

Implementation of Quality by Design:

An Office of Biotechnology Products Perspective

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Overview

- OBP Products & Manufacturing
- Quality by Control
- Quality by Design for OBP Products
- Product Knowledge
- Implementation

Office of Biotechnology Products

- Therapeutic Proteins
 - Growth Factors
 - Enzymes
 - Cytokines
 - Chemokines
 - Angiogenic factors
 - Toxins
 - Soluble Receptors/Receptor antagonists
- Monoclonal antibodies
 - Related Products

Office of Biotechnology Products

- These proteins are usually produced from:
 - Cell culture
 - Recombinant & non-recombinant
 - Mammalian, bacterial, yeast, etc.
 - Transgenic plants & animals
- Products transferred from CBER to CDER in October 2003
- ONDQA regulates some protein products

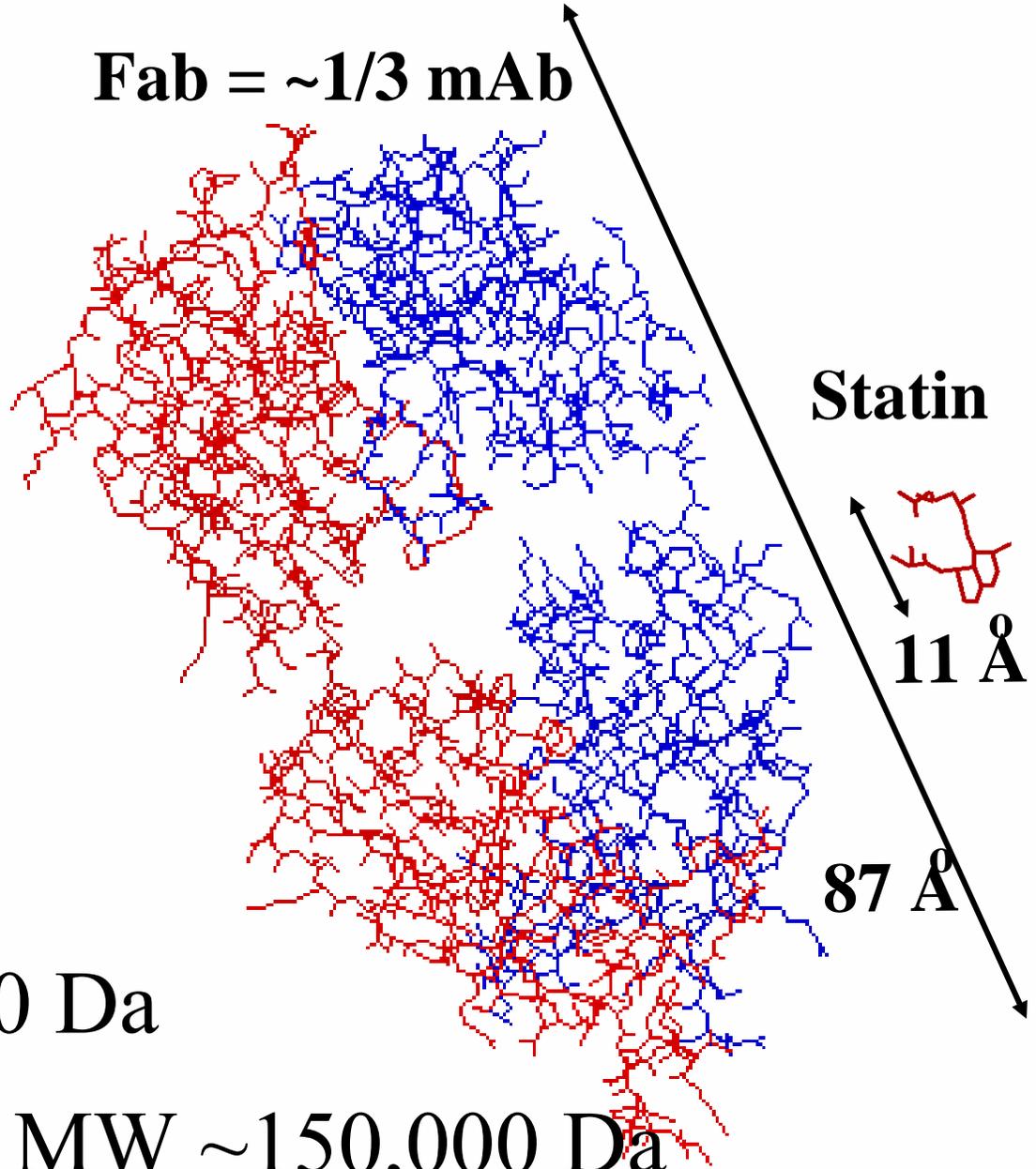
Structure of complex molecules

- 1° structure
- higher order structure
- post-translational modifications
- heterogeneity

Statin MW ~400 Da

Monoclonal Ab MW ~150,000 Da

Fab = ~1/3 mAb



Manufacturing Issues

- Bioreactor (or source material)
 - Desired product
 - Contaminant/impurity load
- Downstream processing
 - Desired product
 - Viral clearance/inactivation
 - Removal of in-process reagents
 - Linkers/chelators
 - inactivating chemicals
 - other reagents used in synthesis
 - Removal of host cell proteins and DNA
 - need for sensitive assays

Manufacturing/Industrialization

- In-process controls
 - Process & hold times
 - Process parameters & in-process tests
 - Reprocessing
- Comparability studies
 - Scale-up
 - bioreactor
 - downstream processing
 - Significant manufacturing changes
 - New facility

Examples of Problematic Process Designs

- Processes that promote product variability
 - Heat treatment step added after aggregate clearance step
 - Process performed at room temperature with negative impact on quality
 - Recloning is used to establish new WCB
- Processes that are difficult to control
 - Roller bottle processes (open, multiple fermentations difficult to control)

Formulation

For Biotech products heterogeneity of the API is a major factor and less complex liquid formulations are common

- **Stability a big issue**
 - Proteins tend to be unstable
 - May change protein conformation
 - Compatibility problems with some excipients
 - (pH, buffers, preservatives)
 - Silicone in syringes/ Tungsten
- **Alternative dosage forms**

