
LIVE WEBCAST
July 21, 2010
at 12:00 PM EDT
INTERNATIONAL
BioPharm
PRESENTS: Quality by Design: From Theory to Practice

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Today's Speakers

John K. Towns, PhD

Senior Director, Global CMC Regulatory Affairs

Eli Lilly and Company

Michael Kosinski, PhD

Distinguished Senior Investigator

Merck & Co, West Point, PA

Duncan Low, PhD

Executive Director, Process Development

Amgen Inc.

Current Consensus Thinking on QbD

John K. Towns, PhD
Senior Director, Global CMC Regulatory Affairs
Eli Lilly and Company

BioPharm International Web Seminar
Wednesday, July 21, 2010

The Desired State: A Mutual Goal of Industry, Society, and the Regulators

A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.

Janet Woodcock, M.D.
October 5, 2005

- A regulatory process that is consistent, transparent, and science and risked based
- A regulatory process that allows for efficient and effective continuous improvement
- A pharmaceutical sector that understands the product and process, uses risk assessment/mitigation tools and modern, effective Quality systems and takes full ownership of the product.

Principles of QbD

- Products are designed to maximize efficacy while minimizing adverse affects (e.g. to meet patient needs including availability, value and convenience)
- Processes are designed to be robust and consistently deliver the desired product
- Requires knowledge of
  - the mechanism of action of the API
  - the attributes of the API and their impact on safety and efficacy
  - how impurities impact Quality, Safety and Efficacy
  - how formulation impacts product quality (stability)
  - analytical methods to fully characterized products
  - Critical attributes of incoming raw materials
  - Equipment and process parameters
  - Output performance parameters linked to critical quality attributes
- With this knowledge, appropriate product design strategies and process design and control strategies are developed

Global Value

- Leverage QbD understanding and implementation in one region to incorporate best practices across global regulatory agencies

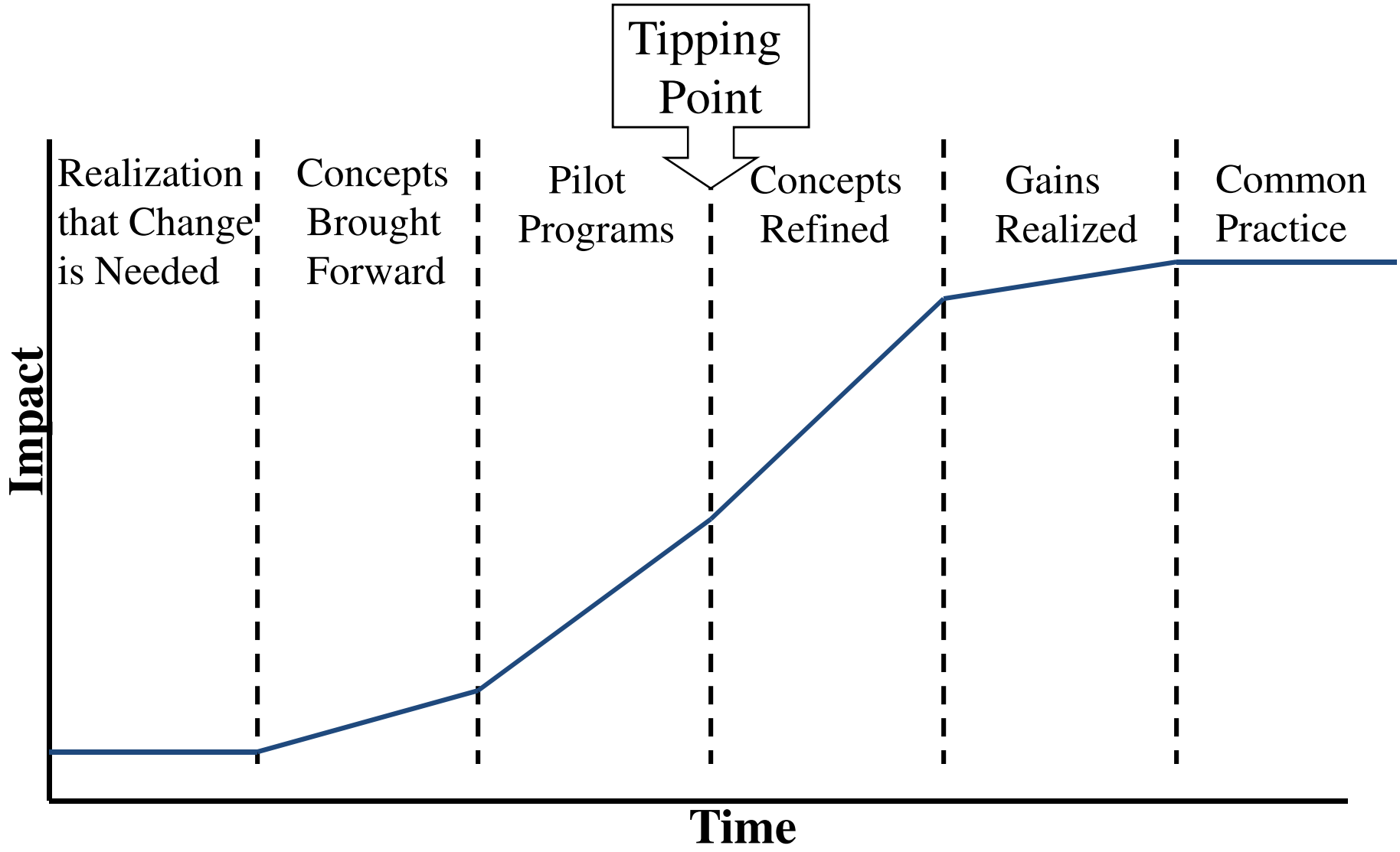
Leading to…

- One global pharmaceutical development strategy and set of studies
- One global marketing application
- One set of global regulatory commitments
- One set of risk-based global post-approval guidelines

