

Industrial Perspective of Quality by Design

Stephen M. Tyler

05-June-2009

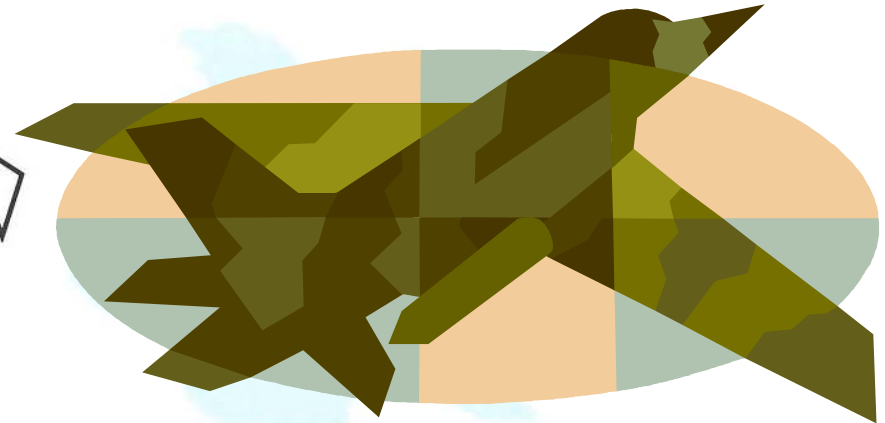
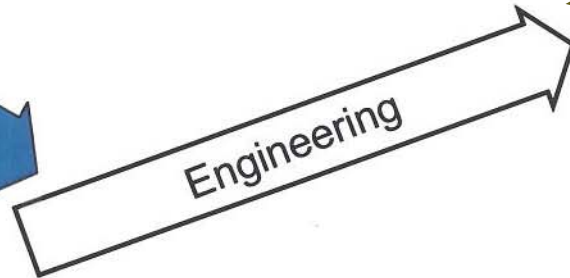
Land O'Lakes

Agenda

- Background
 - Pharma compared to other industries
 - Quality by Design
- Product/Process Knowledge
- Manufacturing Paradigm
- Regulatory View/Update
- Industry View
- Business Cases
- Conclusions

Basic Science is Main Difference with Other Industries*

*Have developed
required science*



*Do not have the Science
to do predictive model-
based design*



Pharma Operations Compared to Other Industries*

Measure	Pharma	Automotive	Aerospace	Computer	Consumer Packaged Goods
Overall Equipment Effectiveness	10% to 60%	70% to 85%	50% to 70%	80% to 90%	70% to 90%
Annual Productivity Improvement	1% to 3%	5% to 15%	5% to 10%	1% to 3%	5% to 15%
First-pass Yield—zero defects	60%	90% to 99%	70% to 90%	90% to 99%	90% to 99%
Production Lead Times in Days	120 to 180	1 to 7	7 to 120	5 to 10	3 to 7
Finished Good Inventory in Days	60 to 90	3 to 30	3 to 30	5 to 50	10 to 40
Labor Value-Add Time	20%	60% to 70%	60% to 70%	60% to 70%	60% to 90%
Direct/Indirect Labor Ratio	1:1	10:1	10:1	10:1	10:1

The Regulation Issue

How Does Pharma Compare?

Aero **Pharma**



Regulated Industry

Yes

How is quality ensured?

Quality by Design Quality by Inspection

Ease of Making Changes to product or process

Difficult and Time consuming Difficult and Time consuming

How is product designed?

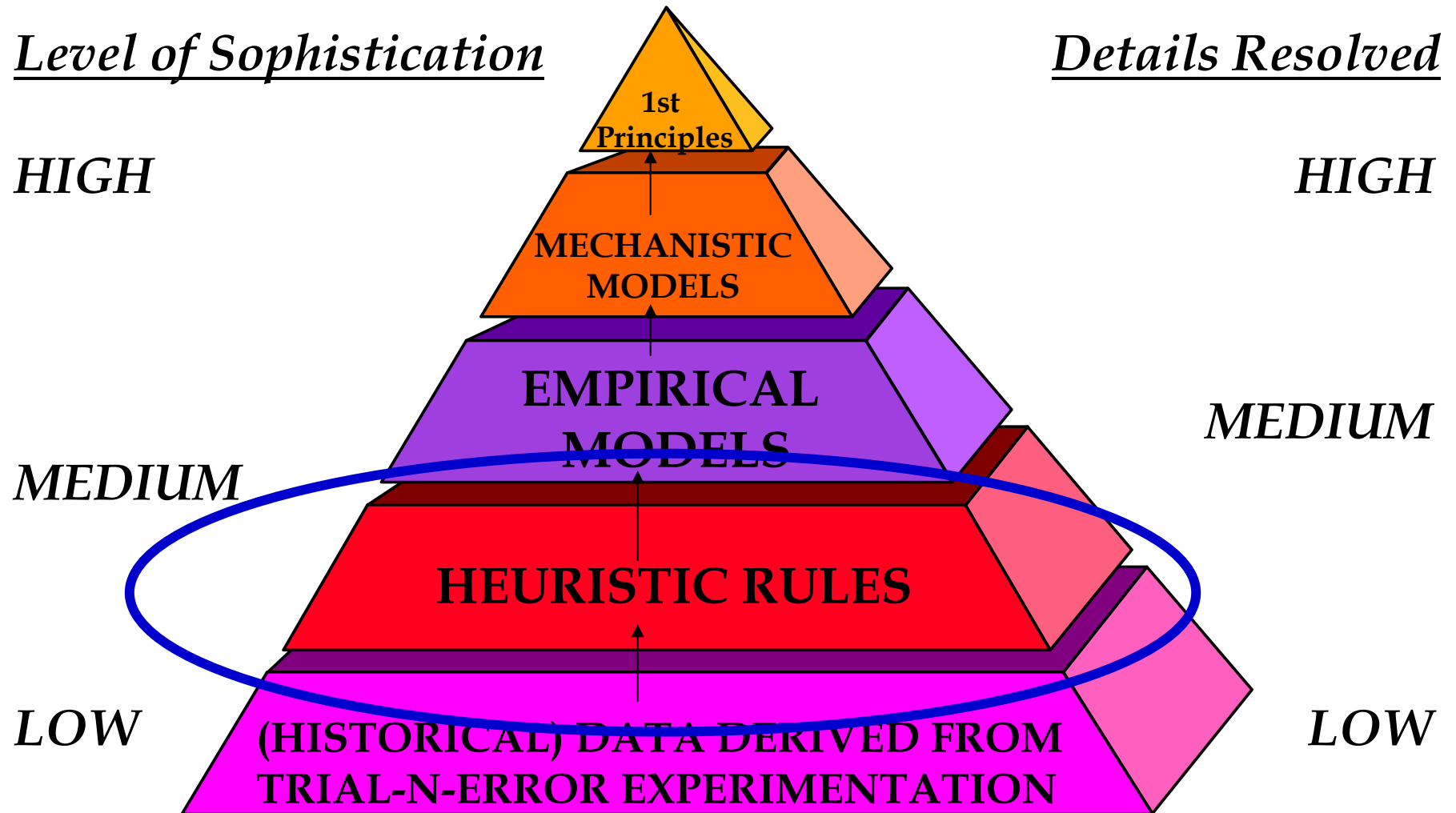
Detailed model-based design Empirical, minimal use of models, multiple scale-ups

Defect rate

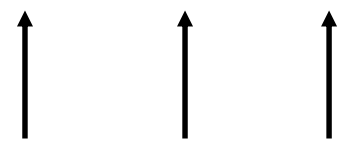
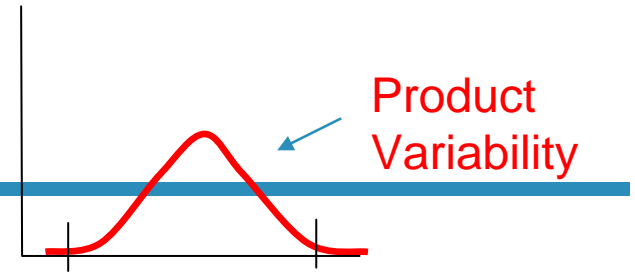
Extremely Low High, 2 to 3 Sigma

> > > Six Sigma

Product/Process Development Knowledge



Traditional Manufacturing Paradigm



Locked
Process Variables

Locked process variables cause variability of the raw materials to become variability of the drug product quality.

