Quality by Design for Biologics: An Industry Perspective

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Quality by Design

- *Integration of patient needs, science and quality requirements during the development of a pharmaceutical product and its manufacturing process*
- *Close collaboration between industry and regulators to achieve a regulatory review based on a scientific understanding of the product and its manufacturing process*
- *Harmonization across regions is critical to allow for a single CMC submission worldwide*
- *Quality by Design principles apply equally well to pharmaceutical products and biological products*

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Quality by Design -cont

- *Well known as standard of practice in other industries (automotive/microchip/electronics/ chemical industries*
- *Less well-known that this has been a evolving standard of practice in vaccines and biologics for some time - due to complexity of process*
- *Continuous improvement including capacity building is a direct result of QbD, and will benefit the patient and the region alike*

Environment needed for successful adoption

- *Regulatory flexibility to accommodate quality by design submissions*
- *Common dossier accepted worldwide by regulatory agencies*
- *Post-approval changes within pre-defined design space can be implemented with regulatory flexibility*
- *Laws and processes in place to protect intellectual property (IP)*

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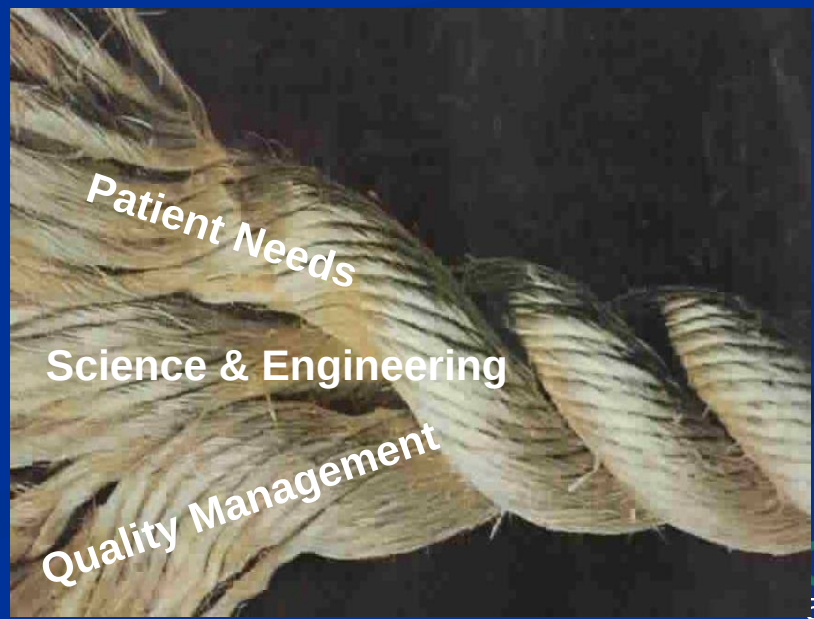
Quality by Design - Culture Shift

FROM: Knowledge exchange

TO: Knowledge integration



Outline

- Quality by Design
  - What does it mean?
- The concepts of design space
  - Example using HPV vaccine as a model
- Benefits of Quality by Design
- A look into the future

"Quality by Design" What does it mean?

- Product is designed to meet patient needs and performance requirements
- Process is designed to consistently meet product quality attributes
- Impact of starting raw materials and process parameters on product quality is understood
- Critical sources of process variability are identified and controlled
- The process is continually monitored and updated to allow for consistent quality over time

Source: Moheb Nasr (FDA)
DIA meeting, 19 June 2006

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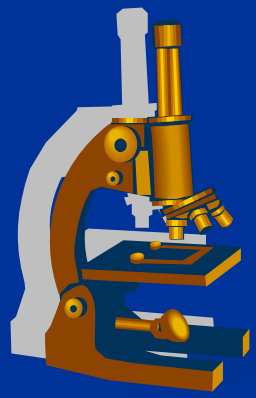
Quality by Design Aspects for Industry

Starting Materials

Product

Patient

Process &
Equipment



Measure &
Monitor

Designed for the patient

- Patient needs
  - Efficacy
  - Safety
  - Value
- Performance requirements
  - Product specifications (potency, stability, etc.)
  - Optimal dosing and administration (ease of use, compliance, dosing frequency, route of administration, etc.)

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Designed to consistently meet desired product quality

- Design space concept
  - Experimentally defined process operating space based on scientific principles
  - Critical process parameters identified
    - Critical = impact product quality
    - Space = operating range yielding acceptable product
  - Critical process parameters are consistently controlled
- Product of process is always desired quality
  - End product testing might be reduced

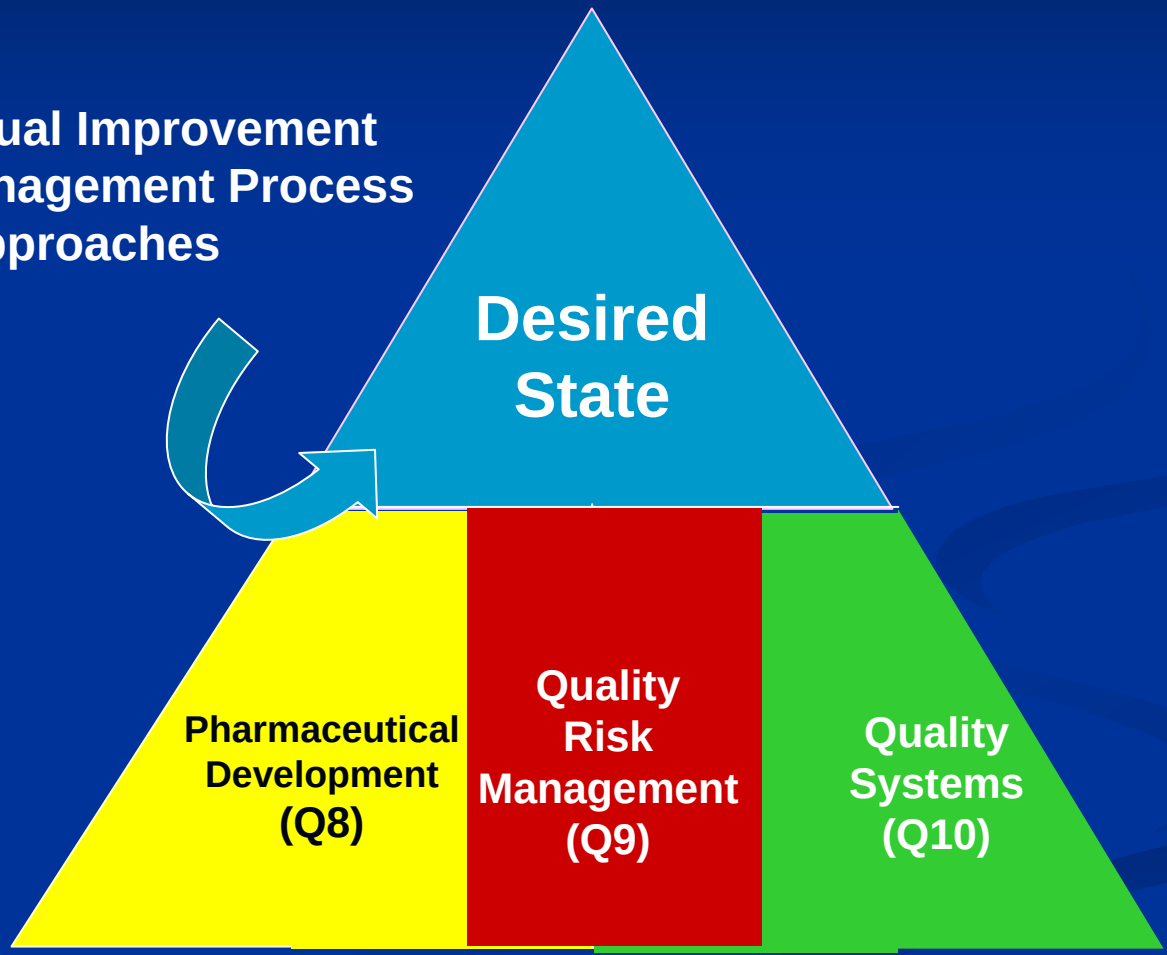
Designed to facilitate continuous improvement

