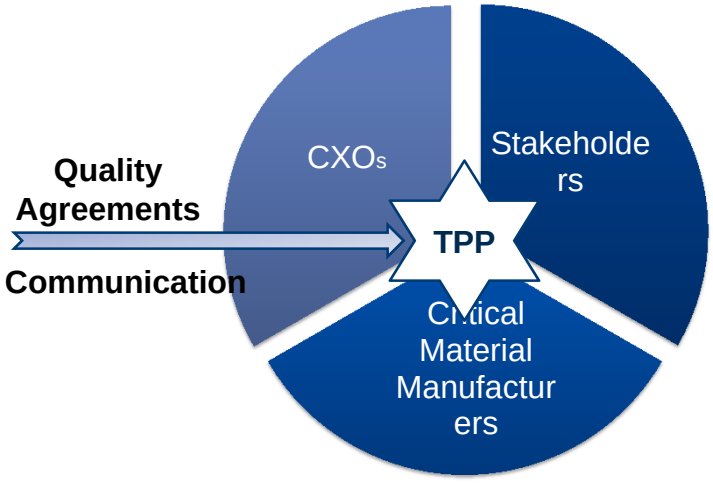
What specifications do your suppliers' products meet?

What specifications do you need for product success?

Manufacturers
CROs
Analytical
APIs
Materials
Sterilization
Internal

Target Product Profile and Quality Agreements

What deliverables are required to achieve your goals?



Leadership, People, and Knowledge Transfer

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

http://www.wkow.com/story/31631022/2016/04/Sunday/silos-toppled-road-closed-in-darlington

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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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For further information, please contact
Amy Lachapelle, QBD Strategies LLC
at Amy.Lachapelle@qbdstrategies.com