Quality by Design

Definition from ICH Q8(R1):

A systematic approach to development that begins with predetermined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Is the Time for QbD Right?

Table 1: The leading pharmaceutical companies will lose between 14% and 41% of their existing revenues as a result of patent expiries

Company	2010		2011		2012		Share of Revenues (%)
AstraZeneca	Arimidex	(\$2.2bn)*	Seroquel	(\$4.7bn)	Symbicort	(\$3.7bn)	38**
BMS			US Plavix	(\$4.8bn)	Abilify	(\$2.1bn)	30
			Avapro	(\$1.3bn)			
GSK	Advair	(\$3.8bn)			Avandia	(\$2.5bn)	23
Eli Lilly			Zyprexa	(\$4.8bn)			22
Merck	Cozaar/ Hyzaar	(\$3.2bn)			Singulair	(\$4.5bn)	22
Novartis	Femara	(\$1.1bn)			Diovan	(\$6.0bn)	14
Pfizer	Aricept	(\$600m)	Lipitor	(\$12.1bn)	Viagra	(\$1.7bn)	41
			Xalatan	(\$1.6bn)	Detrol	(\$660m)	
					Geodon	(\$1.1bn)	
sanofi-aventis	Taxotere	(\$2bn)	US Plavix	(\$3.8bn)	Lovenox	(\$3.1bn)	34
			Avapro	(\$2.1bn)			

Source: AXA Framlington

Notes: * Estimate of global sales in 12 months prior to patent signing

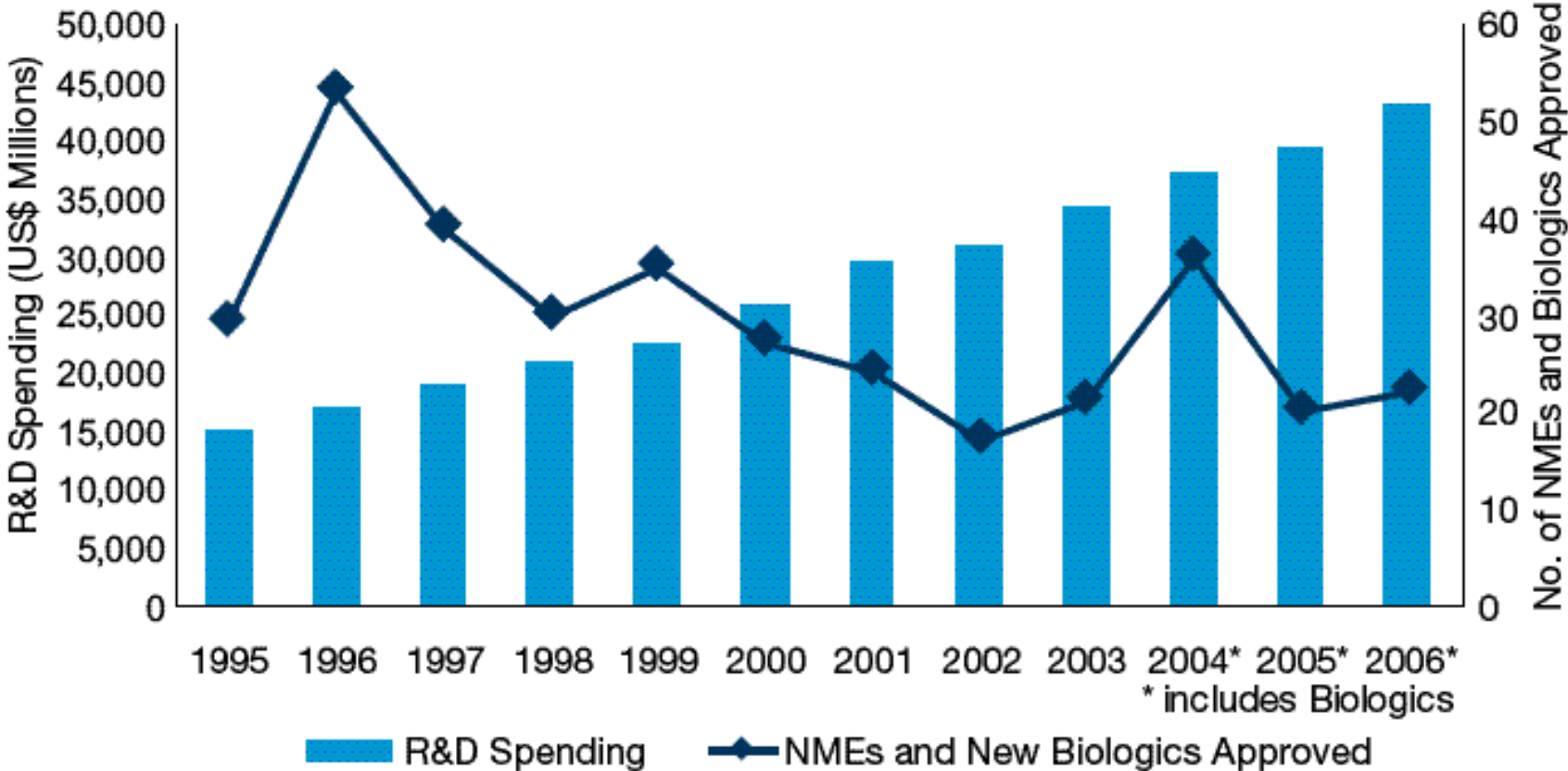
** Value of products losing patent protection as a percentage of total company sales over next five years

Pharma 2020: The vision

9

Will QbD Help?

Figure 2: R&D spending has soared but the number of NMEs and biologics approved by the FDA is down



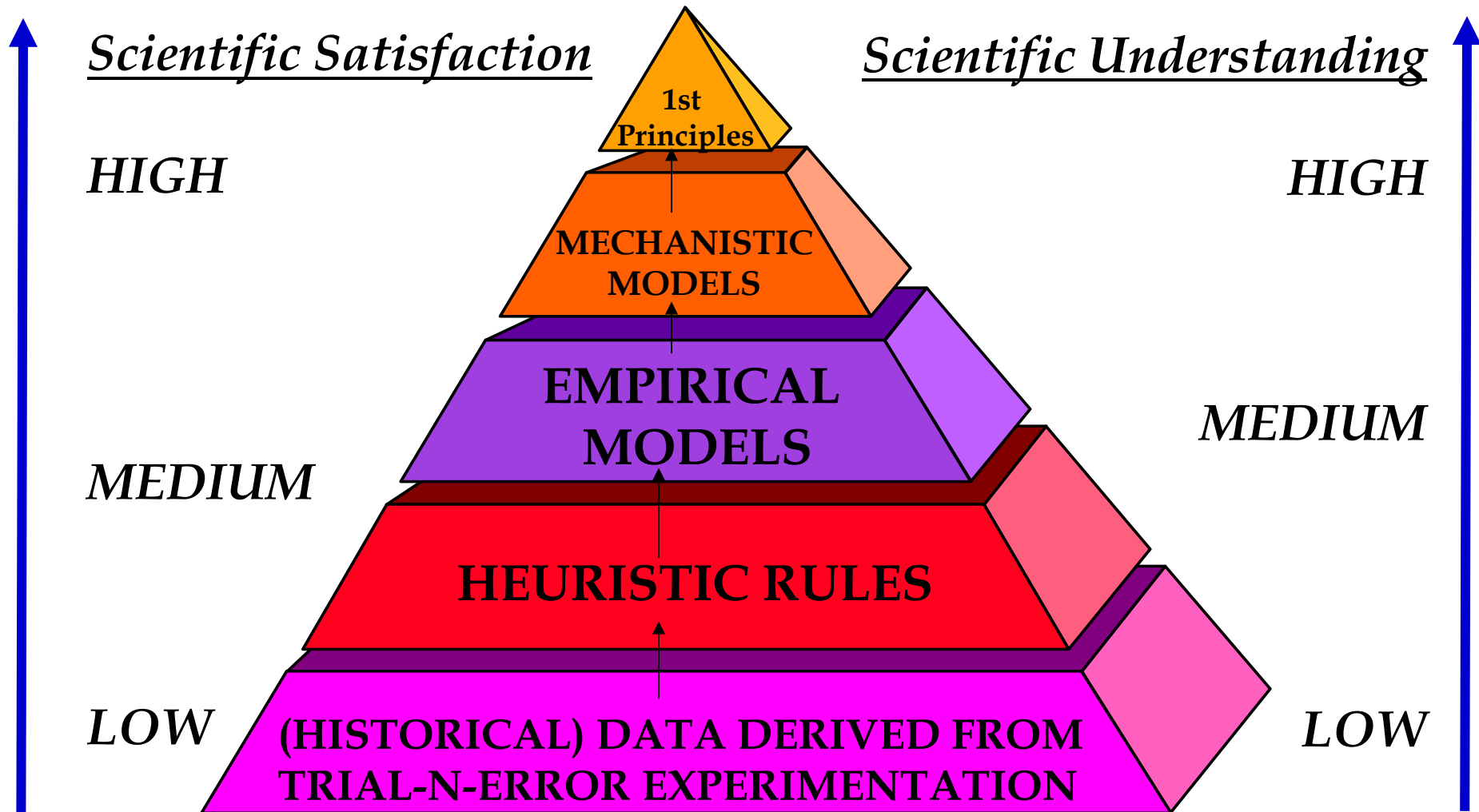
Implementing QbD*

- Challenges:
 - Long Development Timelines
 - Lack of Product and Process Understanding
 - Sub-optimal Products/Processes at Launch
 - Resource Deployment