Formulation is critical in controlling product variability

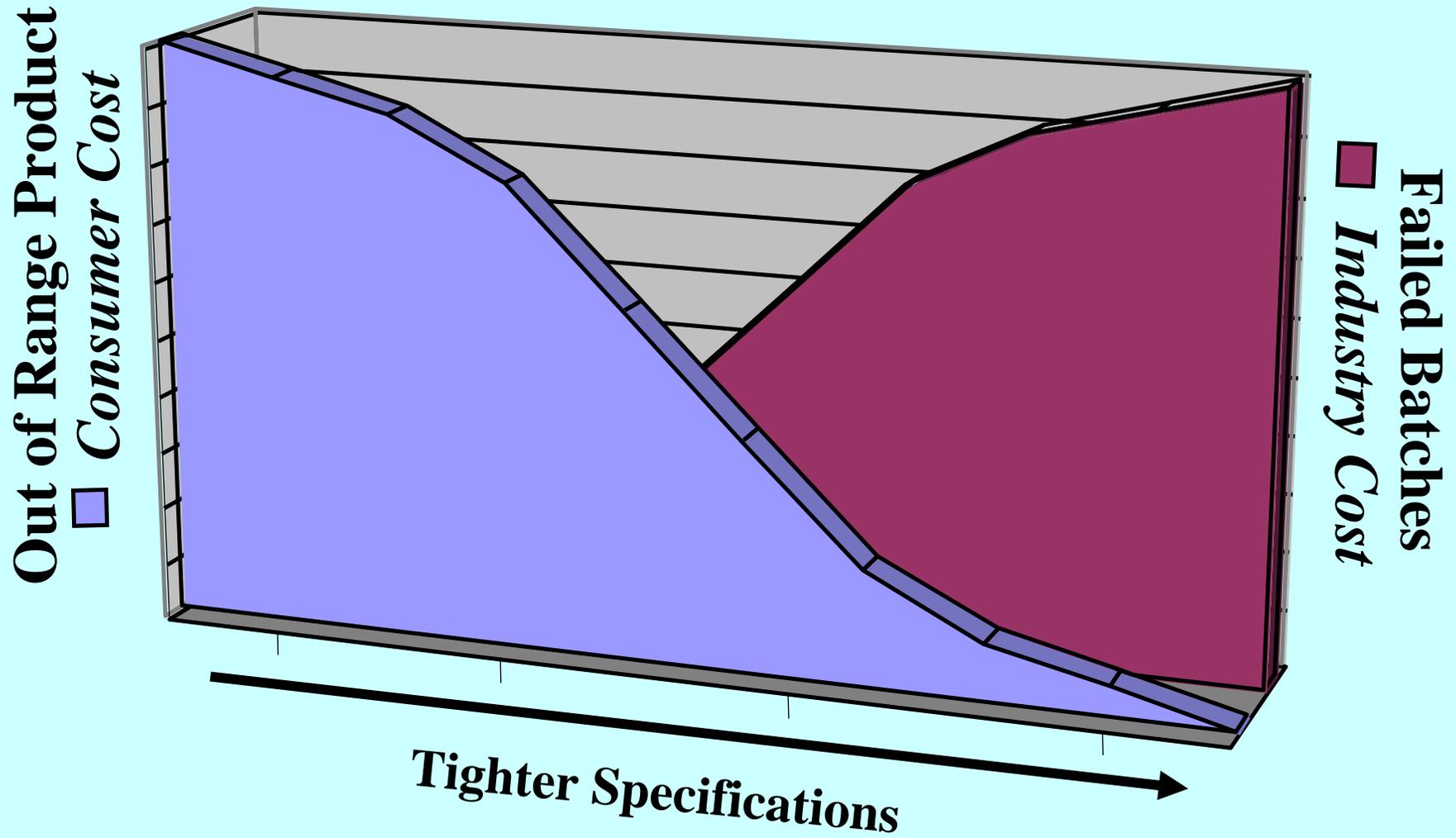
Keeping the End in Mind

- Consistently providing the desired product
 - Product that reflects material used in clinical trials
 - Safety & Efficacy
- Testing
- Process
 - validation
 - control

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Trade Offs



Consequences of over- or under- dosage (Digitalis vs PCN)

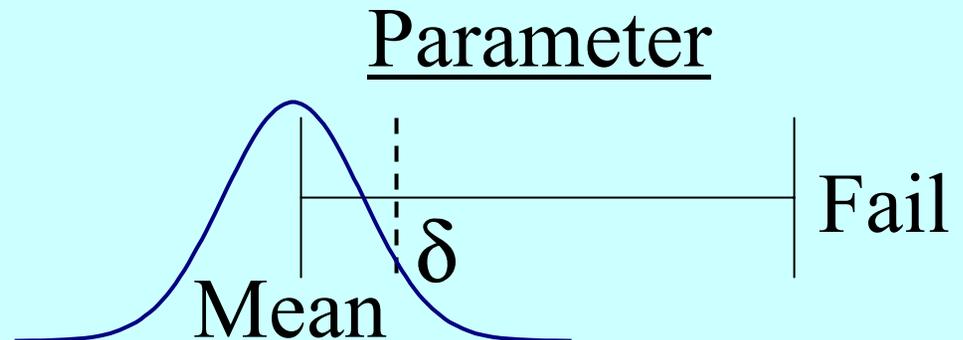
Incentives for product development

Specification Issues

- Sampling
- Statistical burdens
 - $(0.99)^{30} = 0.74$
- Process control specs
 - Limits vs specs?
 - Process validation (clearance)
- Relationship between process capability & specs
 - Correlates of safety & efficacy vs process capability

Quality Control

- 6δ (Standard Deviation)
- long term 4.5δ
 - assume greater variability over time
- 3.4 failures/million products



Industry Control of Variability

	Sigma	ppm Defects	Yield	Cost of Quality
 Pharma	2 σ	308,537	69.2%	25-35%
	3 σ	66,807	93.3%	20-25%
	4 σ	6,210	99.4%	12-18%
 Semicon	5 σ	233	99.98%	4-8%
	6 σ	3.4	99.99966%	1-3%

Ref: Productivity and the Economics of Regulatory Compliance in Pharmaceutical Production by Doug Bean & Frances Bruttin PWC Consulting Pharmaceutical Sector Team, Basel. 2002.