Process control strategy: control of the process performance and continuous process improvement

- Real-time process feedback
- Process improvements within design space
  - Knowledge builds with experience
  - Leverage information/new technologies to improve process efficiency
  - Key opportunity to continuously improve the process. E.g. increased supply, more efficiency

ICH Q8, Q9, Q10: The foundation of QbD

Innovation and Continual Improvement
Optimized Change Management Process
Flexible Regulatory Approaches



Source: Dr. M. Nasr, FDA 12v

Quality by Design relative to ICH

- "Quality by Design" in ICH Q8
  - Concepts aligned
    - Design Space – *Key to understanding*
    - Process robustness
    - Design of Experiments (DOE)
    - Quality management

Critical Concept: Design Space

- Multidimensional combination with interactions
- Input variables (e.g. raw material attributes) and process parameters
- Demonstrated to provide assurance of quality
- Defined by applicant and reviewed by regulator
- Once design space is approved, regulatory post approval change requirements will be simplified
  - Inside vs. outside design space
  - Regulatory flexibility to operate within the design space

ICH Q8

Design Space - Merck Experience

- **Development of Design Space**: ***Science-based Product and Process Design in Development***
  - Enhance process understanding to support science-based approach
  - Integration of drug substance and drug product process development at the interface
    - Drug substance properties designed for downstream manufacturing process
- **Utilization of Design Space**: ***Effective Process Control and Quality System***
  - Use of extensive monitoring during development to enhance process understanding
  - Use science-based control during manufacturing
    - However, process control may be limited by time needed for biological assays

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Design Space - Merck Experience

- **Process Analytical Technology (PAT) is an integral part of Quality by Design**
  - Used in development to gain process understanding
  - Implemented in routine manufacturing to monitor process, control product quality and reduce release testing
  - PAT testing can replace additional laboratory testing

Case Studies to illustrate the use of QbD principles: HPV Vaccine

I. Introduction to Human Papillomavirus
   HPV burden of disease and epidemiology

II. HPV vaccine*
   1. Bioprocess development
      Multifactor experiment
   2. PAT
      Process monitoring

* Aspects of QbD used in development of Merck's quadrivalent HPV vaccine

HPV Burden of Disease

Cervical Cancer

- Leading cause of cancer deaths among women in most developing countries
- Kills over 270,000 women annually, 85 percent in developing countries
- Almost 500,000 new cases detected each year, the vast majority in developing countries
- 99.7% of cervical cancer cases are associated with HPV

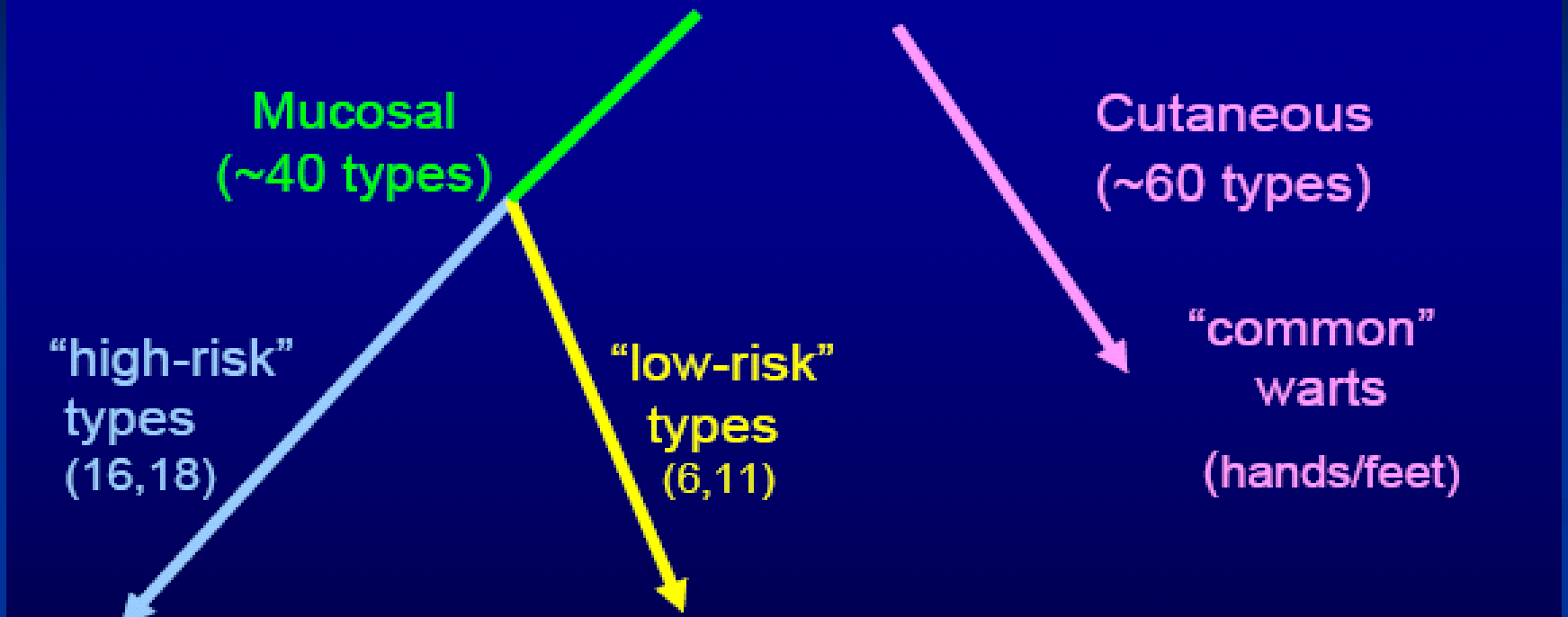
Human papillomavirus and HPV vaccines: technical information for policy makers and health professionals, WHO, 2007