Journey to Enhanced Understanding

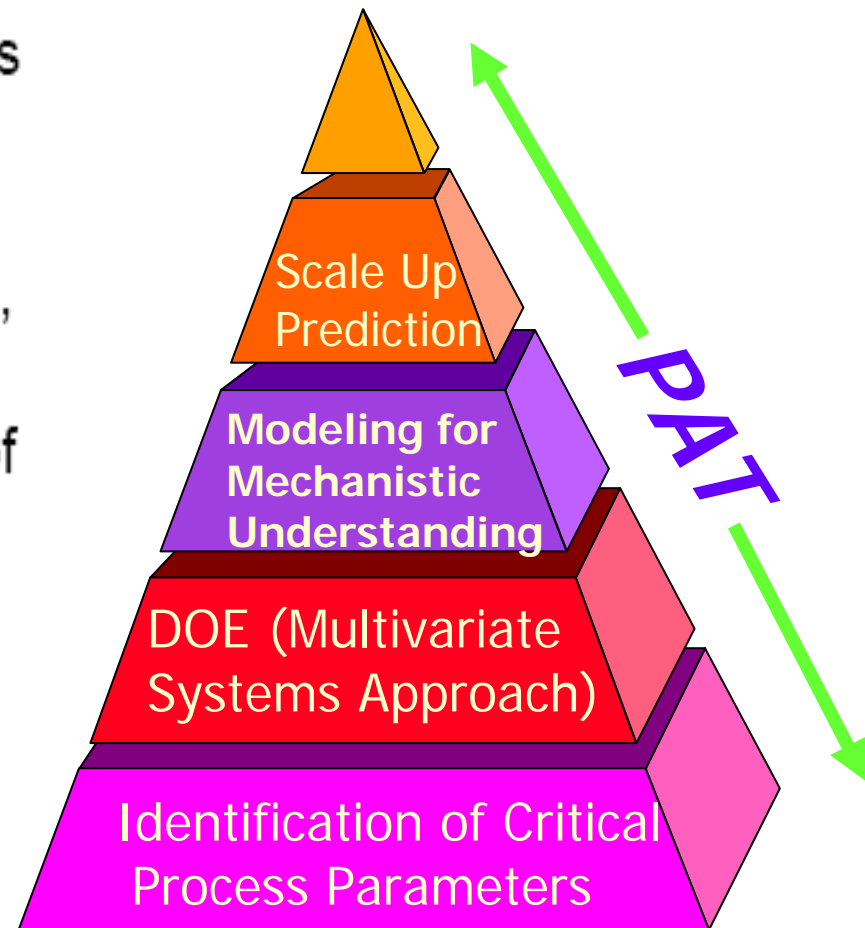
- Today 'Quality by Design' is Mostly Empirical
 - Experimentation Based
 - Multiple stages of Design of Experiments (DOEs) are required to develop a meaningful Design Space
 - Costly DOEs Required to Develop a Design Space
- Tomorrow's Desired State
 - Science and Engineering Based
 - Smart DOEs utilize hypothesis based on 1st principles to develop predictive models
 - Predictive Modeling
 - Directs/avoids Time Consuming, Costly Experimentation

QbD Value Added Proposition for the: Engineer, Pharmacist, and Research Scientist



Process Analytical Technology

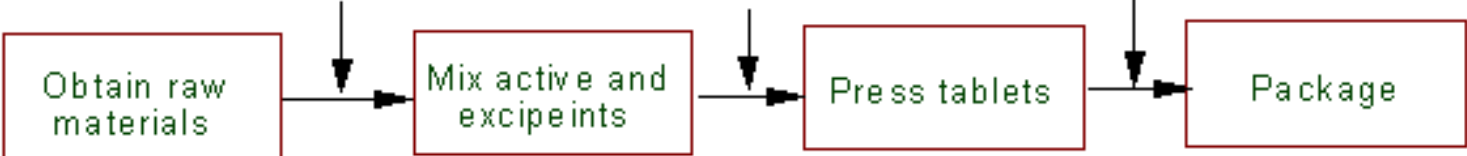
- Process Analytical Technologies
- FDA considers PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes
- Goal - ensure final product quality



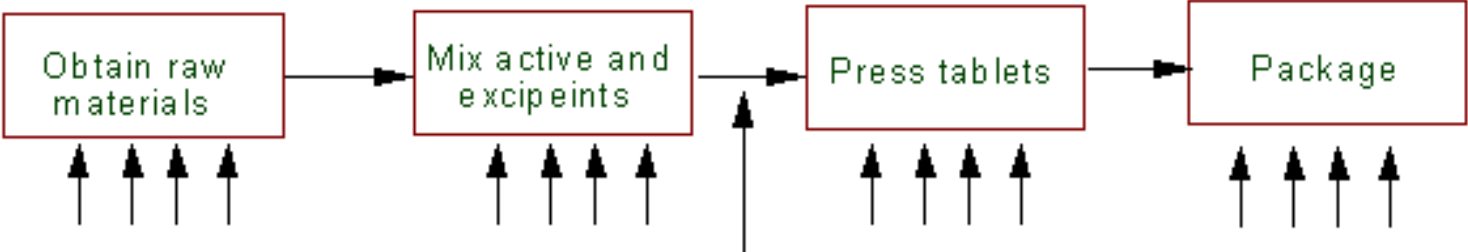
QbD Process Utilizing PAT – A Paradigm Shift