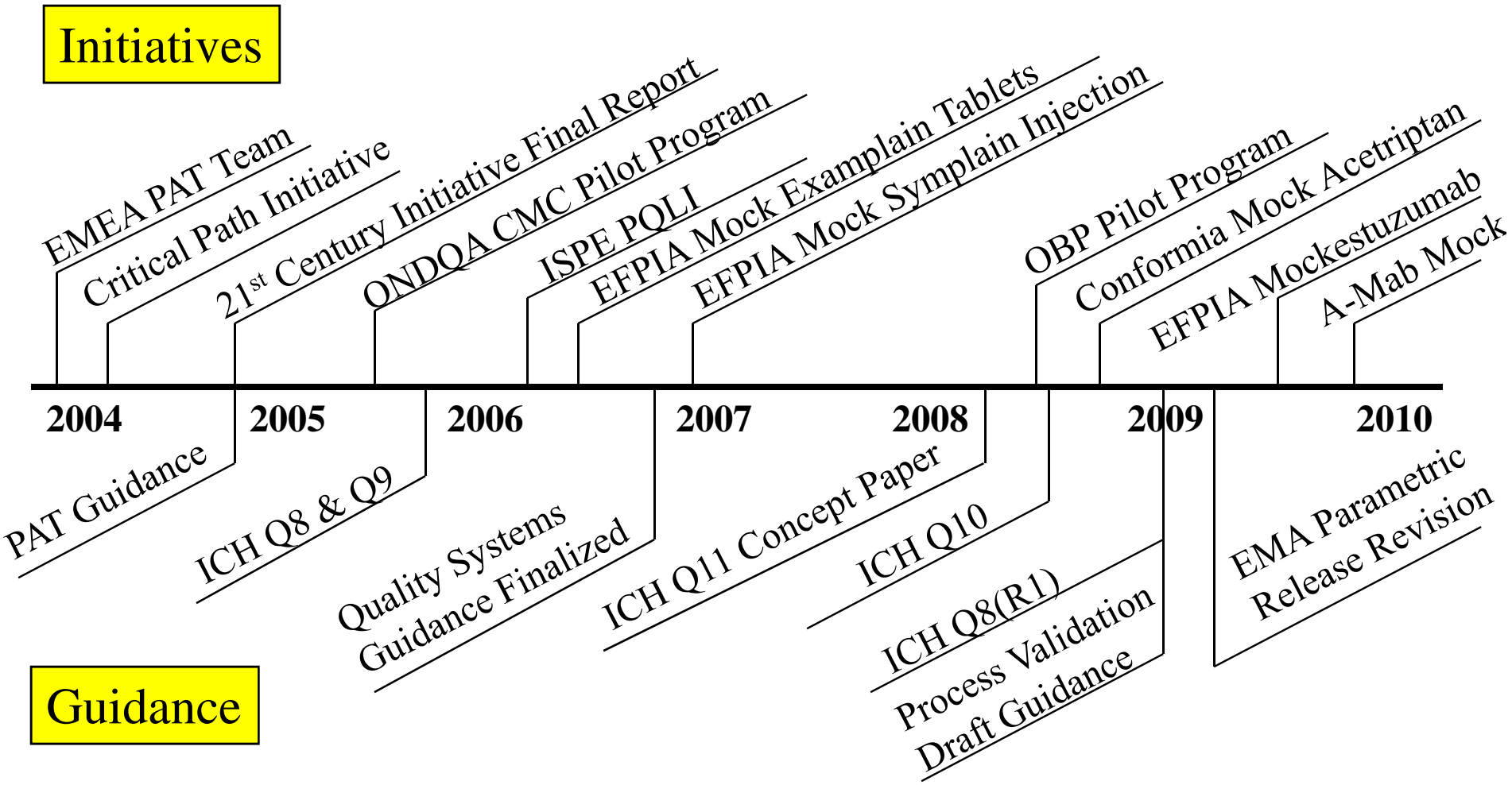
Large Molecule Case Study

- US
  - Standard – 1 Round Q&A, PA Commitments(1)
- EU
  - Standard – 120day(51Q2M), 180day(9Q1M), PA Commitments(7)
- Japan
  - Standard – 3 Rounds of Q&A, PA Commitments(2)
- Rest of World
  - Mid-Major Countries
    - Mexico - Sourcing and stability
    - Brazil – Process and stability
    - Australia – Multiple sets of questions over 10 months
      - Device(3Q), Tox(1Q), Micro(8Q), CMC(20Q,8Q,3Q)
  - Over 30 Sets of Country Q&A
    - Constant stream of Qs to respond to over 18 months