Cervical Cancer Incidence and Mortality Estimates by Region

- 2002 estimated cervical cancer incidence and mortality by region[1]:

1. Ferlay J, Bray F, Pisani P, Parkin DM. Lyon, France: IARC Press; 2004.

HPV types differ in disease association



The present state of bioprocess development

- Increase speed to market
- Greater robustness and process understanding
  - Address process issues early
  - Establish process validation ranges
- More economic processing
- Platform technologies

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Merck quadrivalent HPV vaccine development – GARDASIL®

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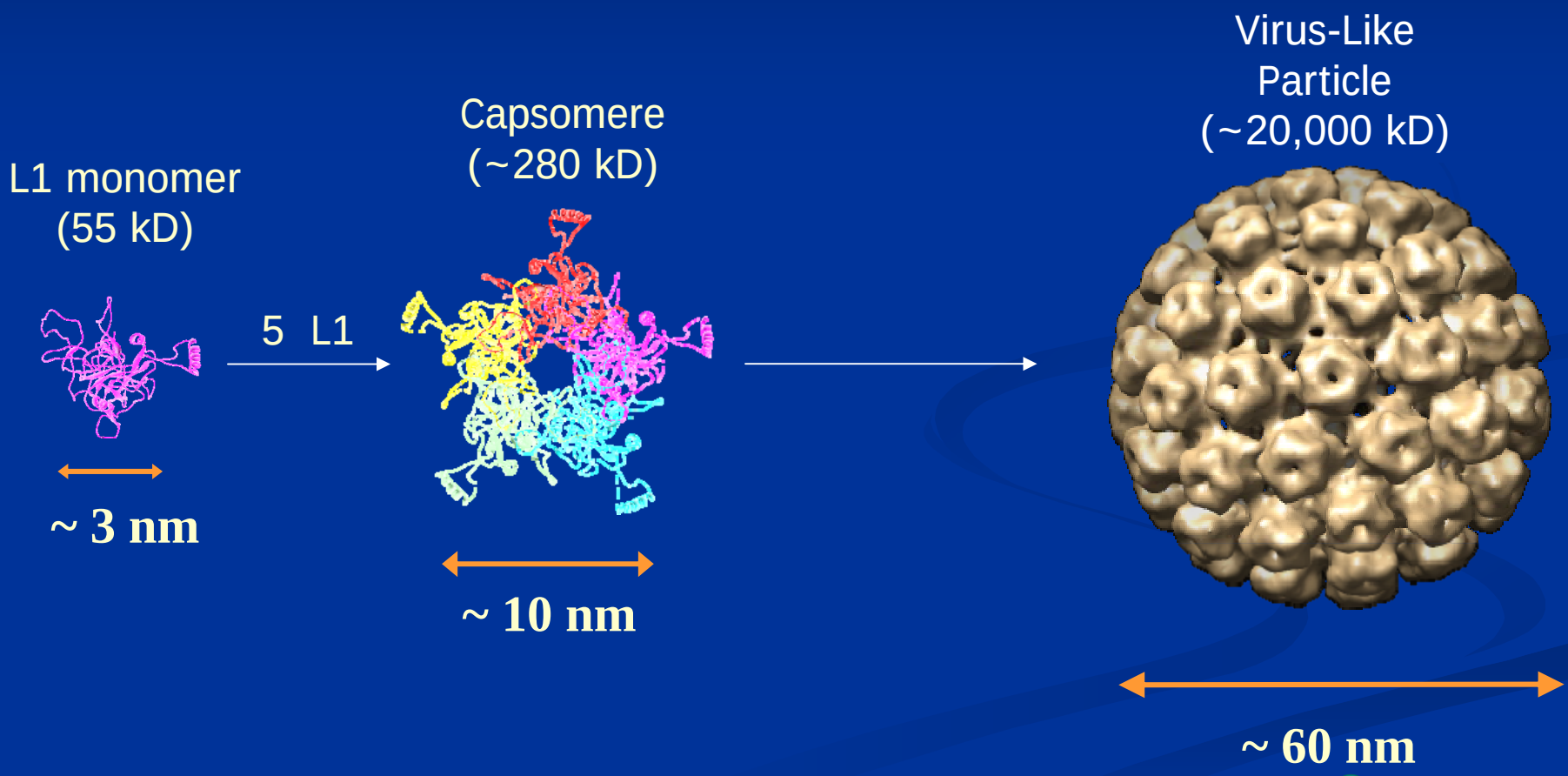
Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) L1 VLP Vaccine

Recombinant HPV Capsid Proteins Expressed in *S. cerevisiae* (Baker's Yeast)



- Crystal structure coordinates courtesy of Prof. S. C. Harrison,Harvard University
- VLP structure courtesy of B. Callagher, Scripps Institute

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Laboratory-scale purification for assessing upstream process changes

Mechanical Cell Disruption

↓

Cell Debris Removal -100's of mL
(Centrifugation or Microfiltration)