Conventional approach - lab based

End of phase testing of quality, to reduce the risk in moving to the next stage

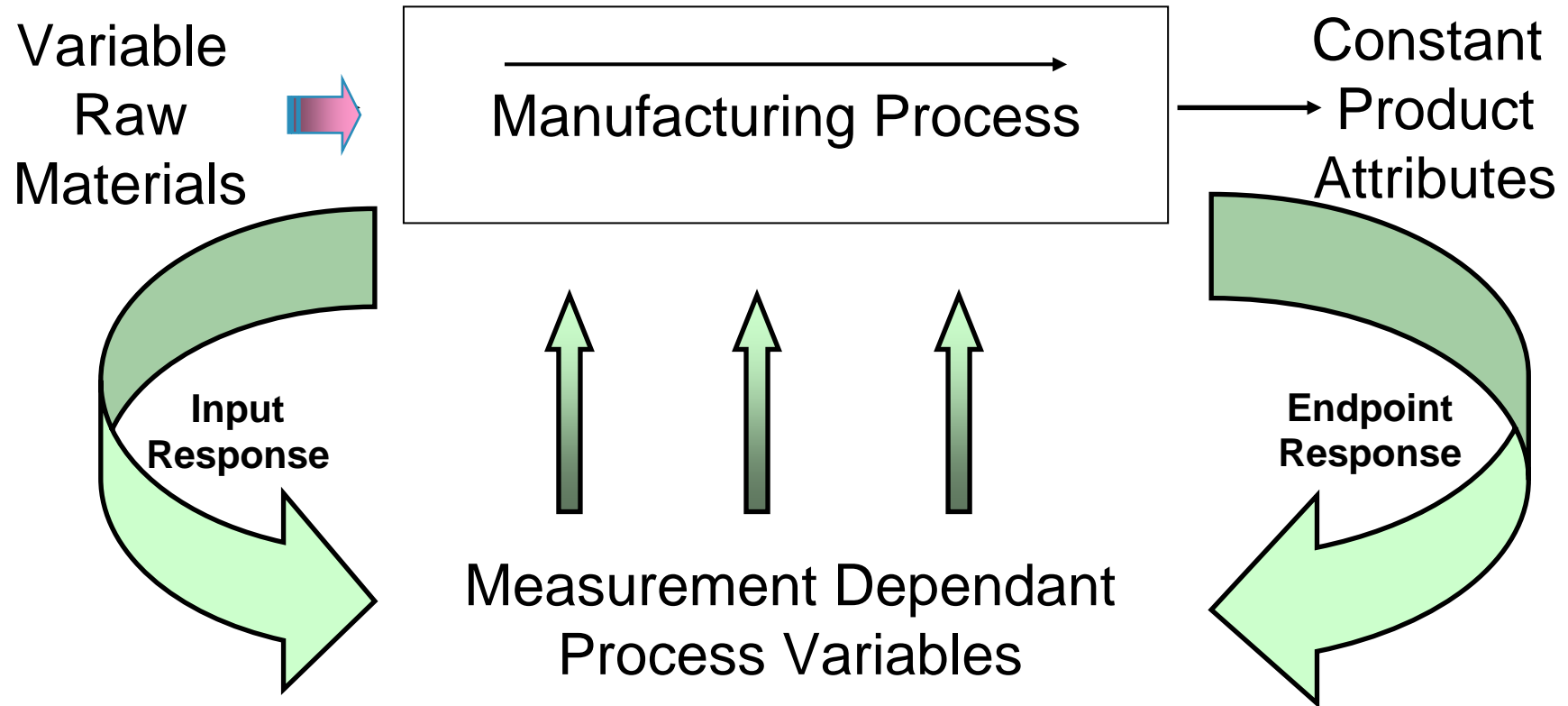
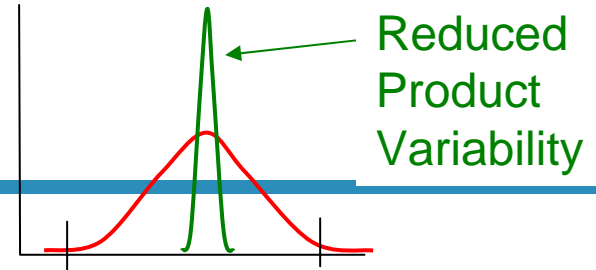


P.A.T approach - process based, at-line or on-line



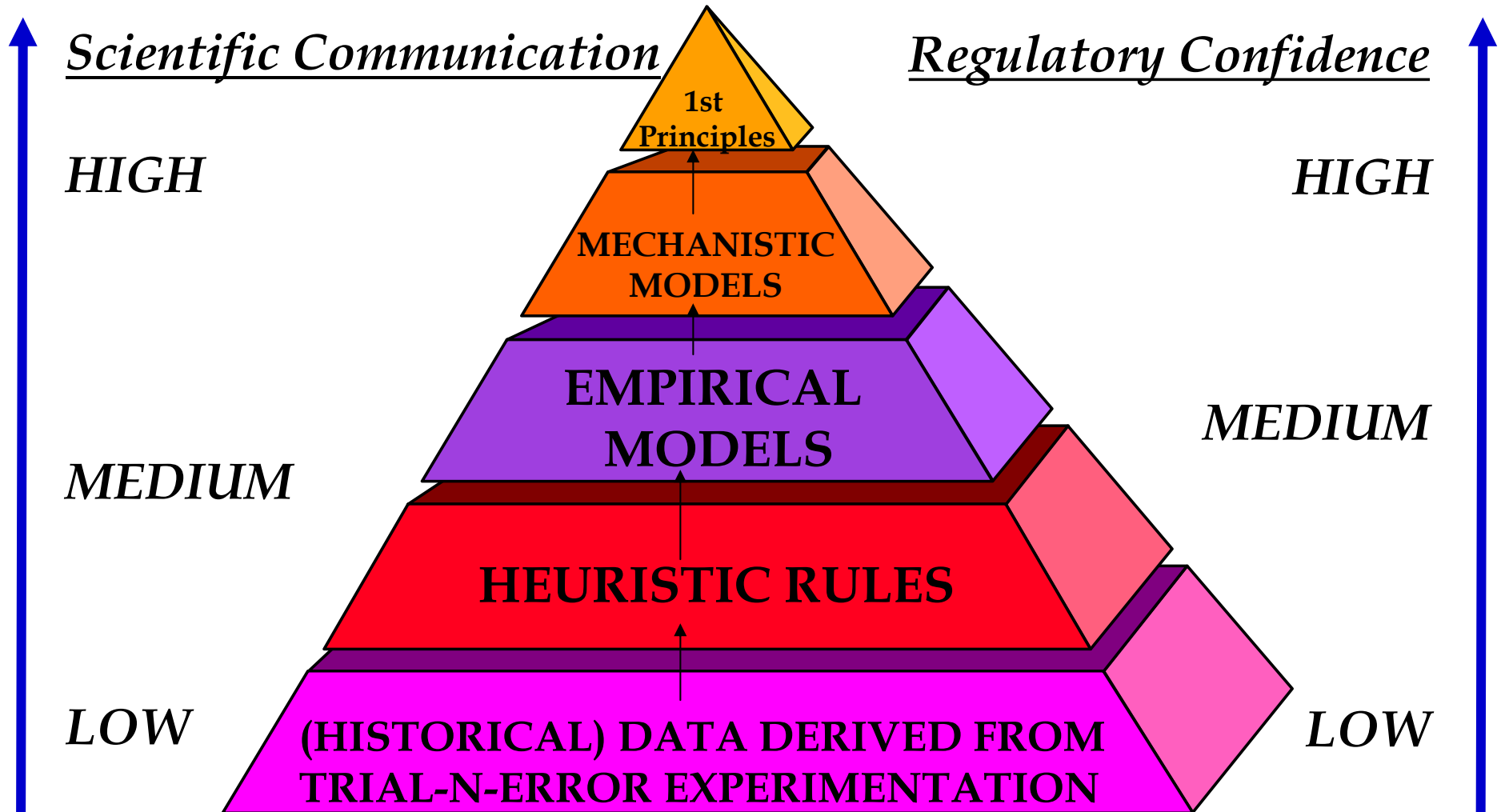
Continuously or more frequently test quality during each phase, to remove the risk in moving to the next stage

QbD Manufacturing Paradigm



PAT allows immediate feed forward or feedback to modify process variables. The product will have lower variability & a lower cost basis

QbD Value Added Proposition for the: Assessor and Inspector



A Regulator's View on QBD

- Holistic and Proactive approach to Pharmaceutical Development through commercialization (lifecycle)
- Lifecycle view: Each batch adds to knowledge
- Quality by Design IS MORE THAN:
 - Development through trial and error
 - Formulation and process optimization
 - DOEs to determine a design space
 - Demonstration of reproducibility

Washington ISPE PQLI Conference

Regulatory Status

- CMC pilot
 - 9 original and 2 supplemental NDAs
 - Through May 2009: 11 submitted, 9 approved and 2 under review
 - Common factors include submission of DS, use of RA and flexible regulatory approaches managed under firm's QS
 - Wide variety of DS proposed
 - Wide variety of CS utilized
 - Valuable experience for FDA and industry to implement QbD
- QbD submissions outside of pilot
 - 12 NDAs, 3 sNDAs and 18 INDs
 - <10% of NDAs
- QbD has moved into the implementation phase

Washington ISPE PQLI Conference

Recent Discussions on Regulatory Flexibility

- Design Space for material attributes and process parameters
- Real time release approaches
- Design Space for analytical methods
- Reduction of stability for site transfer
- Starting Material Selection
- Regulatory flexibility on a case by case basis
 - Comparability protocols are available for flexibility
 - Issuance of PMP not clear

Washington ISPE PQLI Conference

QbD Regulatory Considerations

- Considerations for QbD meetings
 - EOP II discussion initiation
 - Pre-NDA for details and format of QbD submission
- Considerations for QbD Applications: Development (S.2.6 and P.2)
- Considerations for QbD Applications: Manufacturing Description (S.2.2 and P.3.3)
- Considerations for RTRT: Specifications
- Considerations for RTRT: Models
- Considerations for Design Space: Maintenance and Update