- **Why?**
- **Market forces**
 - Every failing cellphone is assumed to be product failure
 - Since many pharmaceuticals work 50% of the time or less
 - A small % of product failure is invisible to consumers
- **It still matters**
 - Analogy: Cox-2 inhibitors versus anti-VLA-4

Process Control

- Critical sources of variation (both API and impurities) should be identified and controlled (raw materials/ unit operations)
- Controlled through in-process testing (off line or PAT), process validation (FED) and monitoring operating parameters

Based on long standing paradigm that process consistency = product consistency

Comprehensive Quality Control Strategy

Process



Product

- Facilities and Equipment
 - Control of Raw Materials
 - In-Process Testing (PAT)
 - In-Process Controls
 - Process Validation (FED)
 - cGMPs (QC/QA)
- Method Validation
 - Release Testing
 - Characterization
 - Stability Testing

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What is “Quality by Design”?

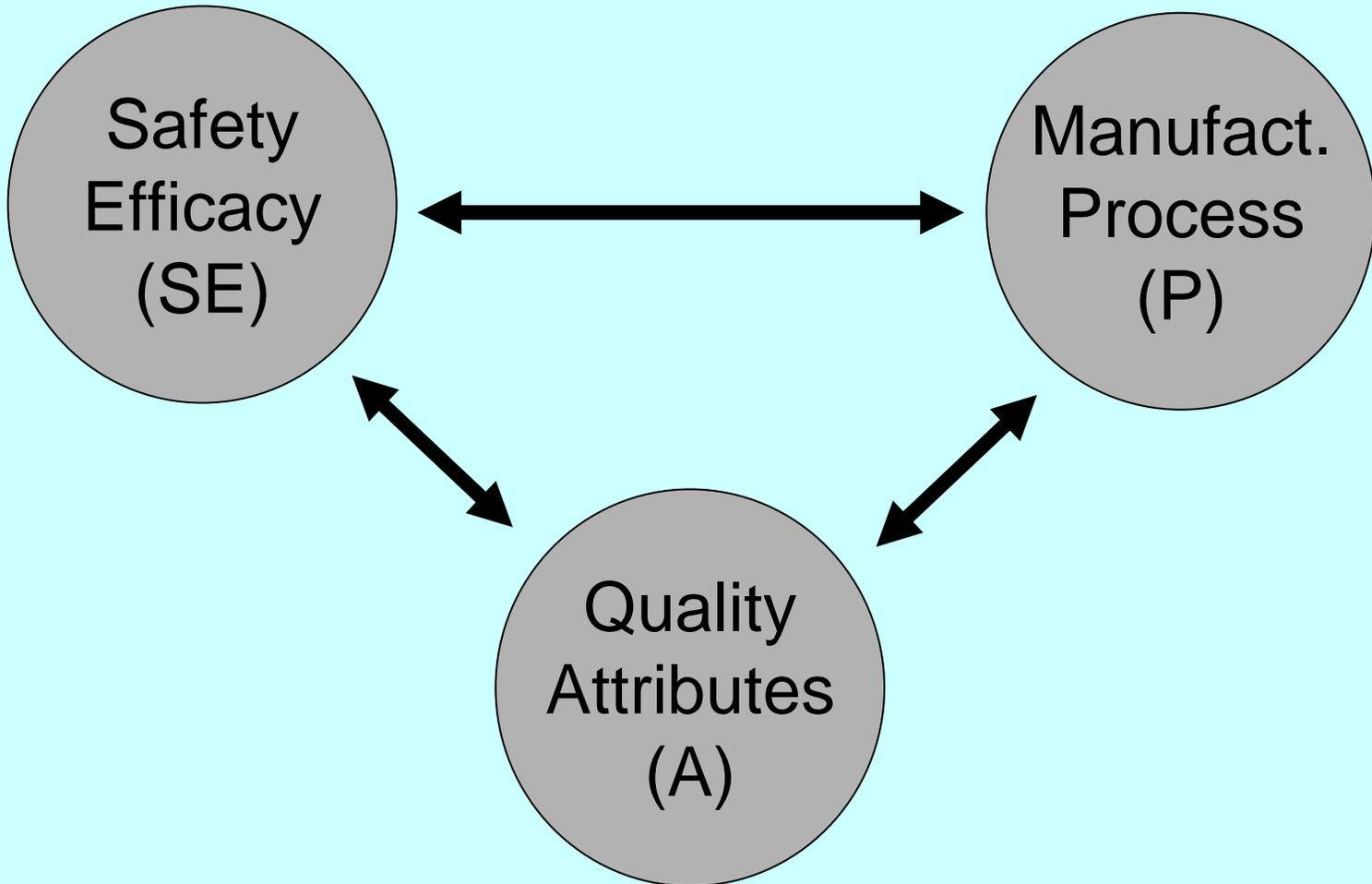
- Quality
 - “Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes.”
- Quality by Design (QbD)
 - “Means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches.”