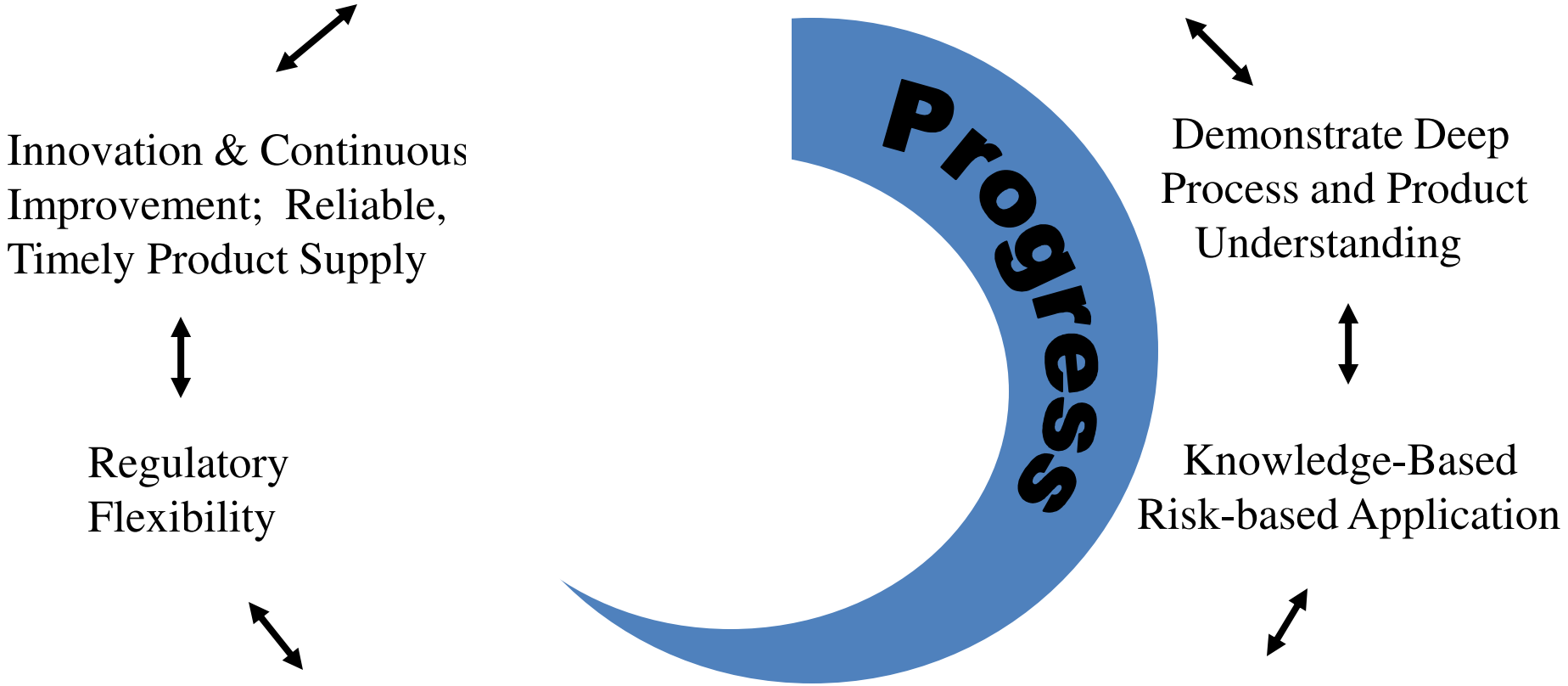
Evolution of Quality by Design



QbD Related Guidance and Initiatives



21st Century Initiative
Quality Systems, Risk Management, QbD Approaches



Innovation & Continuous Improvement; Reliable, Timely Product Supply

Demonstrate Deep Process and Product Understanding

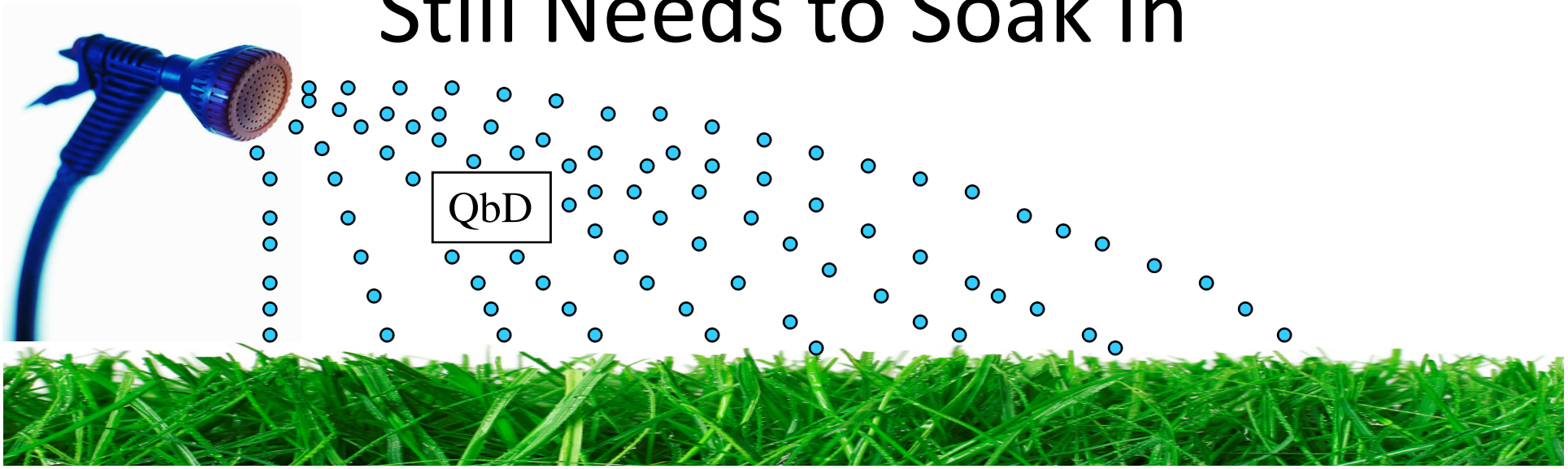
Regulatory Flexibility

Knowledge-Based Risk-based Application

CMC Post Approval Management Plan

Distinguish pharmaceutical process assessment info vs. info that cannot be modified without further review

Still Needs to Soak In



Concepts

Value and Benefits

Workshops

Mock Examples

Case Studies

Best Practices

Harmonization

Down to the Implementers

Scientists

Reviewers

FDA QbD Biotech Pilot Status

Steve Koslowski, June 2010

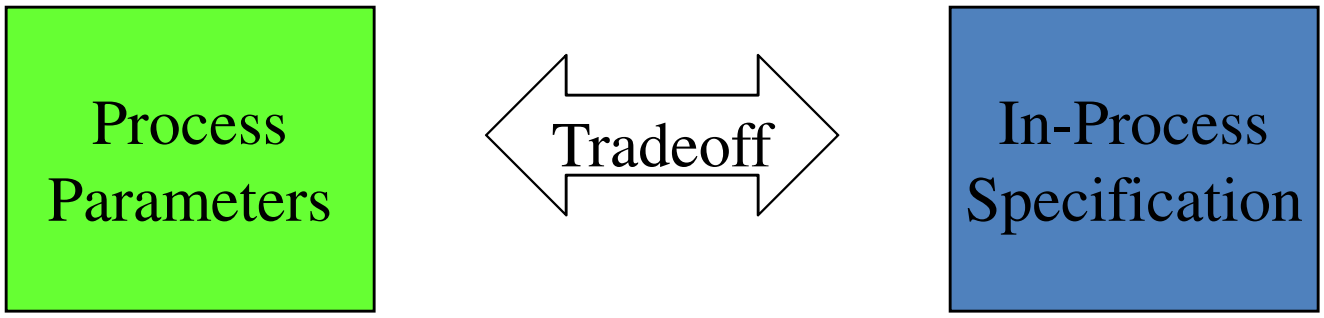
- Applications Accepted in QbD Pilot
  - 5 Original Applications
    - 4 Monoclonal Antibodies and 1 Fc Fusion Protein
  - 4 Post-Approval Supplements
    - 2 Monoclonals, 1 Therapeutic Protein, 1 Multi-product
  - One with Site transfers; Working closely with Compliance
    - MAPP 4730.3 OBP & DMPQ Interactions on BLAs

FDA QbD Biotech Pilot Status

Steve Koslowski, June 2010

- OBP QbD Pilot Meetings
  - 6 meetings held with Pilot Sponsors
  - Additional meetings held – not included in analysis
- Meeting Questions
  - 29 Questions (25 Monoclonals antibodies, 4 Therapeutic proteins)
    - 13 Design Space, 6 Risk Assessment, 4 Control Strategy, 4 Expanded Change Protocols, 3 Small Scale Models