Washington ISPE PQLI Conference

QbD Regulatory Considerations

- Considerations for PAI Inspections from a CMC Reviewers Perspective
 - Quality system readiness for QbD, PAT and/or RTRT
 - Knowledge Management is key to successful QbD implementation
 - Trending of process and product quality data are important
 - Useful to have personnel spanning development to manufacturing participate in PAI

Industry Concerns

- Implementation of QbD in manufacturing
- Approval delays due to understanding of dossier content
 - Prior knowledge
 - Submission detail
- Internal selling of QbD business case
- Questions regarding general acceptance of QbD beyond tripartite region
- Modeling and chemometric expertise resources

Industry Dialogue from ISPE PQLI Conference

- True/False: Critical Quality Attribute/Parameter Discussions
 - A CPP is always critical and cannot become non-critical through continual improvement through a products lifecycle
 - Commercial scale process experience always confirms that CPP ranges predicted by process development are appropriate
 - Robust and relevant measurements of the quality of raw materials, in-process materials and finished products provide critical information to delivery of process output
 - A CQA is always critical and cannot be non-critical through continual improvement
 - CQAs cannot be determined through risk assessment alone

Industry Dialogue from ISPE PQLI Conference

- Design Space Model Discussions
 - Types of Models
 - Mechanistic
 - Empirical
 - Hybrid
 - What are models used for:
 - DOE, kinetic, mechanistic
 - Speed up development
 - Develop Design Space
 - Small and Large Molecule- drug substance and drug product
 - Reaction engineering
 - Crystallization
 - Modelling of excipient attributes to meet CQAs

Industry Dialogue from ISPE PQLI Conference

- Barriers are typically within the organization
 - Quality
 - Skill sets are siloed
 - Manufacturing
- How are models developed?
 - Fit for purpose
 - Dimensionless numbers that allow prediction of scale effects
- Confirming Model Adequacy—wide divergence of opinion
 - Maintenance lifecycle plan
 - Model assumptions assessed using FMEA
 - Verification

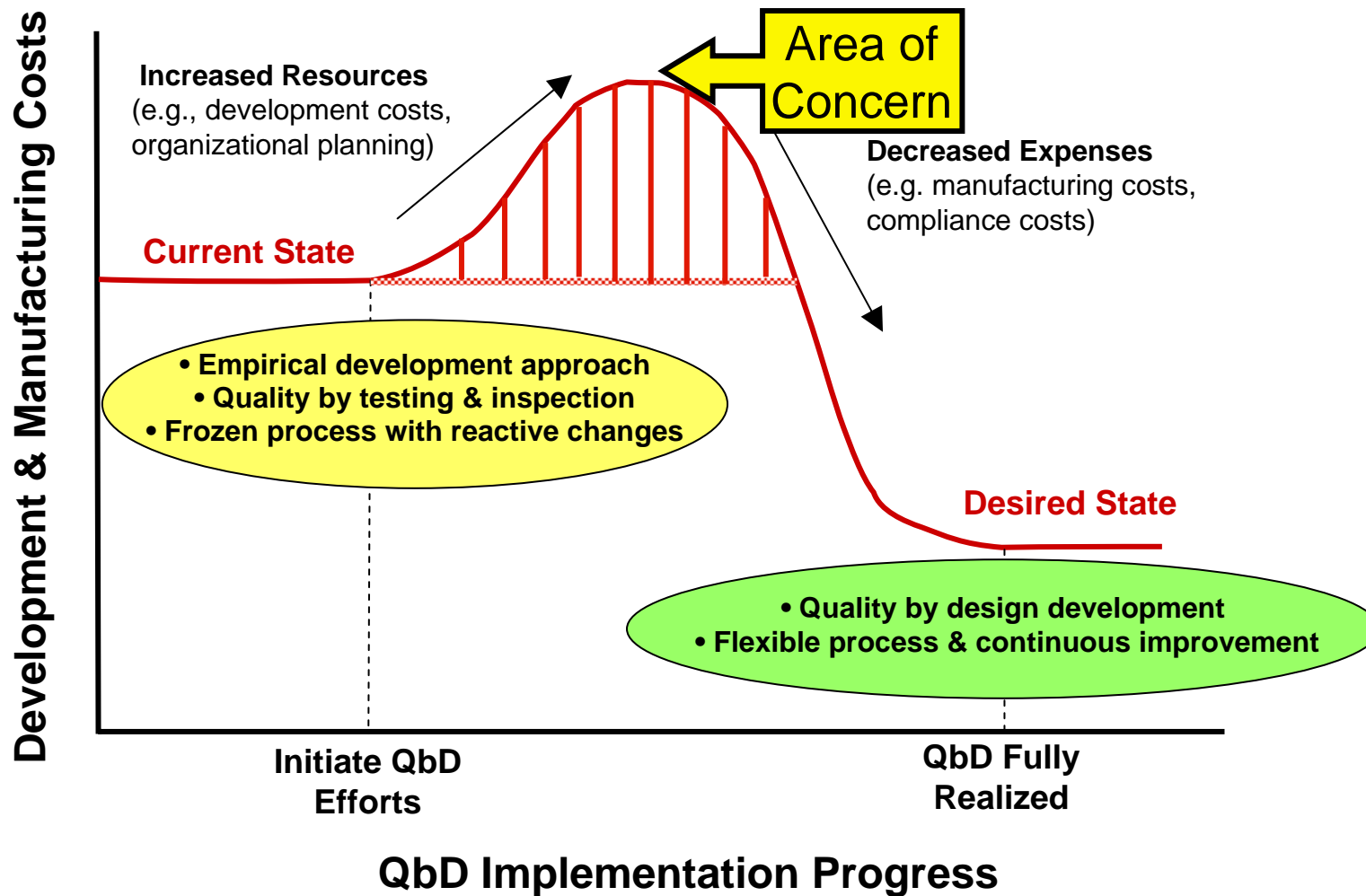
Industry Dialogue from ISPE PQLI Conference

- Where in the dossier are models captured?
 - P.2 and S.2.6 with links to P.3 and S.2.2
- How should a model be captured in batch record or quality system?
- Can a design space be a model?
- Model sharing
 - The need is recognized seeking ‘how’ and ‘how much’
- NO interest in a modeling regulatory guidance
- Managing uncertainty from development of n=2 to manufacturing of n=50

Industry Dialogue from ISPE PQLI Conference

- Control Strategy Discussions
 - Gap in knowledge transfer from R&D to Mfg
 - The burning need for a business case for QbD
 - QRM in manufacturing is still new, but not clear how we will leverage
 - Risk communication including summary of the risk assessment including risk acceptance
 - Product release
 - There is more to batch release than just looking at RTRT data