ICH Q8

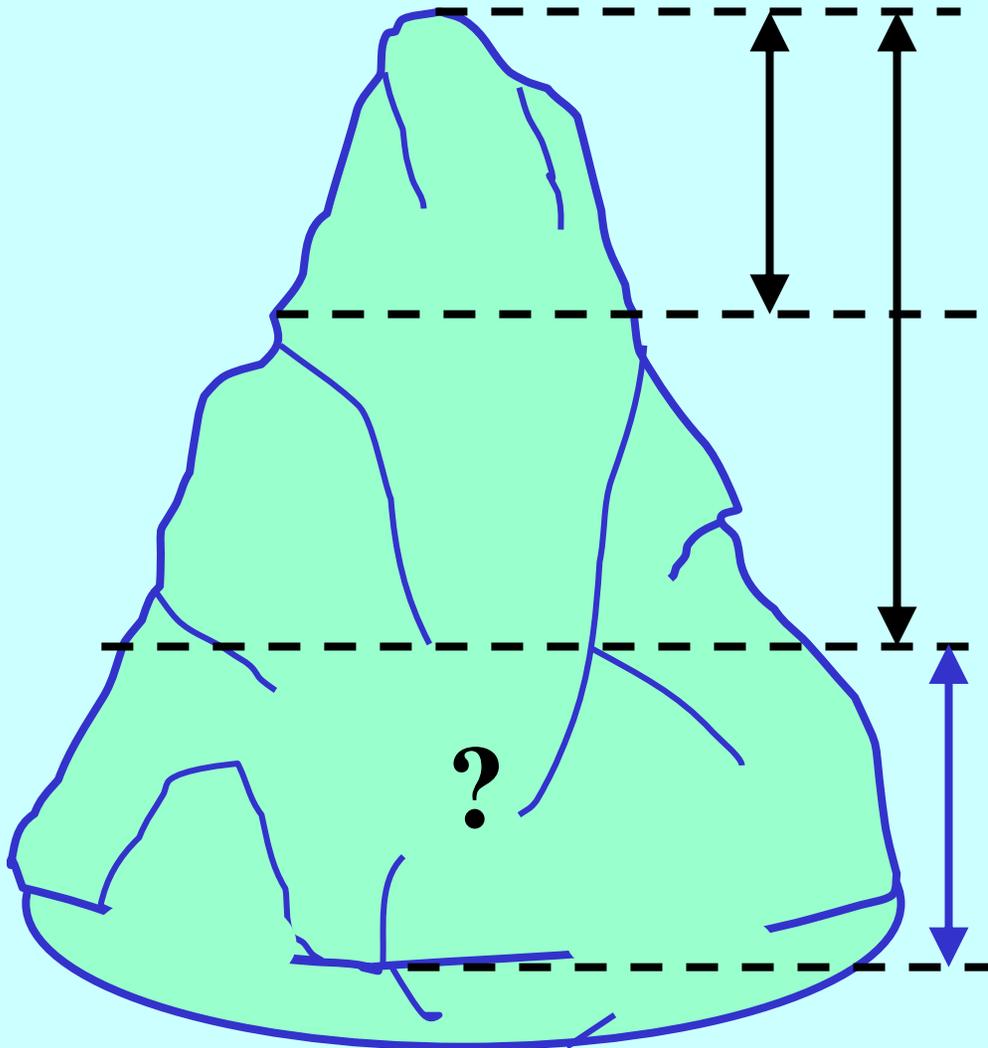
- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- Product specifications based on mechanistic understanding of how ... factors impact product performance
- An ability to effect Continuous Improvement and continuous "real time" assurance of quality

John C Berridge (2004)

Relationships

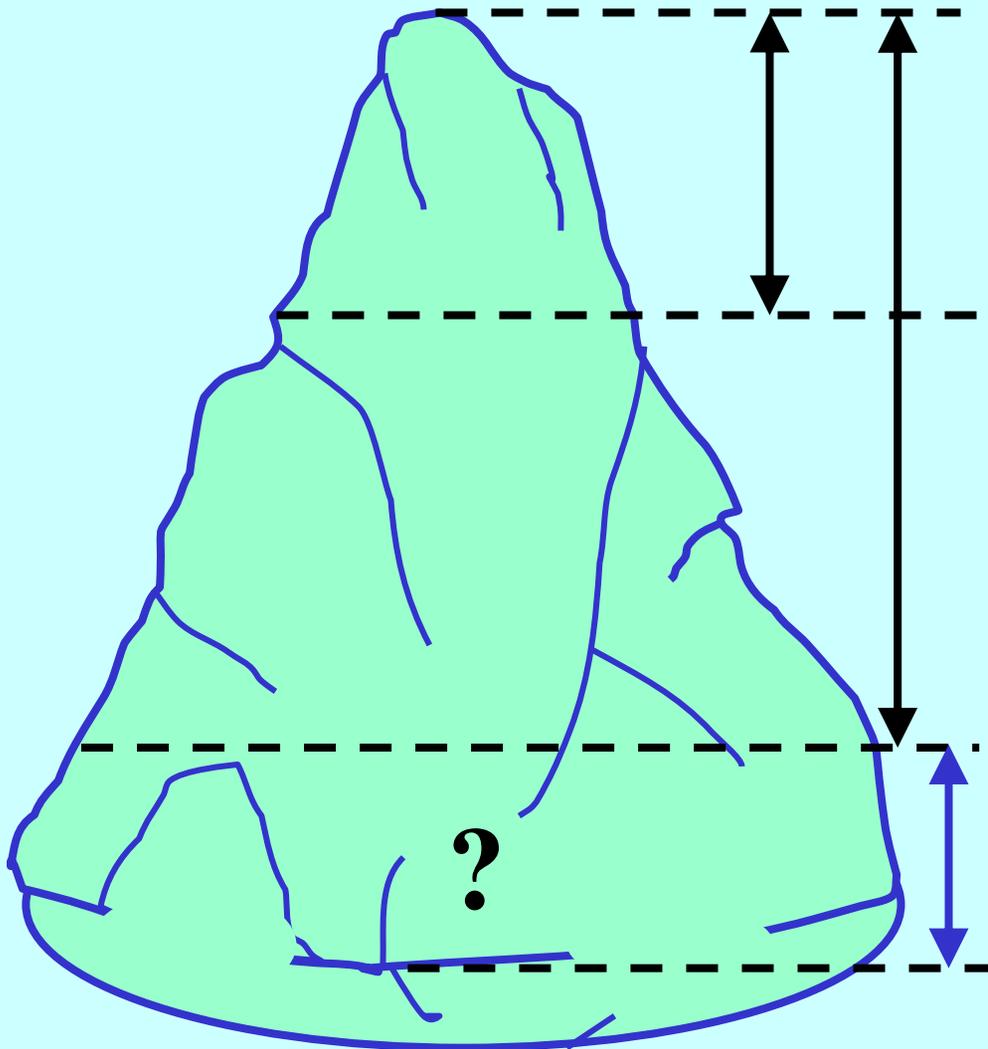


How Much of the Iceberg (Quality Attributes) Can We See?