↓

Cation-Exchange (CEX)
Chromatography - 80 mL

↓

Ceramic Hydroxyapatite (CHT)
Chromatography - 30 mL

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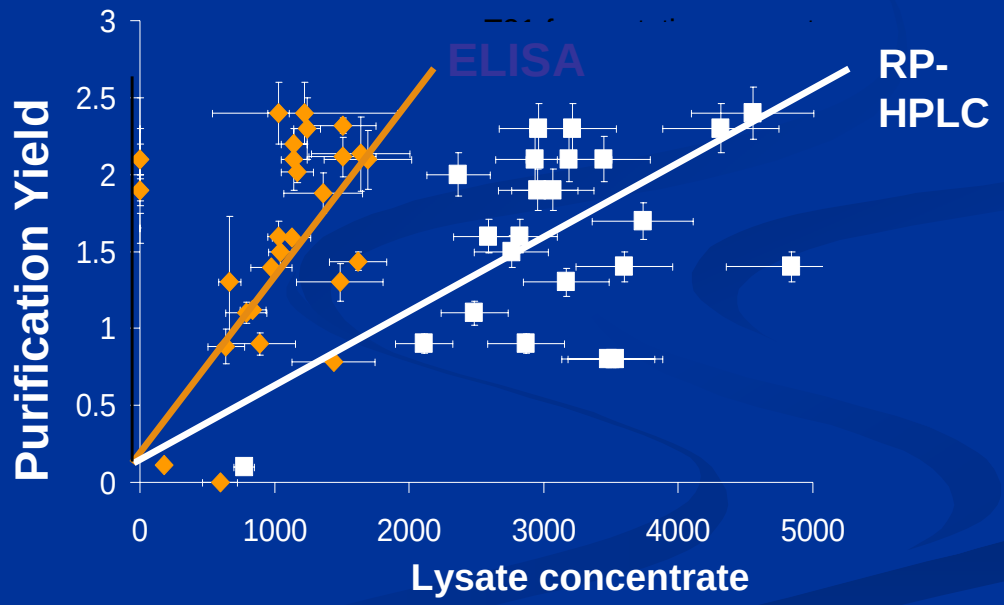
Upstream process development best informed by carrying out a complete purification

- Interplay of upstream effects with downstream purification
  - Clarification
  - Chromatography
    - Low diffusivity
    - Pore inaccessibility
    - Multi-site interaction



Evaluate product recovery and quality

Laboratory-scale purification for rapidly assessing upstream process changes

- Rank-order fermentation performance
- Consistent “baseline” purification for fermentation during downstream process development

- Multi-variable upstream process optimization
  - Range finding
  - Multiple HPV types

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Motivation for ultra scale-down

↑ Speed ↑Throughput ↓ Cost

- Microscale + Automation = faster, more experiments with reduced workload
- Parallel processing
  - Replicates = improved data reliability
  - More content = increased process robustness
- Lower sample/materials requirement
- “Turnkey” system for platform technologies

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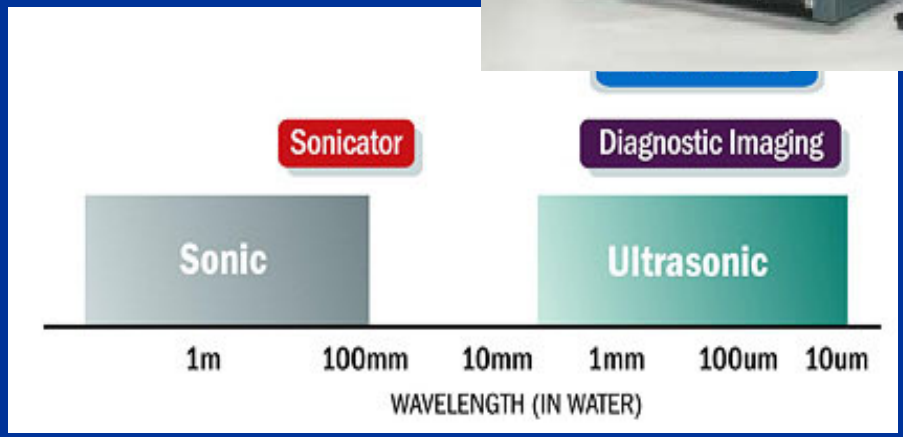
Scale-down of cell disruption: Covaris E210

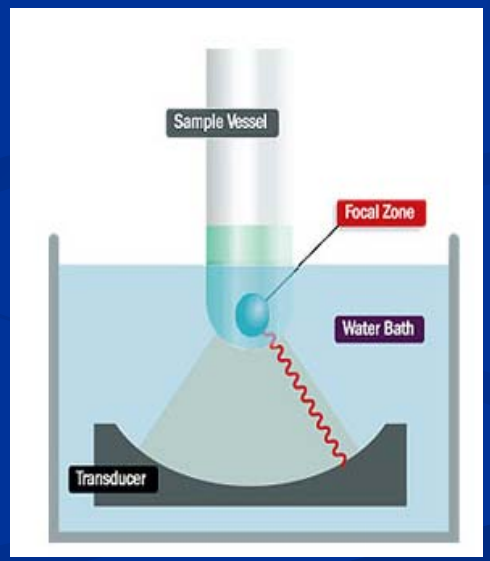
❖Expanding spherical shock wave leads to non-linear sub-m