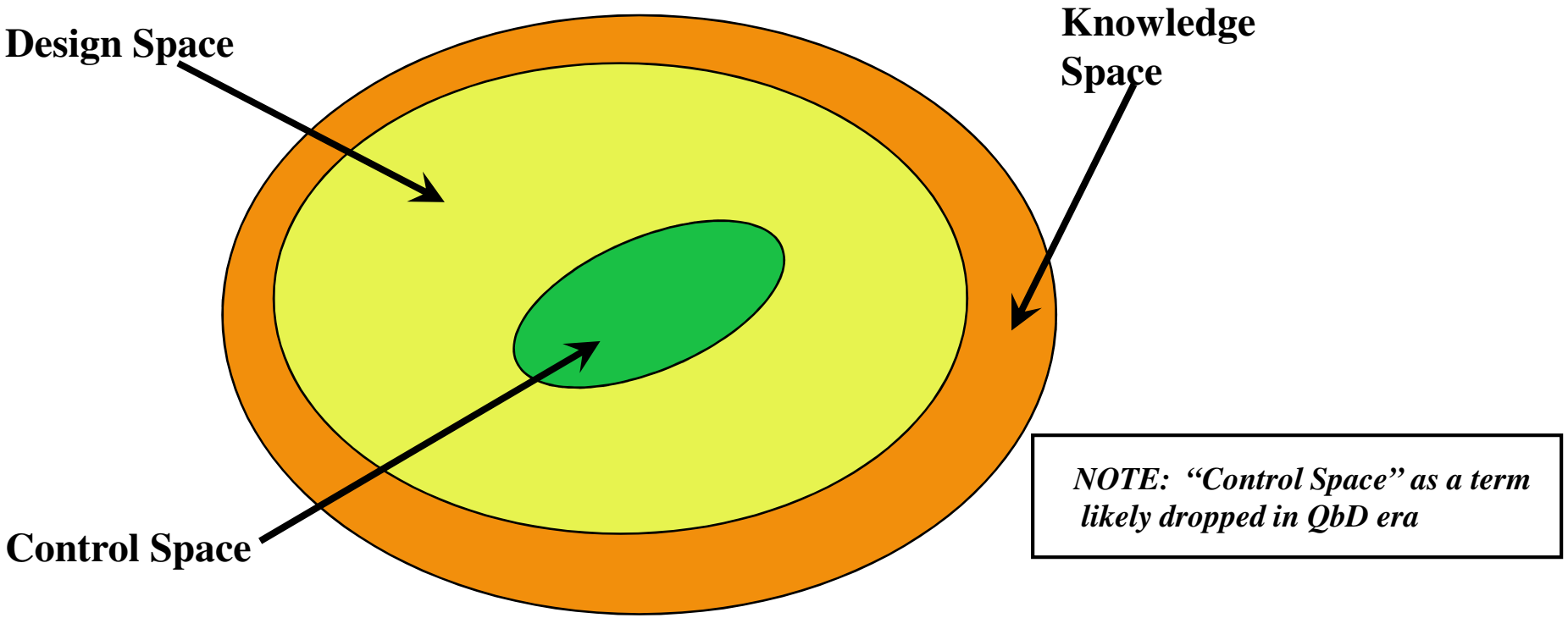
Challenge #1: Control Strategy



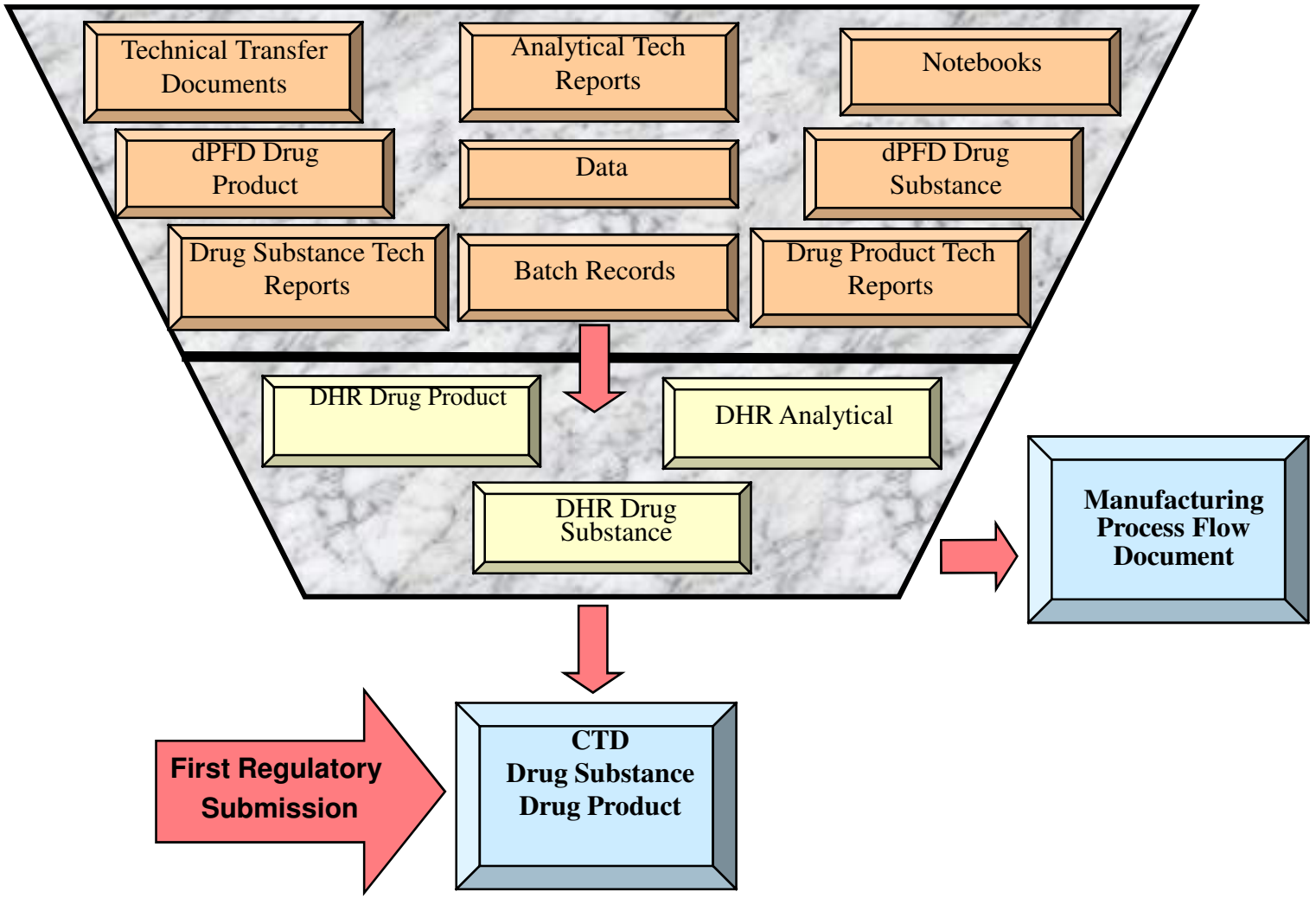
- Move to parameters from in-process tests
- To have both comes across as redundant
- May seem like leap of faith when transferring a new process with little experience
  - Introduces the concept of “sunsetting” in-process controls once appropriate experience has been gained