Cost and Benefit of QbD



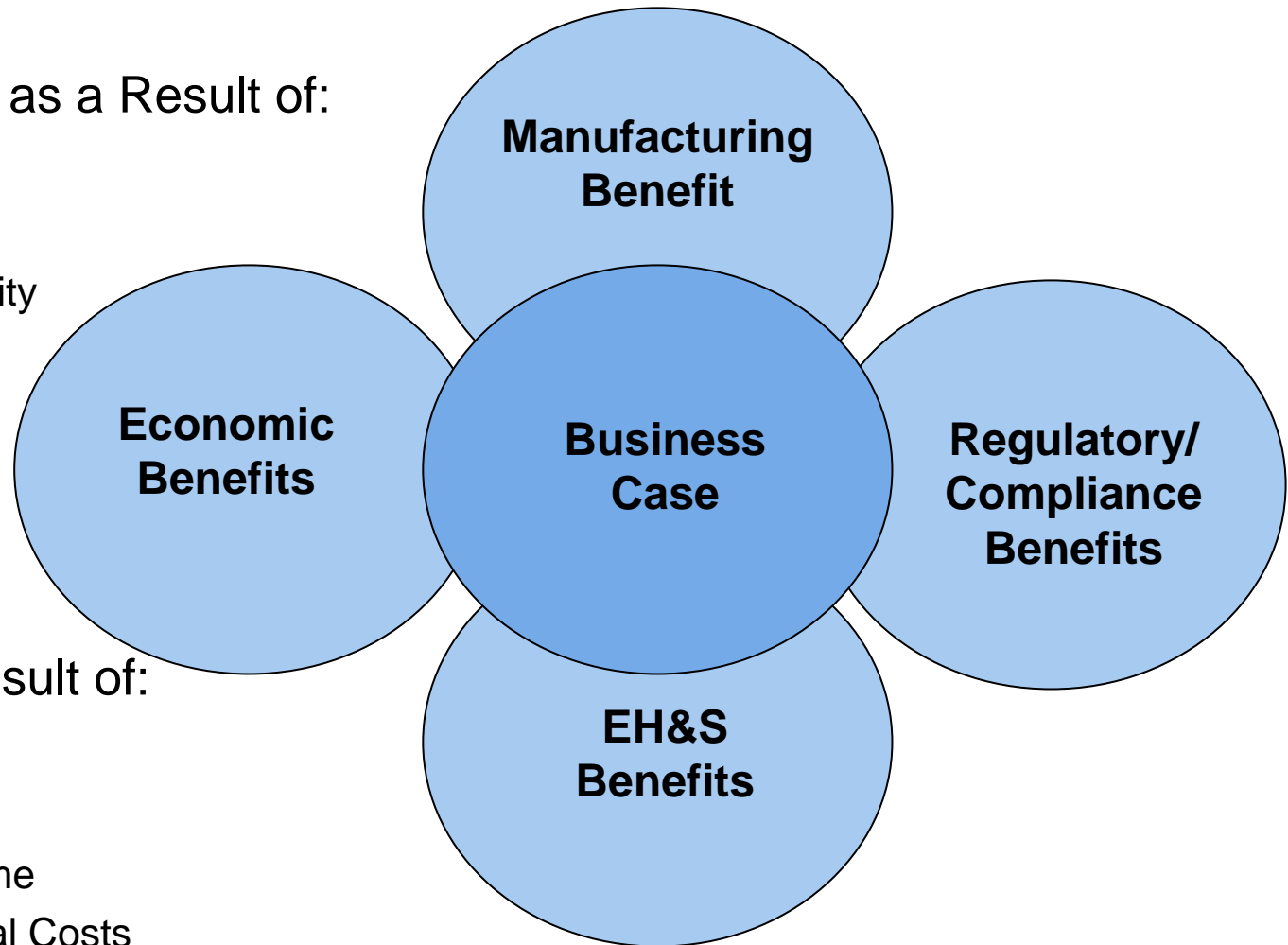
QbD Can Enhance Product Revenue by....?

- Increasing Value as a Result of:

- Faster Launch
- Better Launch
- Increased Exclusivity

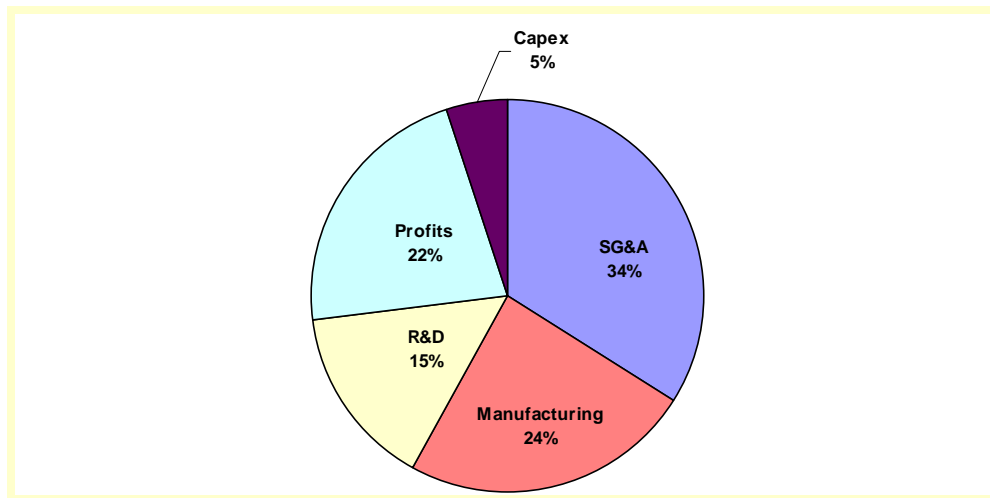
- Increasing Production Revenue as a Result of:

- Higher Yield
- Defect Reduction
- Reduced Cycle Time
- Lower Raw Material Costs

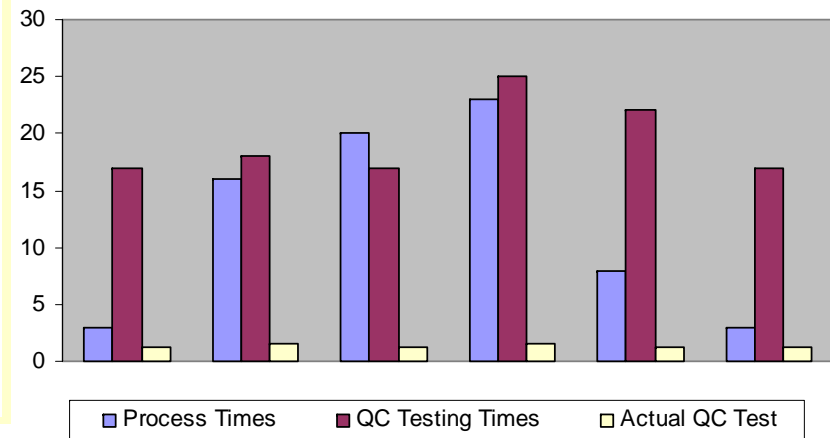


Reaping the Financial Benefits of a QbD Program*

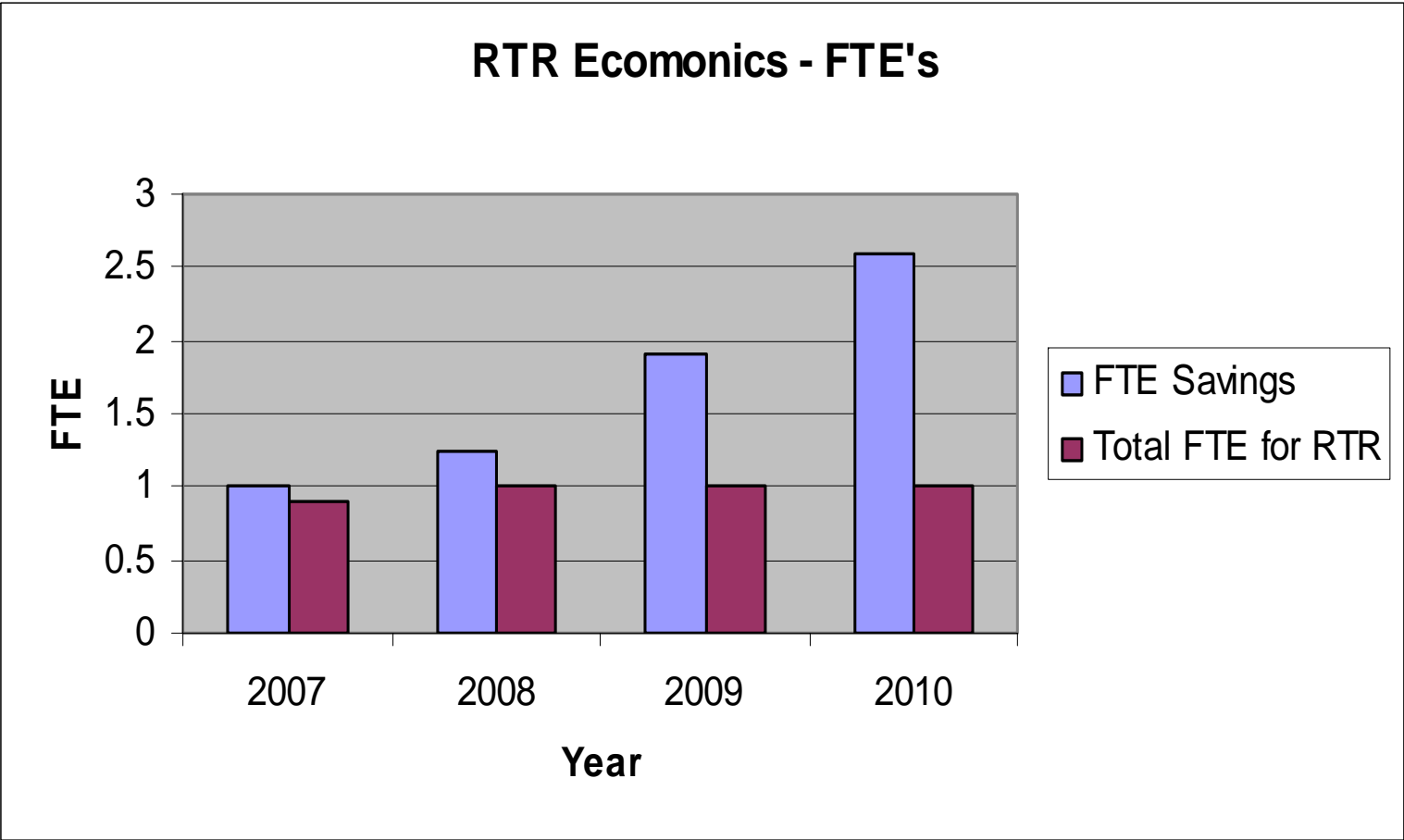
**Figure 1:
Manufacturing
Costs as a
Percent of
Revenue**