- Release tests
- Characterization
- Process

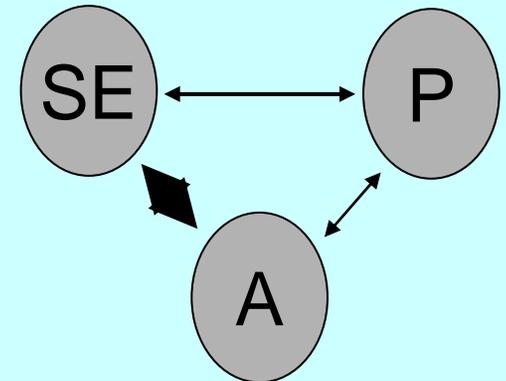
How Much of the Iceberg (Quality Attributes) Can We See?



- Release tests
- Characterization
 - MS, NMR
 - Orthogonal methods
- Process

Characterization

- Setting an unachievable bar?
 - Nat Biotechnol, 2005. **23**(9): p. 1054-8
- No!
- Advances in characterization are opportunities
- Timing
 - Upfront costs
 - Early characterization benefits
- How to deal with greater information
 - flexibility not regulatory roadblocks

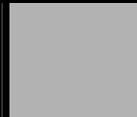


Relevant Attributes

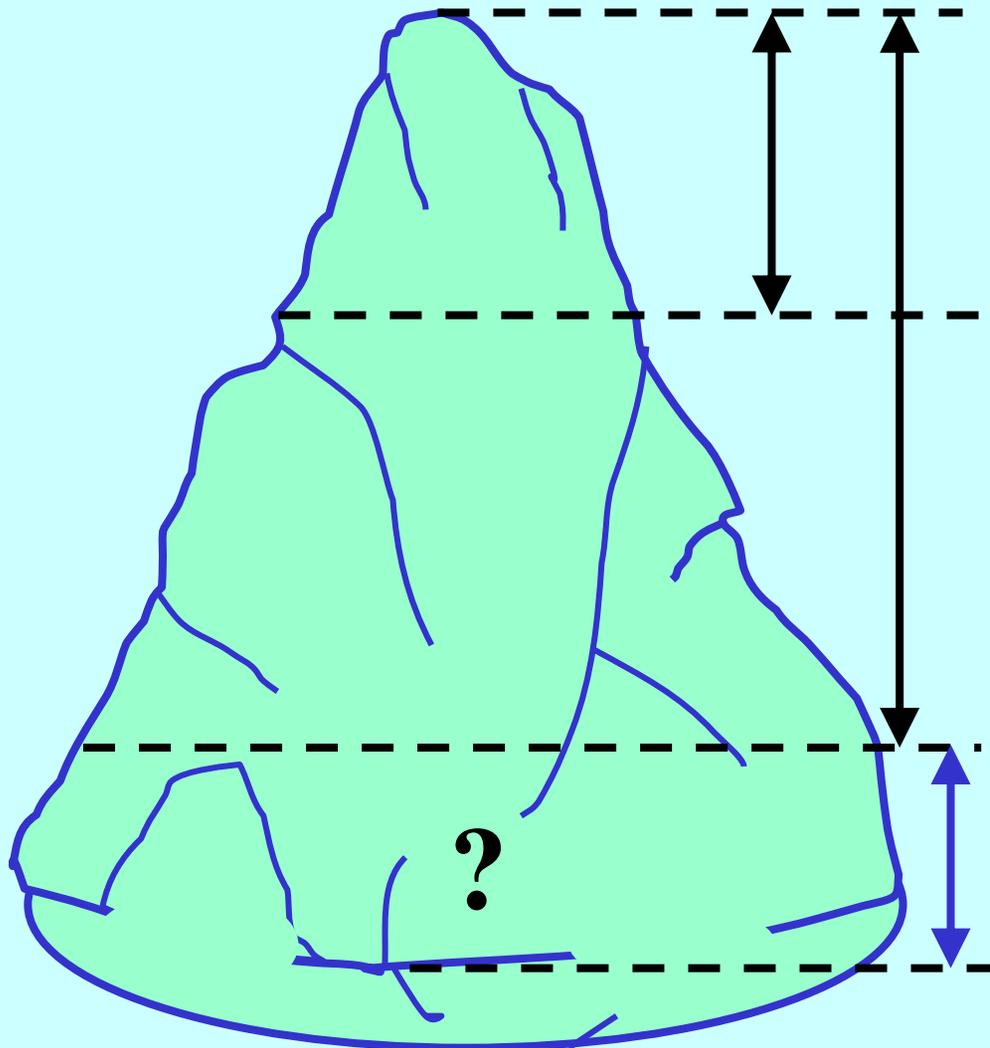
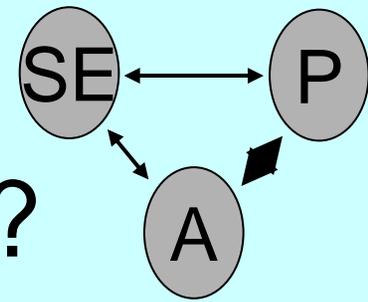
- ... those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product (Q6B)
- Can these attributes be defined?
 - Often difficult
 - Default is to look at many attributes
- Biological Characterization
 - Structure/function