Challenge #2: Defining the Design Space

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. ICH Q8)



Challenge #3: QbD in Application



DHR: Development History Report
dPFD: Development Process Flow Document

Current QbD Landscape Conclusions

- Many successes achieved and progress has been made in this changing paradigm.
- Open discussions continue to identify and resolve areas that are unique to biotech products
  - Feedback on QbD approach from the FDA: “agree with the approach in principle, but the proof will be in the submission content”
- Leveraging learning from small molecules
- More efficient (e.g. standardize best practices) in a world of growing country specific requirements
- A Quality Management System is critical to developing a regulatory pathway for QbD
  - Timing of regulators chemistry review of marketing application and assessment of manufacturing site’s quality system

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Case Study in QbD Implementation: Risk Assessments for Raw Materials Management

Duncan Low

Introduction

- High quality medicines need high quality materials
- Classical raw material issues
  - media variability, trace components, residues,
  - proprietary media and cell lines; sole sourced resins, filters
  - Excipients quality and device standards
- Increasing regulatory scrutiny and expectations
  - Residual solvents, melamine contamination, GM crops

Risk Assessments Are Conducted At Multiple Points Throughout Development

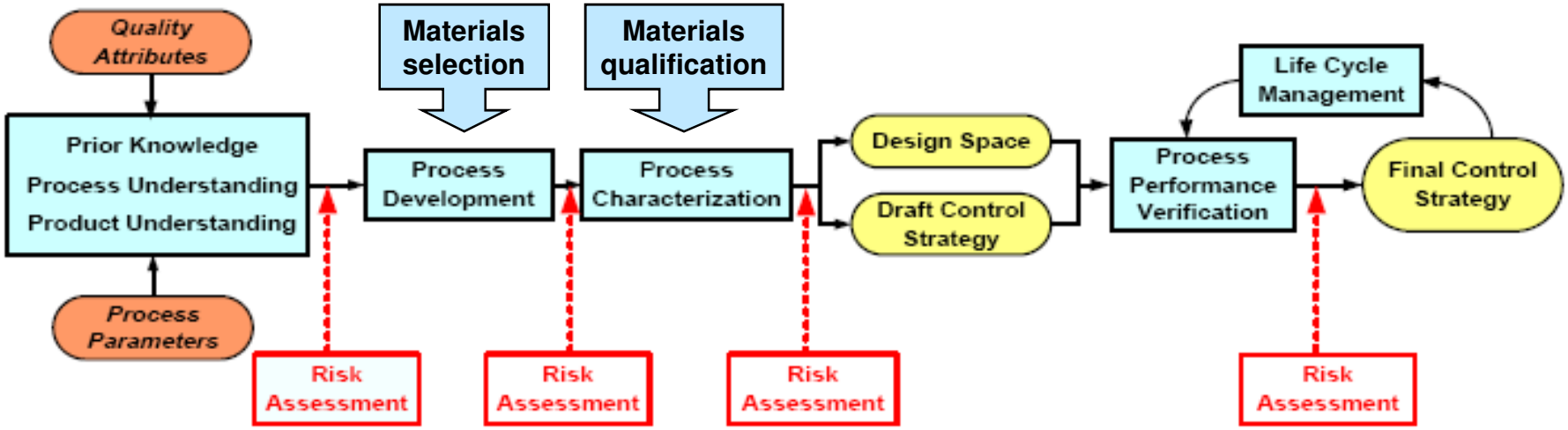

Figure 1.2 Risk Assessment Approach Used through A-Mab Development Lifecycle

Initial assessments prioritize and focus studies
Additional assessments confirm and lead to control and mitigation