❖ Collapsing cav ce high speed liquid jets >100m/sec = m

Adaptive Focused Acoustics



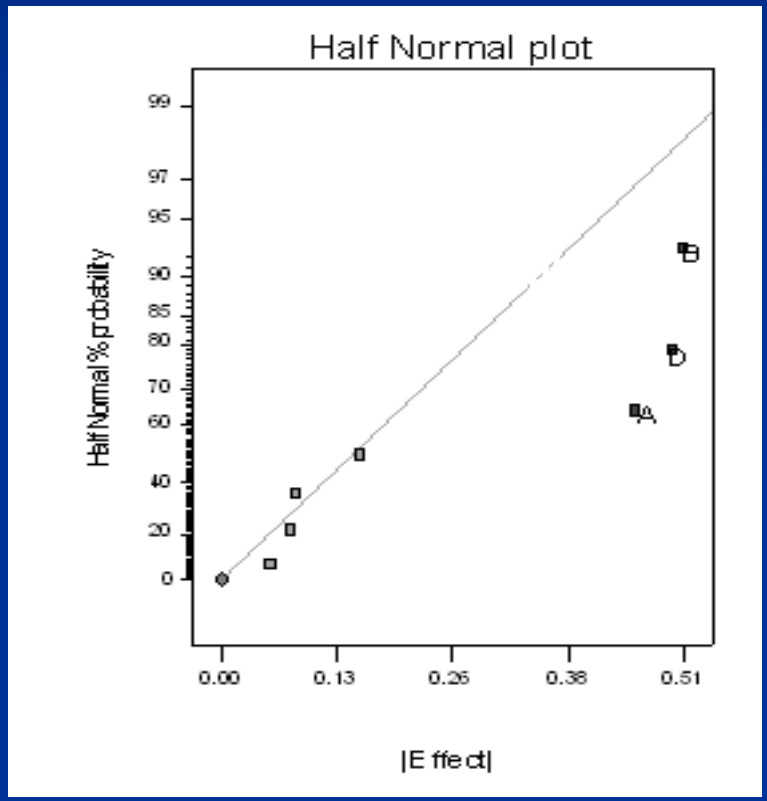
Isothermal, Non-ionizing



Non-contact
Computer controlled

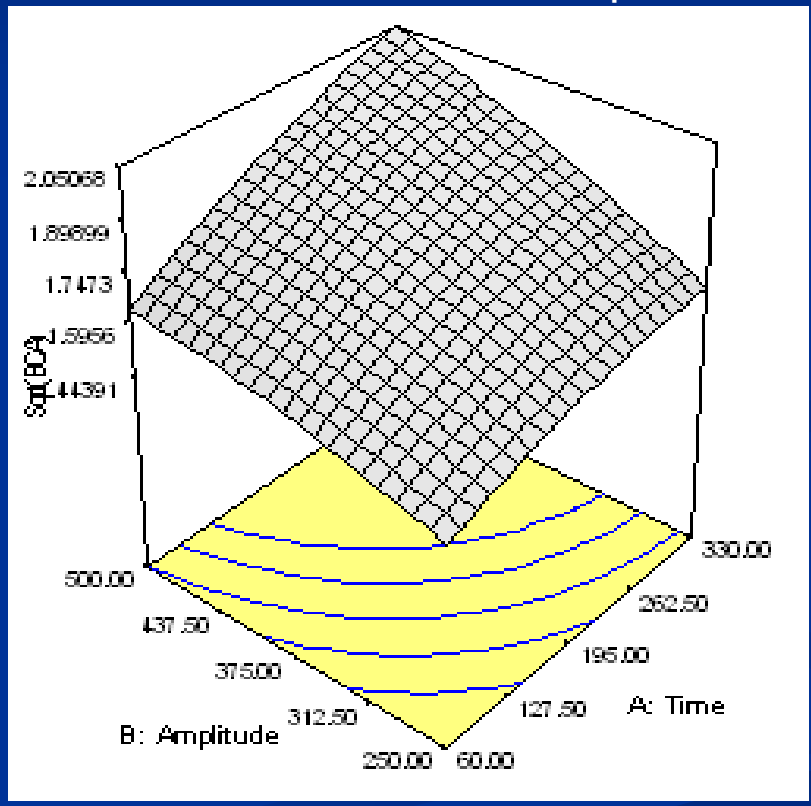
DOE optimization of Covaris parameters

Partial Factorial



Response Surface

Response surface



Critical operating parameters: ↑ Duty cycle, ↑ Amplitude, and ↑ Time

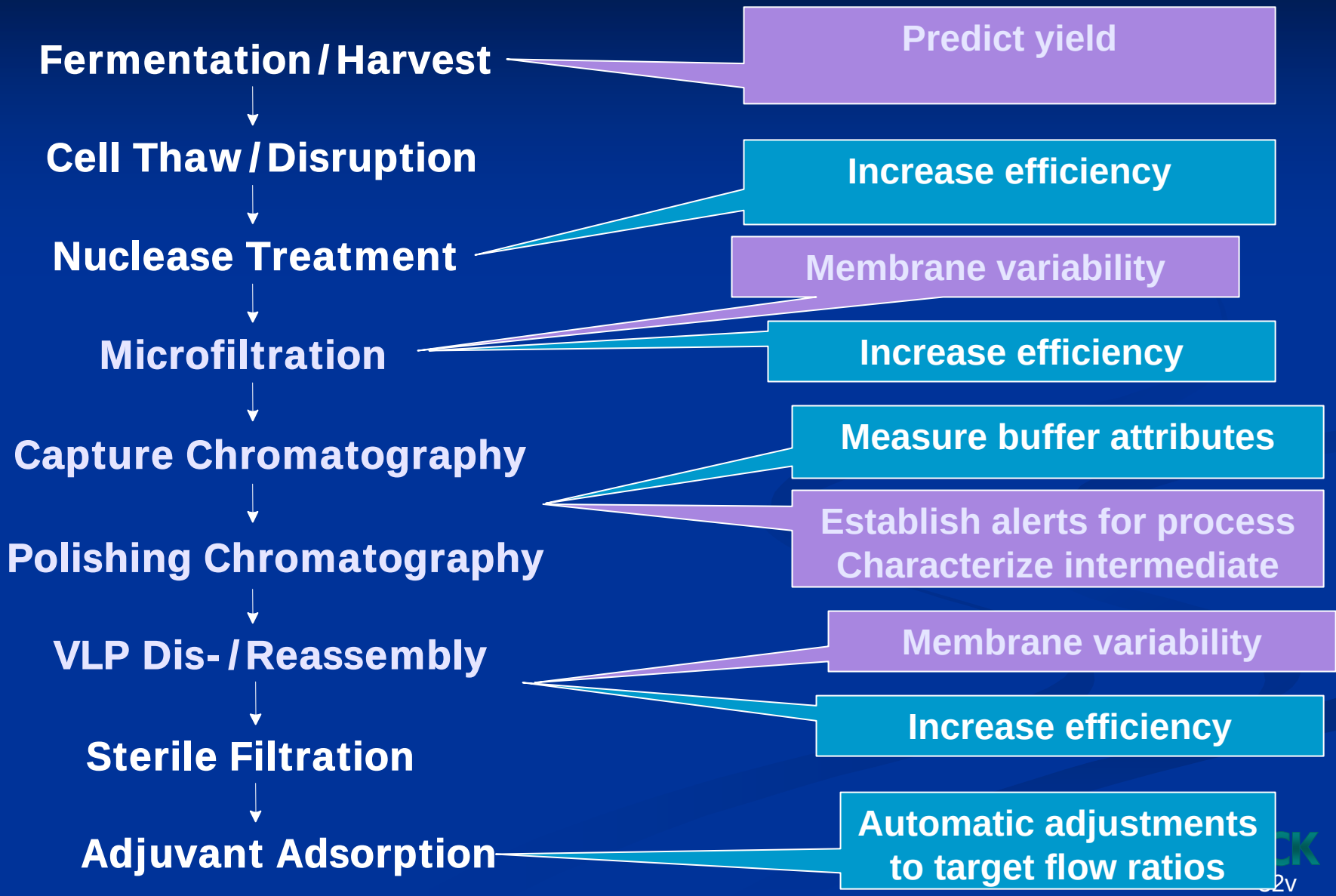
Process Analytical Technology (PAT)