Biological Activity Matrix

	One to some lots
	Many lots

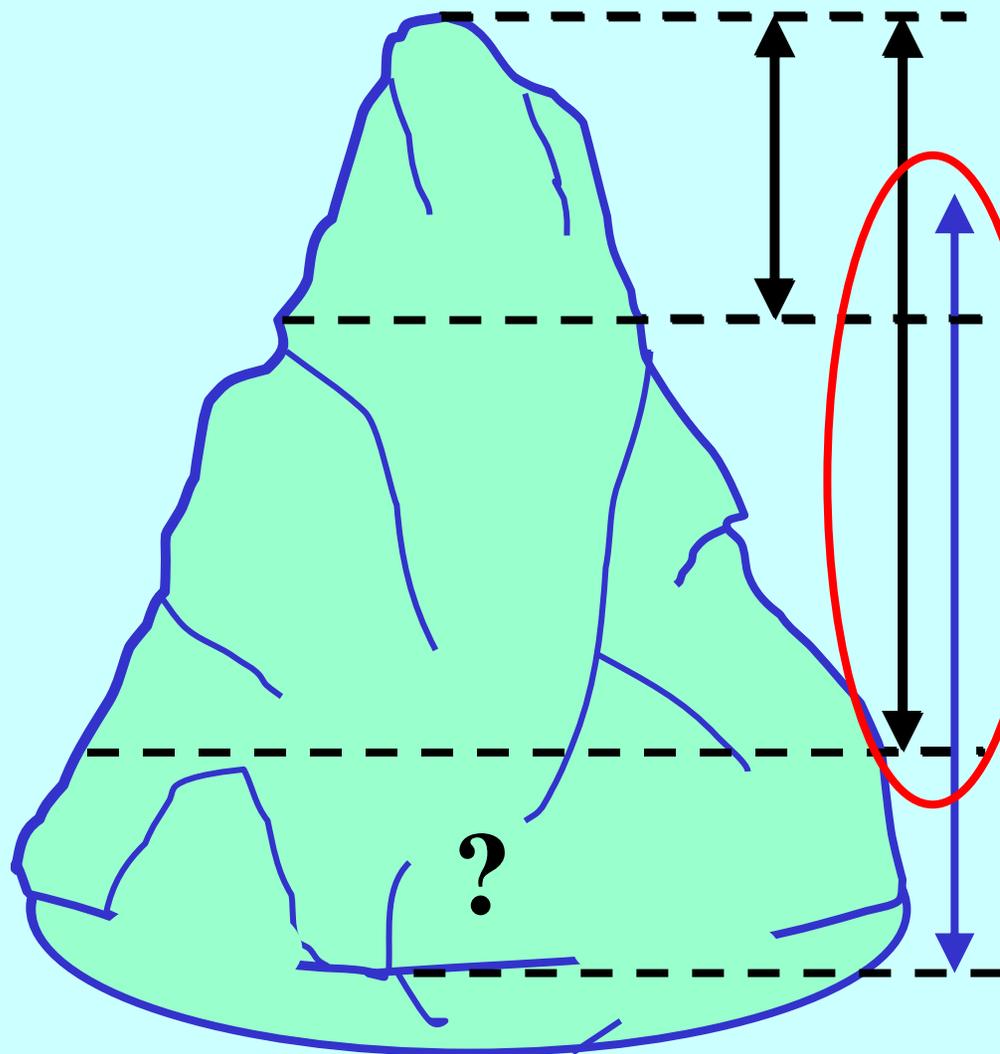
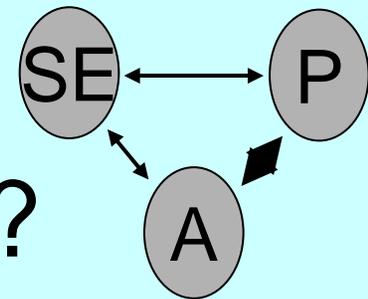
	Clinical Lots	Clinical Lot Extremes	Purified/Induced Variants	Stressed Lots	Developmental Lots
Multiple Binding/Cellular Assays					
Small Animal/Complex Bioassay					
Clinical Pharmacology (PK/PD)					
Clinical Studies					
Validated Bioassay					

What is the Relationship Between Attributes & Process?



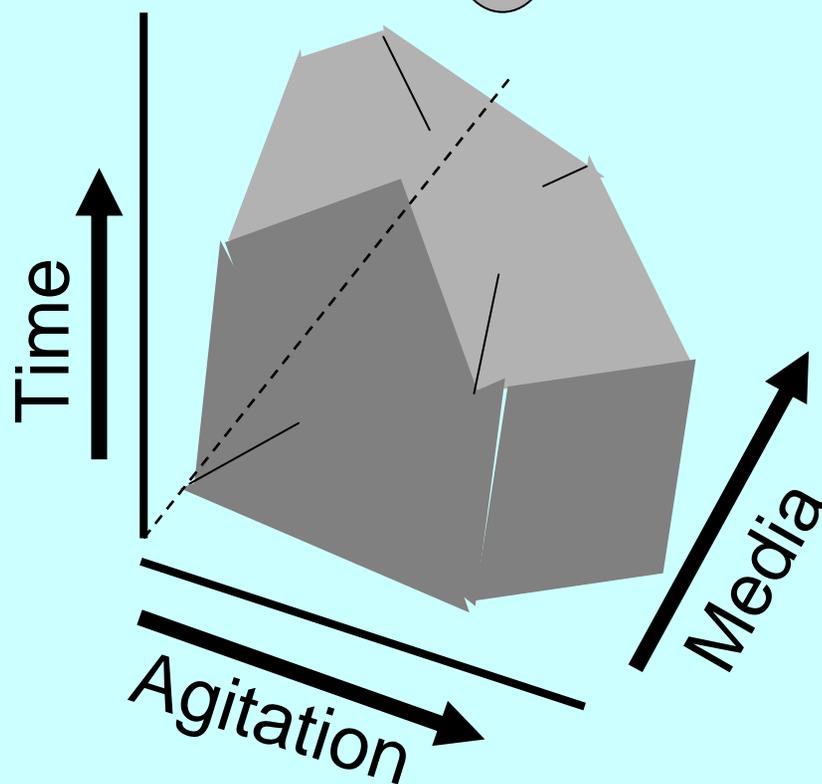
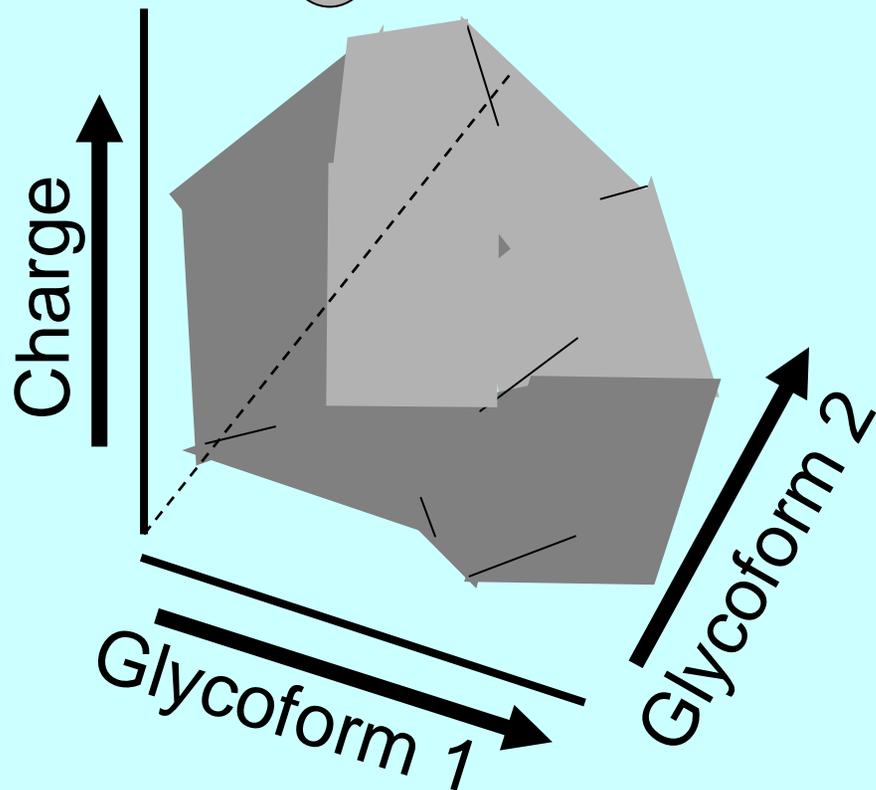
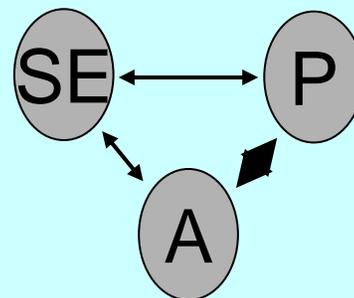
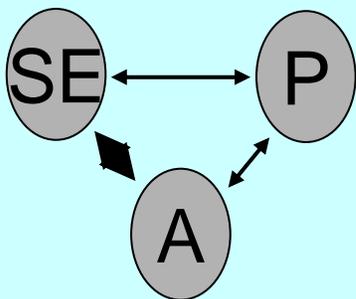
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Design Space