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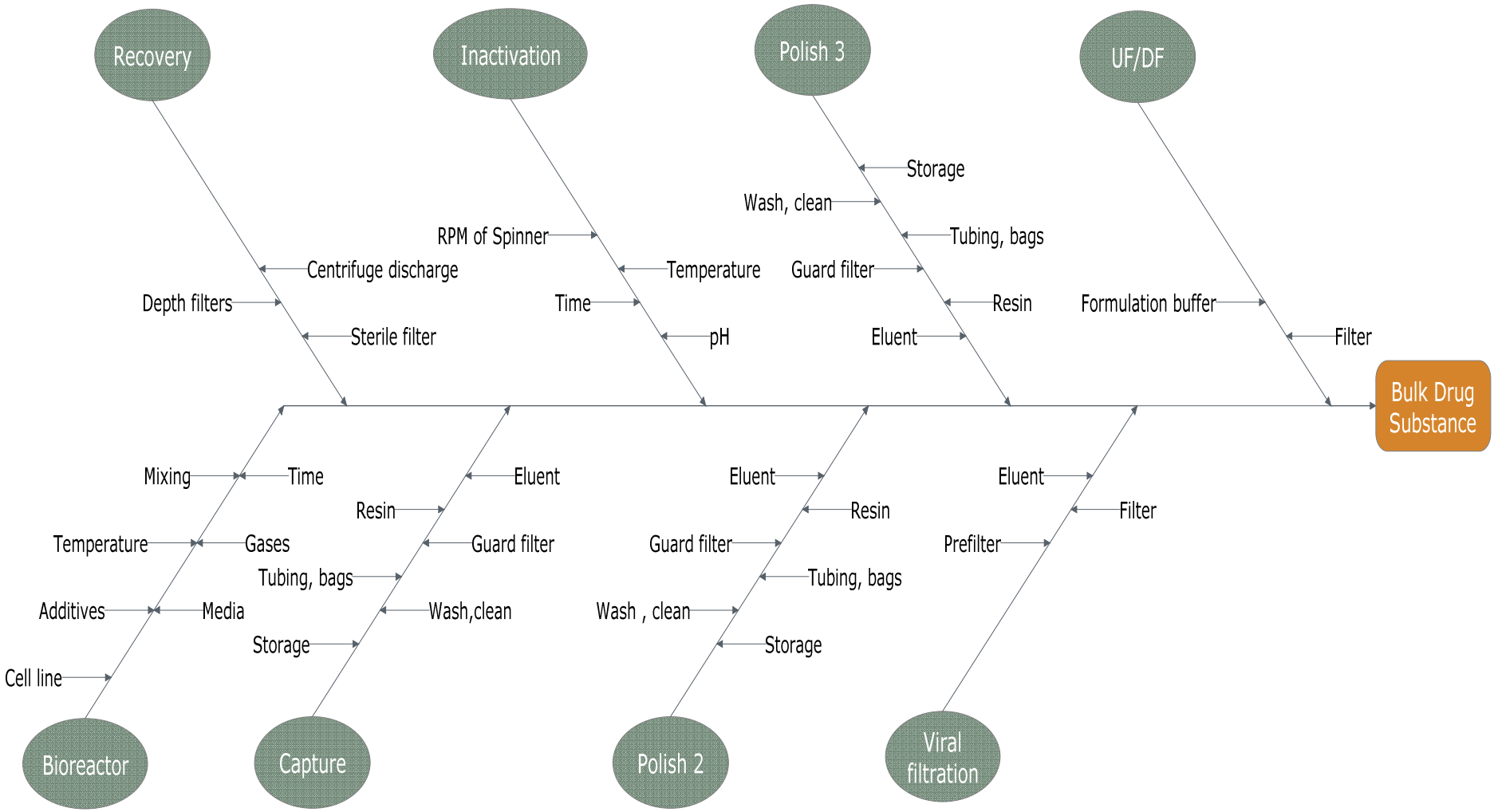
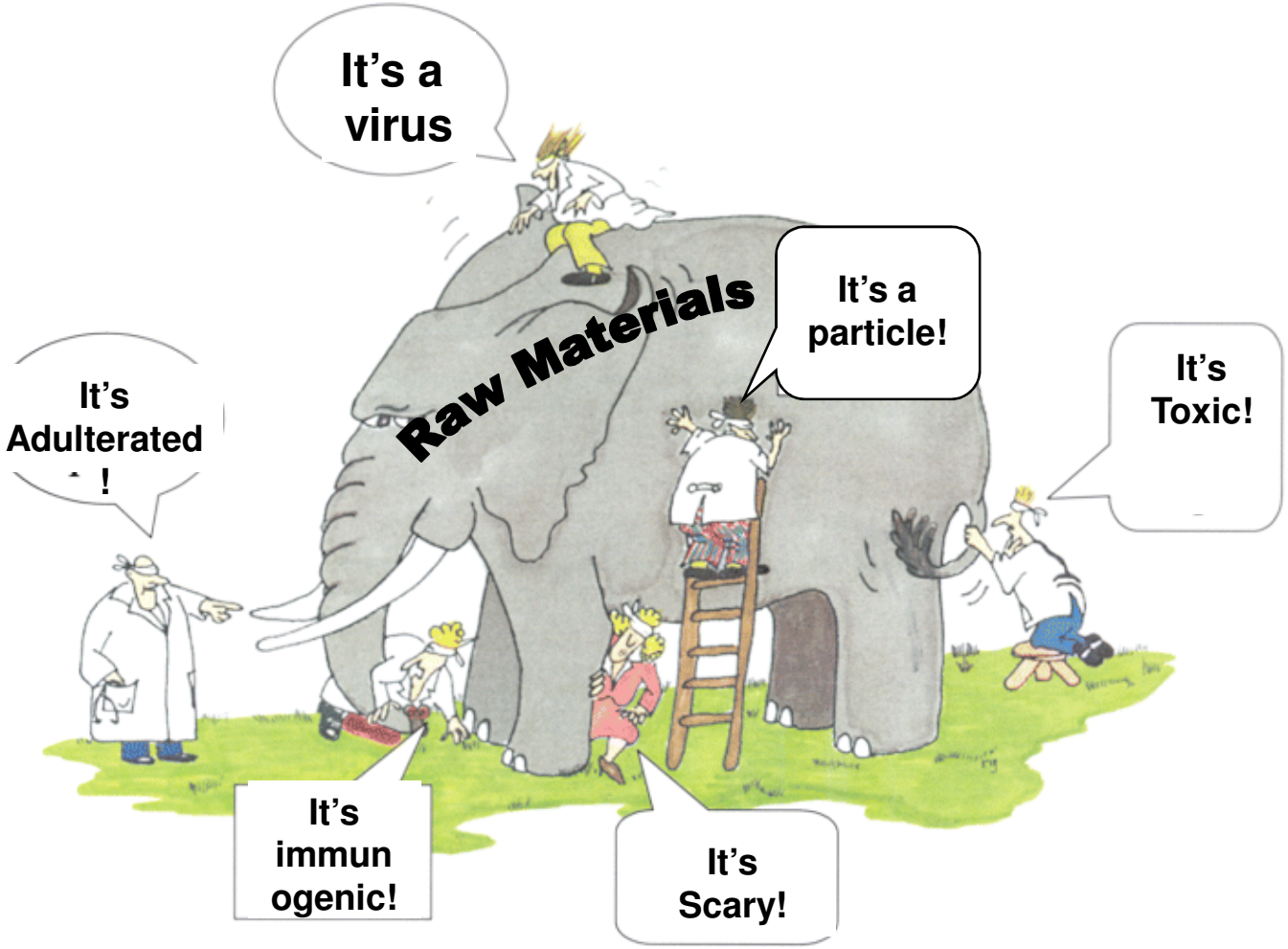
Components of material risk

Supplier risk	Material risk	Process impact
Business continuity • Capacity • Sole sourcing • Disaster recovery • Business fit	**Material safety** • Toxicity, carcinogenicity • Immunogenicity • Viral safety • Residual solvents, metals	**Quality** • Purity • Contaminant profile • Product variants • Point of use
Supplier Quality • Audit • Change control • Supply chain transparency	**Material complexity** • Compendial chemicals • Complex nutrients • Integrated systems	**Process performance** • Titer • Yield • Throughput
Technical capability • Process/product understanding • Applications development • Service and support	**Handling** • Lot-to-lot consistency • Clumping, particles • Cleaning, disposal	**Facility fit** • Available equipment • Tankage • Local regulations

Consider where in the process the material is used



Inexperienced teams may have a scary and inconsistent view of materials



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Use experienced SME's to build baseline assessments

Platform assessment	Low	Medium	High
Excipients	1	0	2
Resins	0	5	0
Filters - viral*	0	1	0
Buffer, vent	11	2	1
Growth media	10	8	3
Biobags	2	2	2
Additives	0	2	2
Chemicals	26	7	0