HPV Vaccine Manufacturing Process

Fermentation / Harvest	*Produce in recombinant yeast*
↓	
Cell Thaw / Disruption	*Release intracellular HPV VLPs*
↓	
Nuclease Treatment	*Digest DNA/RNA, facilitate clearance*
↓	
Microfiltration	*Clarification*
↓	
Capture Chromatography	*Remove majority of yeast impurities*
↓	
Polishing Chromatography	*Reduce nucleic acid and host cell proteins*
↓	
VLP Dis- / Reassembly	*Improve VLP stability*
↓	
Sterile Filtration	
↓	
Adjuvant Adsorption	

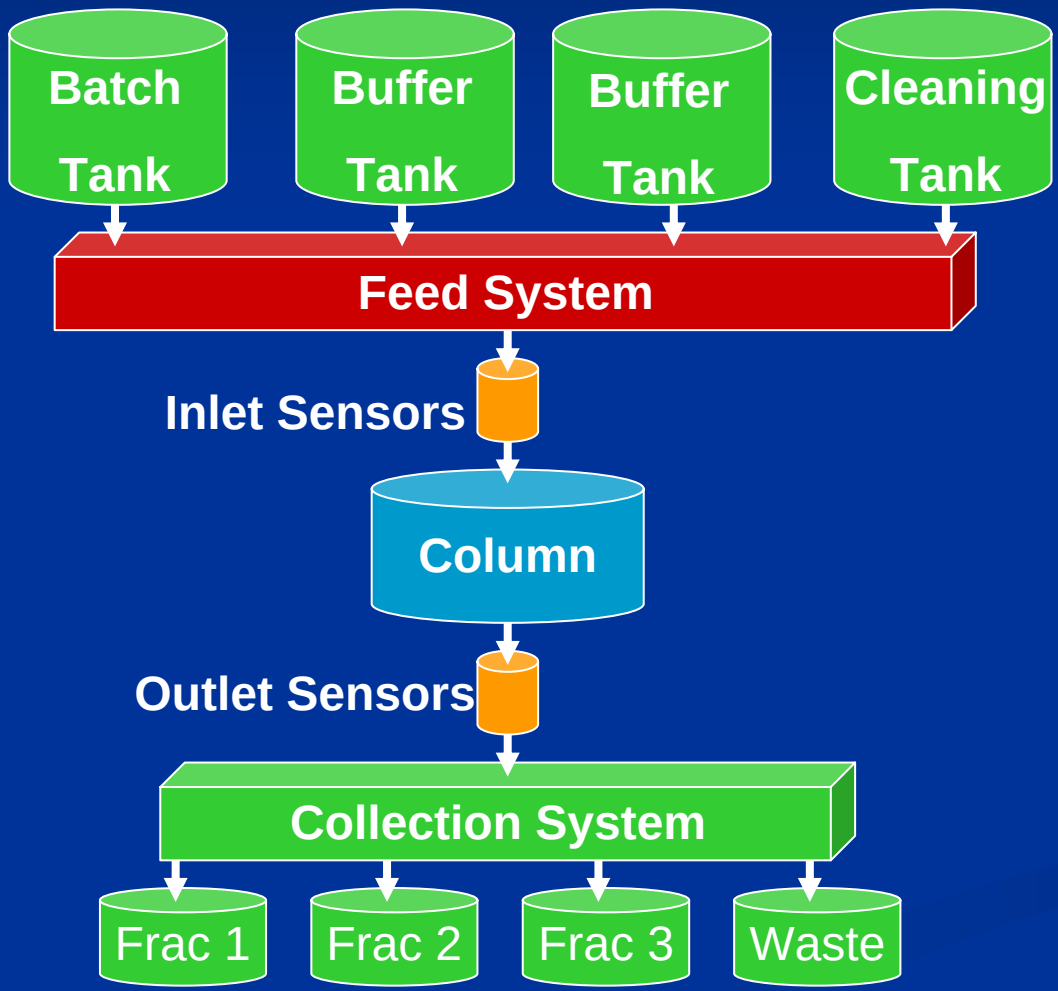
Jansen et al. (Merck & Co.) US Patent 5,888,516, 1999;
Volkin et al. (Merck & Co.) US Patent 6,245,568 B1
Cook et al., Protein Exp. Purif., 17, 477, 1999

PAT Mission #1: Identify Opportunities



Basic Chromatography System

- **Goal: Increase Product Purity**



PAT-Enabled Chromatography

- **Collection based on intelligent criteria**
- **Column quality/packing tied to process performance**
- **Trend analyses across batches to identify sources of process variability/shift**
- Multiple sensors and standardized chromatogram analysis linked with expert systems (warning alerts)