**Figure 2:
Quality Control and
Processing Time
Overall Cycle Time
Components**



Real-Time Release Testing Business Assessment*



* G. Thureau, Merck & Co, Inc., 2008

Retrospective QbD Business Case Examples from Wyeth*

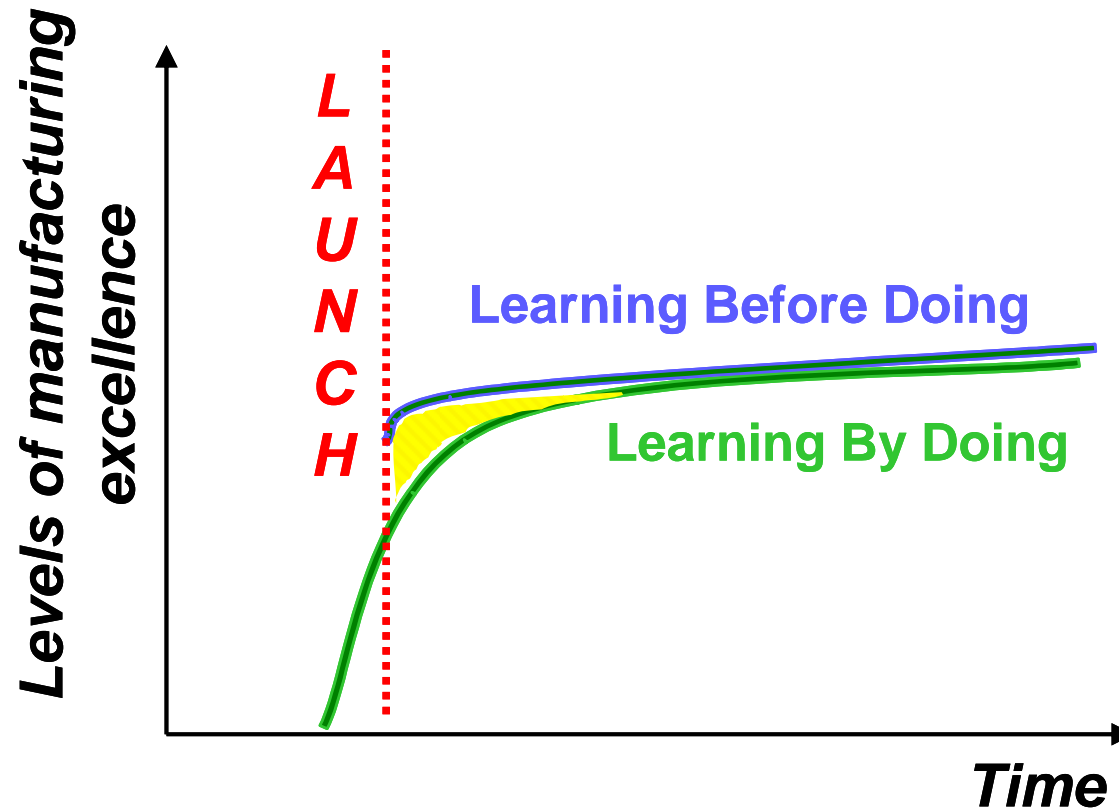
- Drug X
 - Wurster Coated
 - If 850 spray rate was available from launch vs 250
 - COGS savings in the region of \$10M
 - Capital avoidance due to increased capacity on earlier equipment over \$250 M
- Drug Y
 - Expensive API
 - If API yield was optimized
 - Annual savings of \$ 2M and substantial filing requirements avoided
- Drug Z
 - Enteric Coated
 - Tablet defect was observed at launch.
 - Tax savings benefits of \$ 12M lost (production on hold for 4 months).
 - Production losses avoidance of \$ 2.5M/yr.

Pfizer Post-Approval Changes Benefits*

- Background
 - IR Tablet
 - BCS Class-1
 - Participant in FDA Pilot Program
- FDA agreement to following proposals:

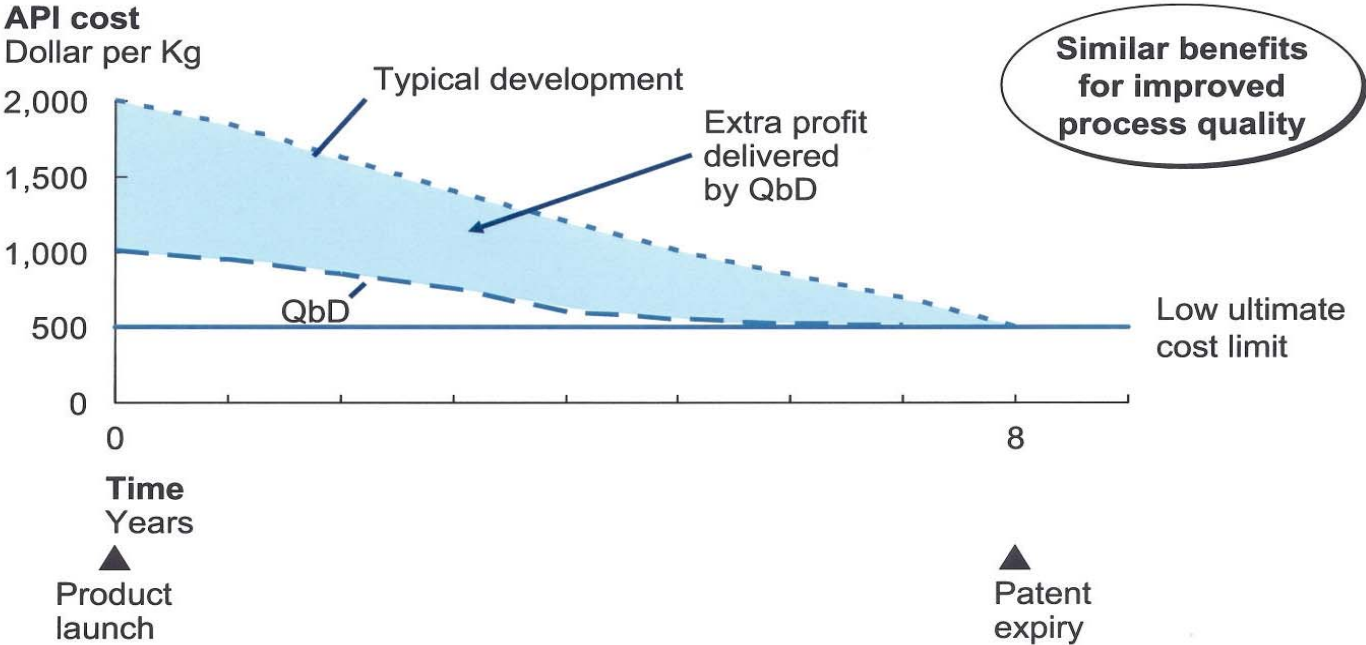
Change	Notification
API intermediates manufacturing sites	Annual Report
Site change and scale-up of tablet manufacture	Annual Report
Press shut off point end of compression	CBE-0
Moisture determination from KF to NIR	CBE-0
Dissolution/Stability Testing	Waived

Ask Yourself, Can QbD Improve Launch Efficiency?