Use internal and external expertise

Table 2.19 Platform and Product Specific Experience with Leached Protein A

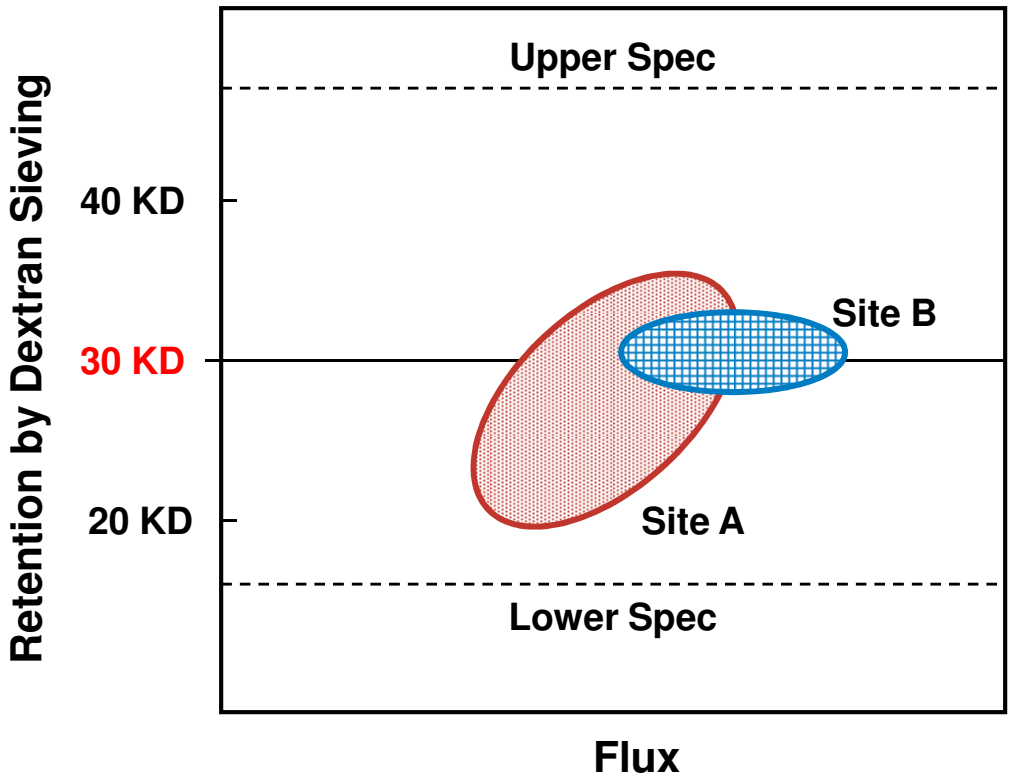
Prior Knowledge	In-vitro Studies	Non-clinical Studies	Clinical Experience	Claimed Acceptable Range
Protein A is used in approved therapy (PROSORBA)	None	Primate studies showed doses up to 1 mg/kg well tolerated	None as protein A is always cleared from the process	No range claimed due to low to moderate criticality

Table 2.20 Scoring Criticality of Leached Protein A using Risk Assessment Tools #1 and #2

Tool #1 (Impact x Uncertainty)				
Efficacy	**PK/PD**	**Immunogenicity**	**Safety**	**Risk Score**
12 × 1 = 12	12 × 1 = 12	16 × 1 = 16	2 x 3 = 6	16
Tool #2 (Severity x Likelihood)				
Severity		**Likelihood**		**Score (RPN)**
5		3		15

Based on prior knowledge and relevant experience Protein A was determined to have moderate criticality

Small changes in materials can have significant effects



Manufacturer improved process control but protein loss increased

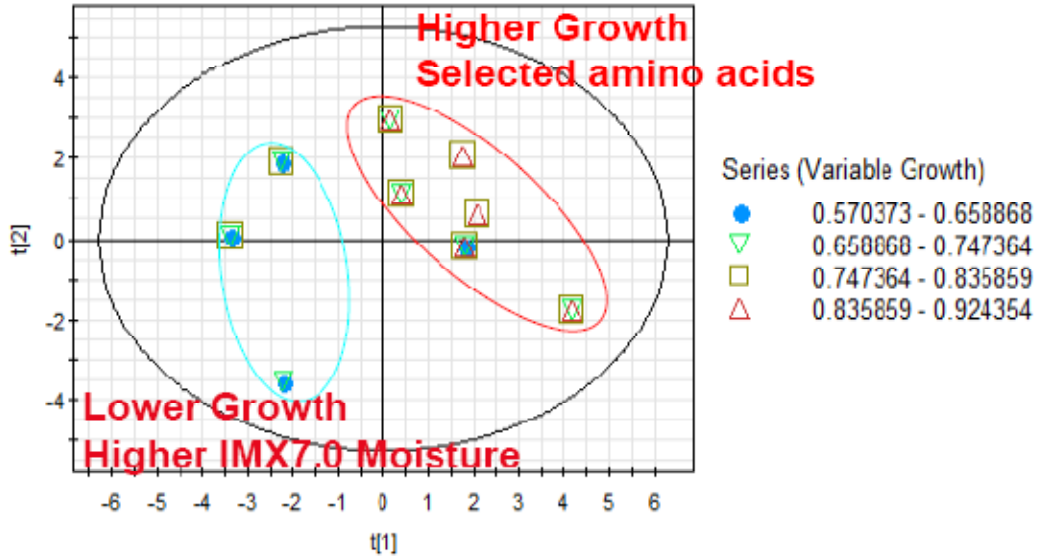
The impact of change on performance can be subtle