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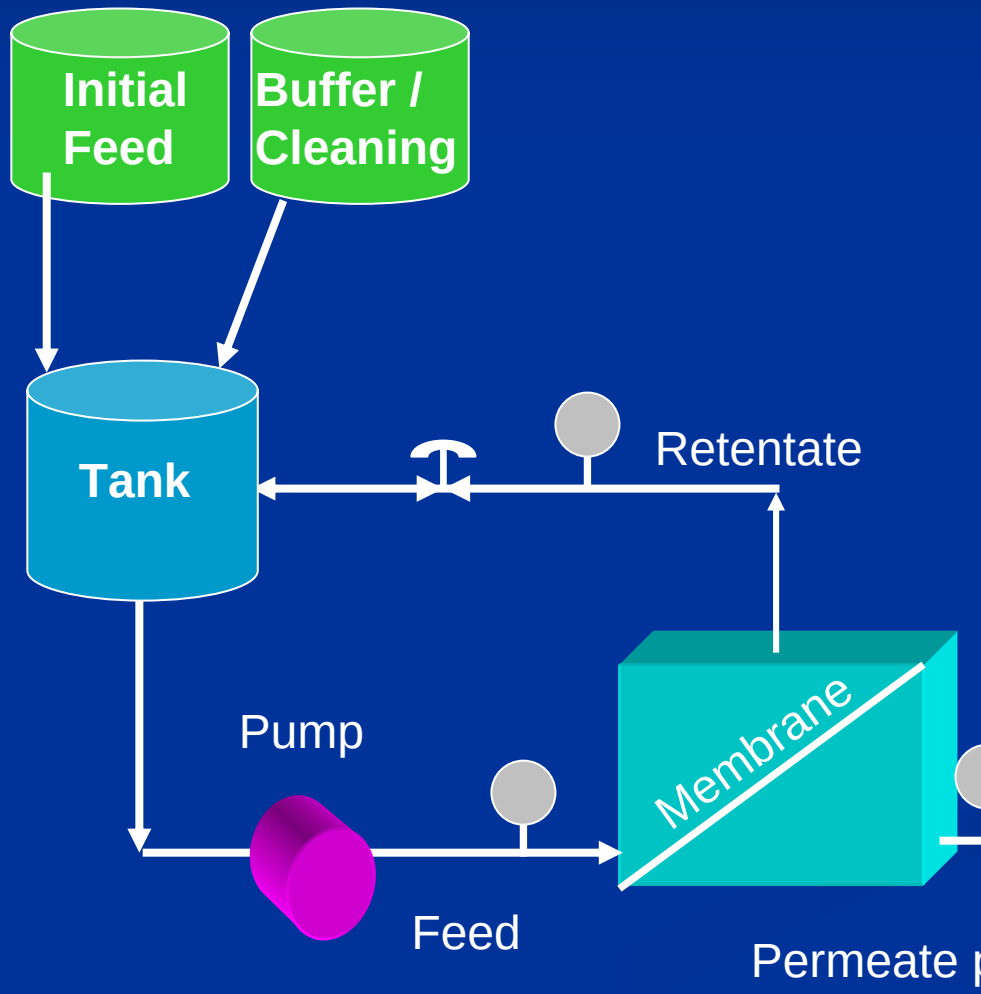
Basics of a TFF System

- Goals of TFF: Concentration, Buffer Exchange, Product/Impurity Clearance

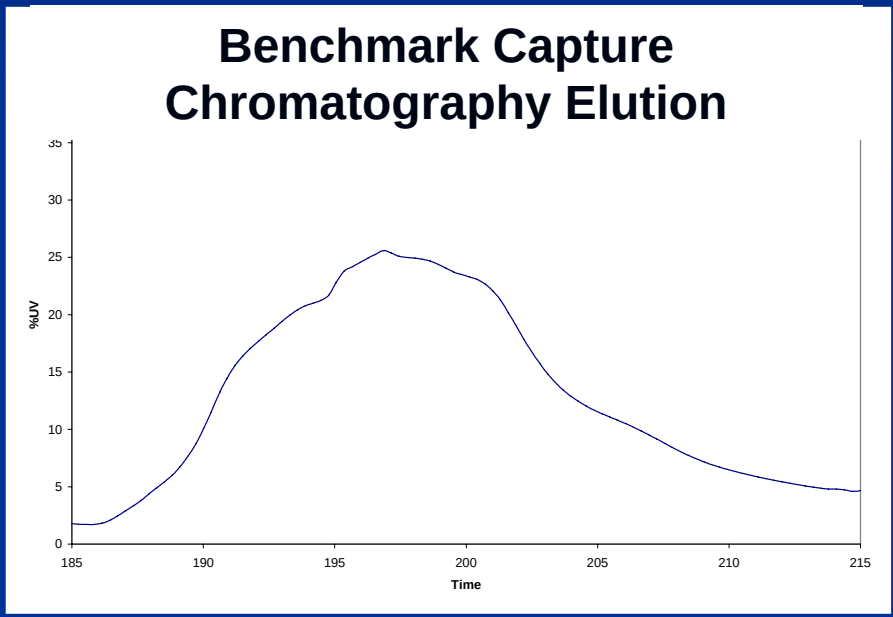


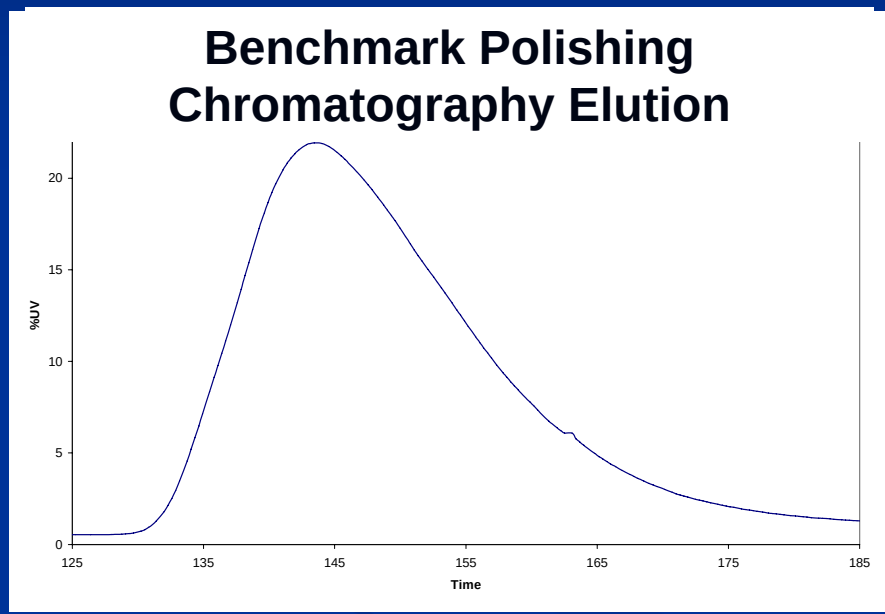
PAT Enabled TFF

- Diafilter until measurement is below target or a key impurity is removed
- **Monitor permeate profiles to ensure filter integrity and consistency**
- **Trend analyses across batches to identify sources of process variability/shift**
- Identify early warning sign from the process using multivariate data analysis