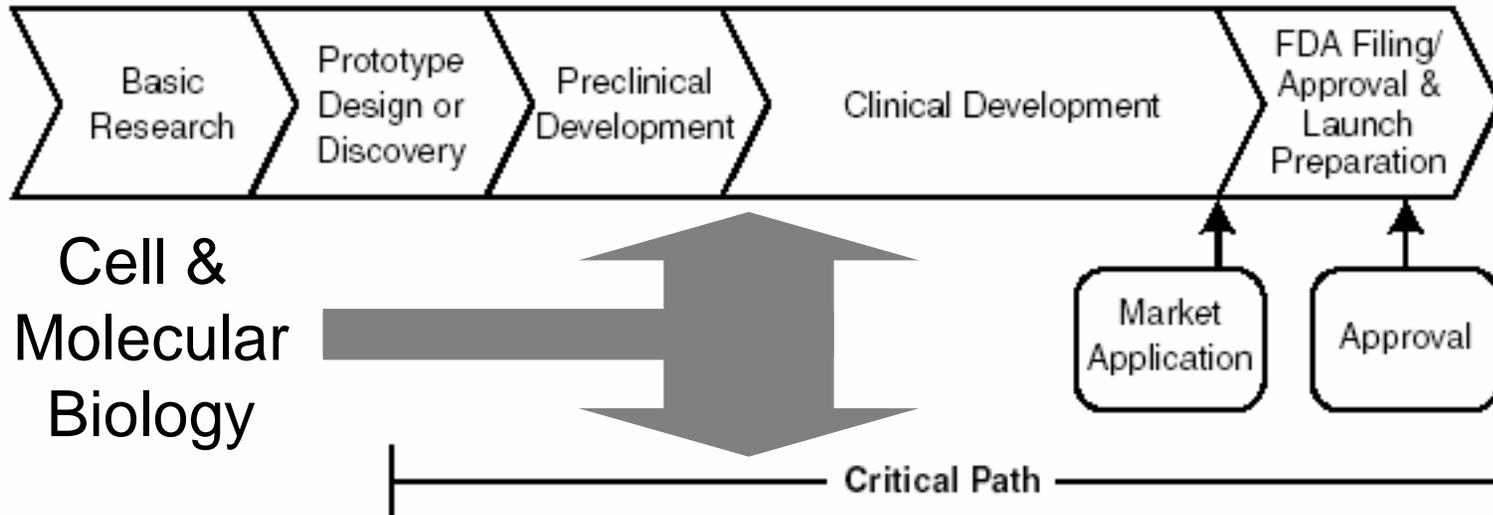
Critical Product
Attributes

Critical Process
Parameters

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Critical Path



Industrial-
ization

Relevant physiochemical properties → QbyD, CGMP & PAT

Safety &
Medical
Utility

Molecular mechanisms → appropriate animal models and clinical monitoring; likely drug interactions

Biological plausibility → support for biomarkers, PGx, etc.