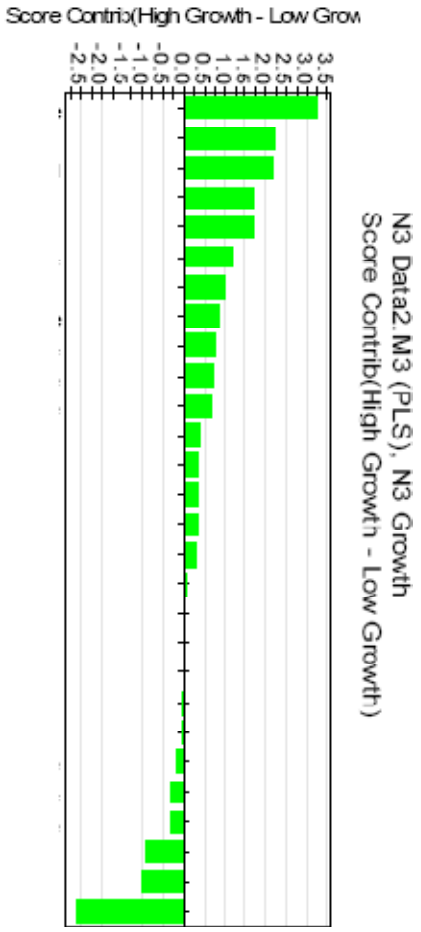
Continuous verification and improvement

- Biotech processes use a wide range of sensors at multiple points
  - Most track product rather than measure quality directly
- Upstream processes are extremely data intense
  - Track multiple parameters and use empirical models in a ‘shotgun’ approach (e.g. multivariate data analysis, MVDA)
- Downstream processes may have better theoretical models
  - Mechanistic approaches based on a smaller number of specific parameters

Proactive analysis of raw materials can identify critical components

- Contribution Scores show possible correlations between high and low VCD batches
- Principal Component scores show clustering of similar data
  - Higher VCD Batches clustering to the right
  - Lower VCD Batches cluster to the left





Mechanistic approaches are more applicable downstream

Materials
pH, conductivity
Ion, counter-ion
Source
Concentrates

Product
Isoelectric point
Titration curve
Glycosylation
Amidation etc

Resin
Ligand, ligand density
Coupling, spacer
Resin chemistry
Particle size, pore size
Surface area

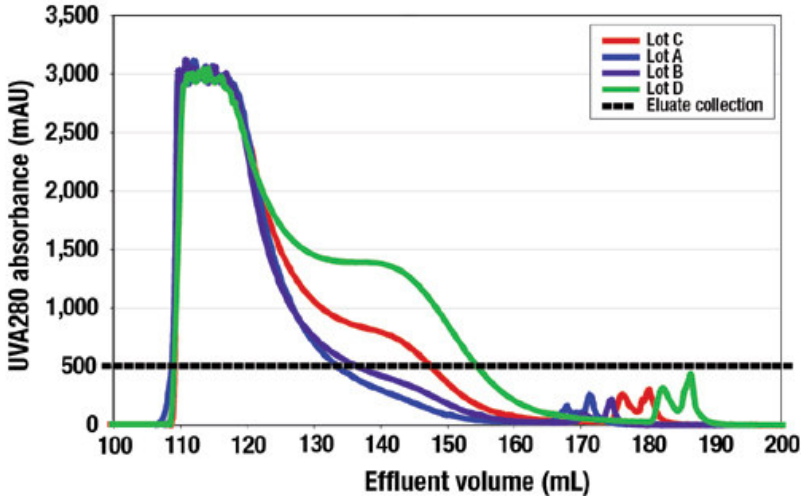
Equipment
Distribution system
System dead volume
Gradient reproducibility
Column packing
Operator training

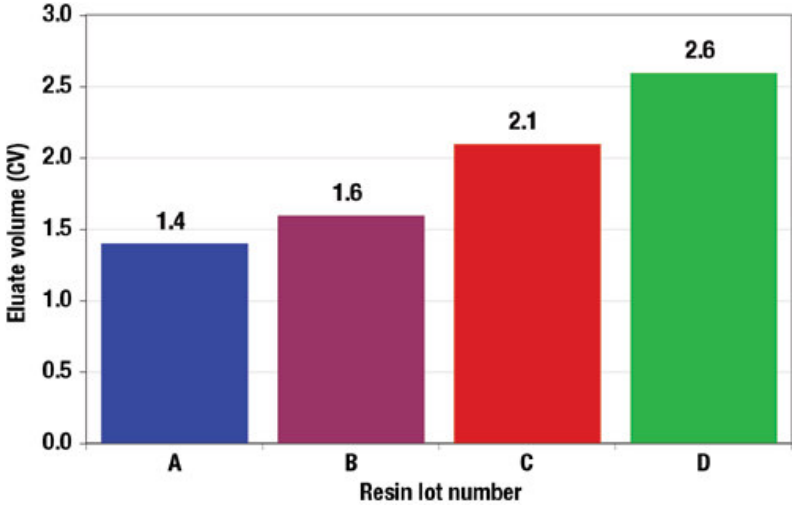
Process
pH, conductivity
Temperature
Step vs linear
Flow rate
Sample size

Measurement
UV, on-line
Fractionation criteria
Forward control
Modeling

Impact of lot-to-lot variability of CEX resin

- Variability caused significant changes in zone spreading/potential loss of product (tank limitations)





From Wahome, J., Zhou, W. and Kundu, A Biopharm Intnl May 2008

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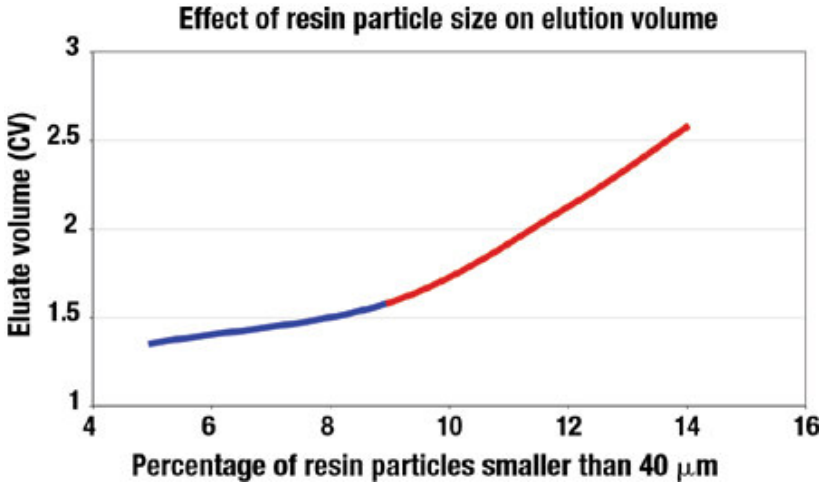
Particle size distribution was the culprit

Table 3. Percent of particles falling within 40–90 μm

Resin lot	Elution volume (CV)	% within 40–90 μm
A	1.4	95
B	1.6	91
C	2.1	88
D	2.6	86



A further example of subtle changes in raw materials

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Conclusions

- Raw materials have a large impact on product quality and process performance
- Risk assessments are a powerful tool for organizing prior knowledge
- Small changes in materials can have significant impact
- Continuous monitoring allows us to build knowledge over the life cycle of the product

Questions

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