The QbD Approach Will Lead to Lower Cost at Product Launch and Greater Profit Through Product Lifecycle*

The QbD approach will lead to lower cost at product launch and greater profit through product lifecycle



QbD Fact or Fiction

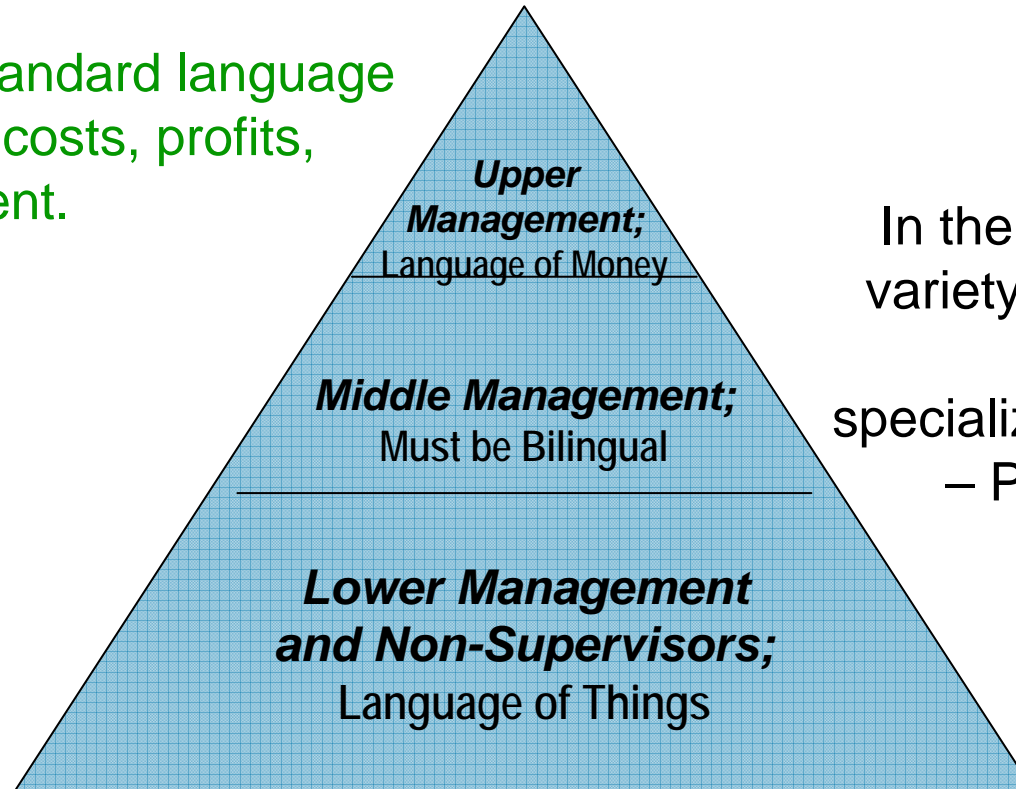
- QbD Can Add \$30 Billion to Pharma Profits
 - \$15B to \$25B from reducing the COGS
 - \$4B to \$5B from improving the productivity of technology development
 - 0 to \$2B from regulatory compliance citation risk reduction
 - 0 to \$4B from
 - Increased Sales
 - Improved Product Design
 - \$0.3B to \$0.4B resulting from regulatory submission reduction as a result of design space

Can QbD Deliver More?

- Linkages between QbD and Clinical Performance
 - Utilization of QbD to ensure product safety by evaluating formulation effects on populations
 - Reduce recalls due to a better understanding of the product formulation and alcohol, i.e. dose dumping
 - Recall reduction prevention by determining variables that cause critical quality issues of clinical significance
- IVIVC correlation models to help link drug quality to safety and efficacy
- Assess changes in drug formulations on clinical performance

The Language of Management

At the top is the standard language of money – sales, costs, profits, return on investment.



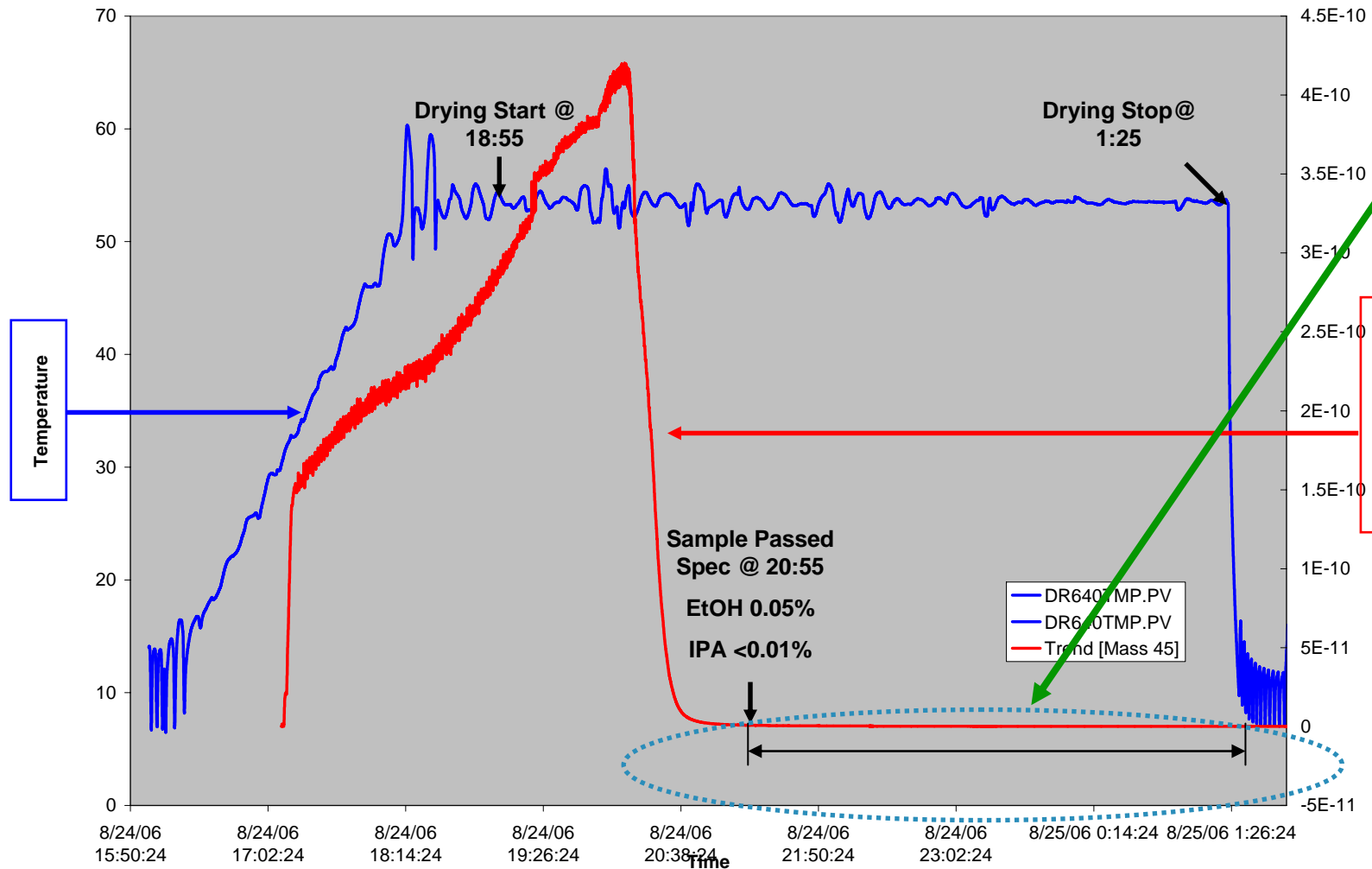
In the middle is a wide variety of dialects used by the various specialized departments – Personnel, Sales, Quality Control.

Juran on Quality

At the base, the language is the standard language of things: tons of steel, square meters of space, kilowatt hours of electricity

Mass Spectrometry Driving Savings

Run 4



Savings Result from:

- Steam
- Electricity
- QC Labor
- Lab Reagents
- Reduced Preventative Maintenance & Maintenance Costs

MS RESPONSE m/z=45

QbD Drives Understanding

- Desired state is a Win-Win-Win benefit for patients, industry and regulators
- More:
 - Assurance of product quality
 - Process understanding
 - Flexible regulatory approaches
 - Opportunities for continual improvement
- Cost savings and efficiency for both industry and regulators
- Applicant shares with reviewer more developmental knowledge
- Increase opportunities for first cycle approval
- Streamline regulatory processes

Conclusions

QbD benefits are there!

QbD discussions are less about what and more to HOW

Shift from Dossier Content to Implementation in Manufacturing

In Summary,

THE TIME TO QbD HAS COME and THE TIME IS NOW!

Acknowledgements

- Azita Saleki-Gerhardt, Ph.D.
- Abdel Zamamiri, Ph.D.
- Chris Linck
- Neville Broad, Ph.D.
- Min Jiang, Ph.D.

Thank You!

And

Questions?