QSE...by Design

- Safety & Efficacy by Design
 - Improving function/new properties
 - Increasing Bioavailability
 - Reduce immunogenicity
 - Selective technologies in development such as phage, ribosome and yeast display
- Quality by design
 - These strategies can also be used to select for product quality and manufacturability

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The Desired Product

- Desired attributes of the API (Focus for Biotech)
 - Opportunity for rational protein engineering
- Customize quality
 - Increase attributes that are desirable
 - Limit attributes that negatively impact product quality (via process or product)
- Understanding structure/function relationships is critical for this approach

Protein Engineering

- Reduce tendency for aggregation
 - Block free sulfhydryl groups
 - Alter amino acid sequence based on computational predictions
 - ❖ Glycine repeats or proline insertions
 - ❖ Maintenance of net charge
 - ❖ Alternate polar and non polar residues
 - ❖ Clusters of hydrophobic residues
 - Human Calcitonin (Zurdo et al PNAS 2005)
 - Immunogenicity considerations

Protein Engineering

- OBP has encouraged development of innovative products (not a regulatory requirement)
- Less enthusiastic concerning the use of products whose design increases uncertainty and has no expected clinical value clinically
 - Histidine tag proteins (Manufacturability versus Quality)
 - Protein domains that potentially adversely impact safety

Regulatory Relief (based on product understanding)

- Understanding of the relationship between the quality attribute and its impact on safety and efficacy can reduce regulatory requirements

Relief: If no likely impact on S and E don't include as a specification (no rejection limit)

- use as a process consistency measure, where exceeding a limit initiates an investigation
- if not a consistency measure, drop the test entirely
- Transitioning to this new paradigm of action versus rejection limits
- Need to discuss more extensively in-house and provide reviewer training

Examples from Biotech

- For a highly glycosylated protein various isoforms were isolated and monitored for relevant bioactivity in a suitable animal model (immunogenicity considered)
Outcome: widen specs for isoform profile
- Monitored product isoforms from human serum samples over time, showed rates of decay were similar concluded isoforms did not impact bioavailability
Outcome: broaden acceptance criteria

Regulatory Relief

(based on process understanding)

- Validate the process is capable of impurity removal to appropriate levels (non toxic impurities)
 - Excess capacity if impurity has variable input
- Relief: Impurity is not routinely measured when operating under the validated state (removed from specifications)

Implementation of Q by D

- Q by D “a major fear from industry is that reviewers will not understand or be receptive to the submission” paraphrased from Dr. Ken Morris, Q by D presentation October 17, 2005
- OBP review is based on scientific merits of the proposal and not simply reliance on existing practice. Guidance helps frame the issue but science and knowledge dictates the outcome.

Implementation of Q by D

Structure of OBP

- Mixture of research/reviewers and full time reviewers
- Experience with new technologies, fermentation/purification processes
- Research in molecular and cellular biology and pharmaceutical science
- Expertise in biological characterization for meaningful risk assessment

Work with OPS, ONDQA & OGD on Q by D

PAT Future Directions

Many dimensions since single unit operations perform many functions

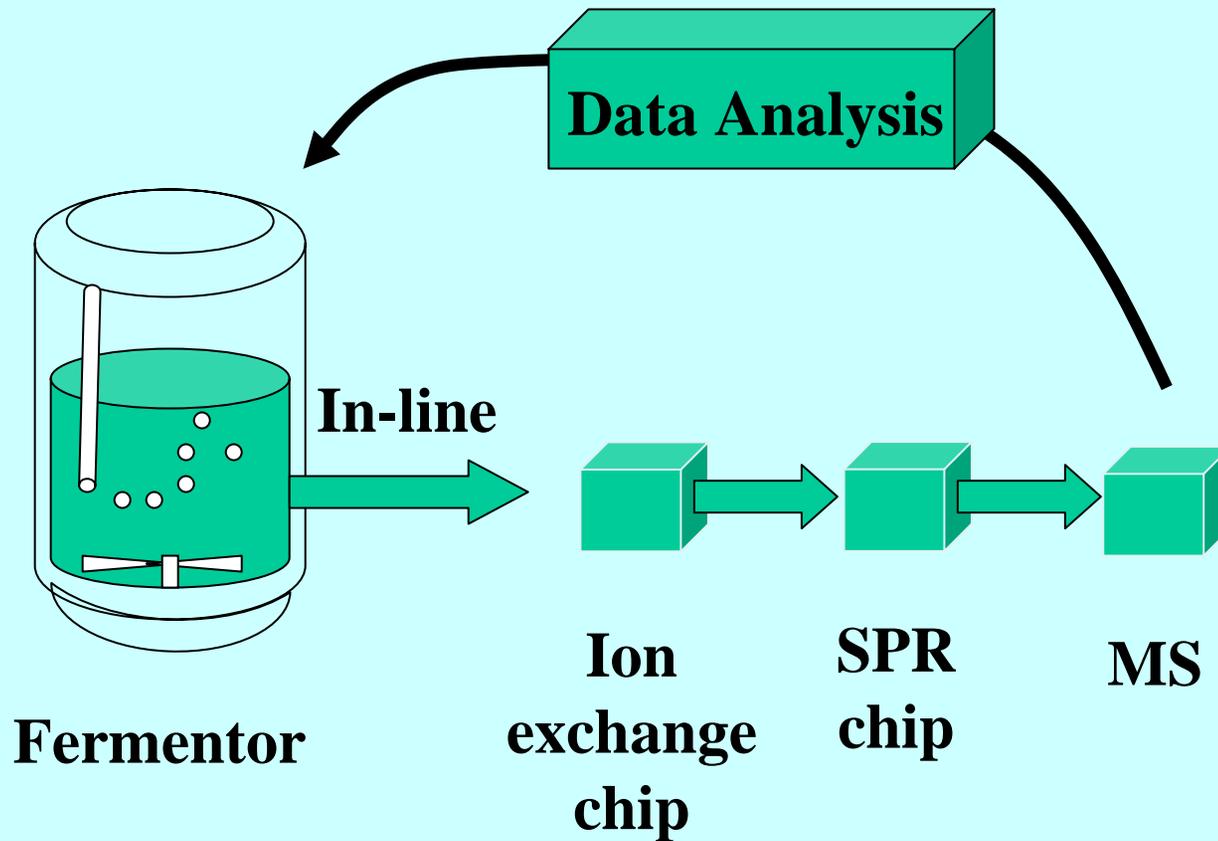
- Desired product
 - Relevant attributes
- Removal of contaminants/impurities

Drug product 100% in-process quality testing:

- Monitor moisture in lyo product by NIR
- Monitor vacuum seal integrity by Frequency-Modulated Spectroscopy
- Monitor visible and sub-visible particulates

Future Scenario

Many steps controlled by product attributes



Credits

- **Barry Cherney**
- Patrick Swann
- Keith Webber
- Ajaz Hussain