Historical Analysis of Elution Profiles

Composite of all batches

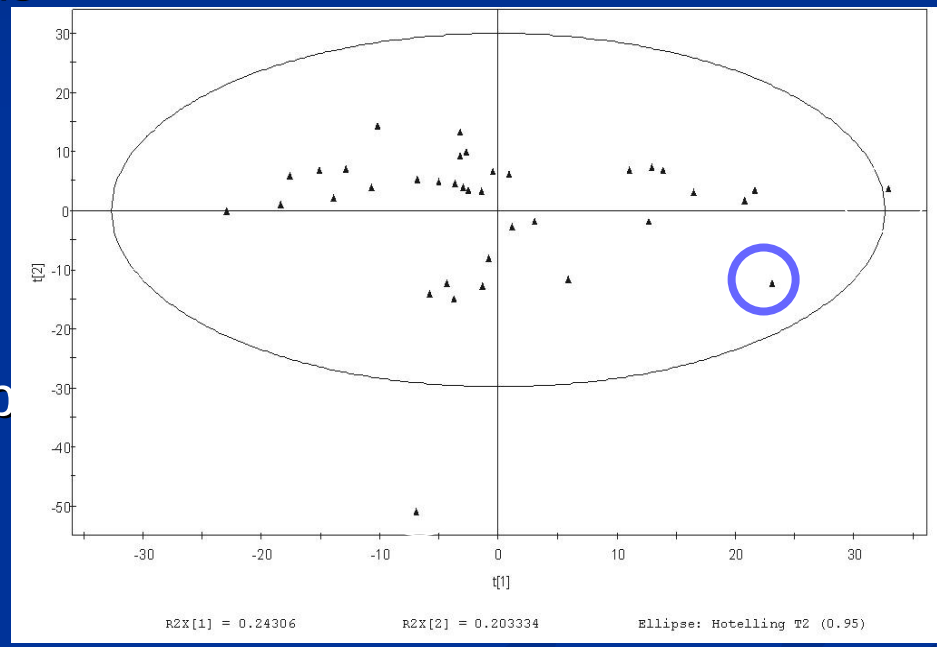




- Profiles can be used to monitor future batches
  - Off-line and/or real-time

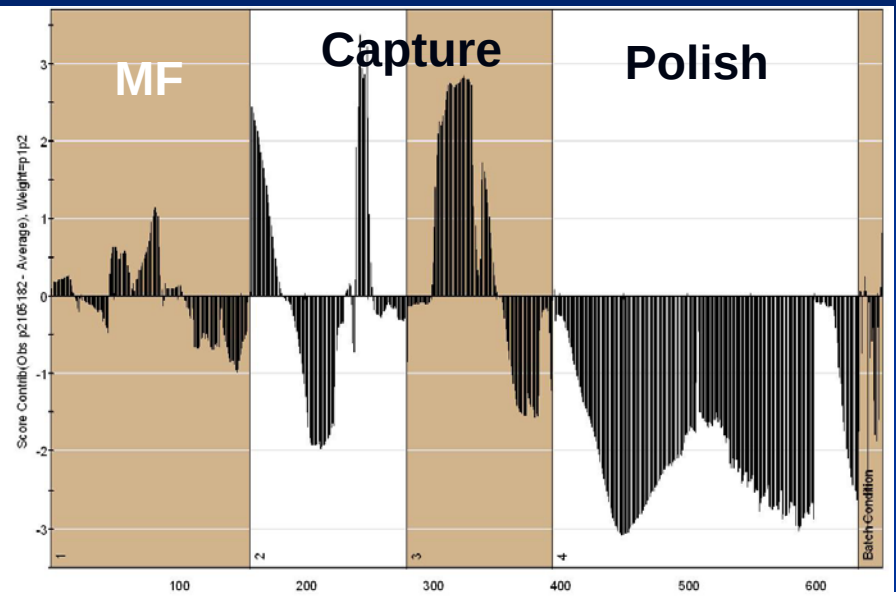
Monitoring of Batch Performance

- Model all batches
  - Principal Components Analysis
- Detect outliers and modify model
- Check future batches against historical batches
  - On-line monitoring/open loop control
  - Off-line end of batch monitoring
- Diagnose out-of-limit batches



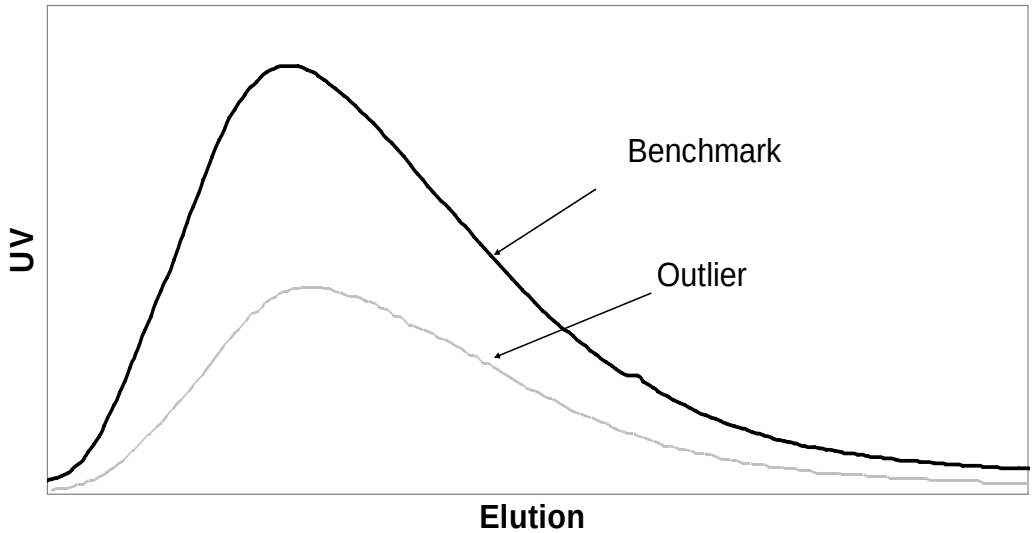
Score Scatter Plot of Batch Data

Identification of Variability



- Majority of difference in polishing chromatography

- Traced to low yielding lot



Summary - PAT Improvements

- Data analysis tool
- Multi-variate data analysis initiated
- Implement feed-back controls
- Collect protein concentration and size measurements of upstream intermediates
  - Track performance throughout process

Summary of Case Studies

- "Fix the problem where the problem lies"
  - Build quality into the process
  - Identify a problem early in the process not by testing the final product
  - Cost savings through less reworks
- Process development was risk-based
- Knowledge gained during development used:
  - To specify appropriate control strategies for the process parameters to minimize risk
  - To develop a rational proposal for streamlined release testing

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Quality by Design - Benefits

- Patient receives consistent high quality, safe and effective products
- Science of pharmaceutical products and their manufacturing processes is well understood
- Industry and regulators focus on critical information
  - Critical to quality aspects
  - Knowledge-based regulatory filings
  - Regulatory approval of design space allows more flexible post-approval process which supports continuous improvement and innovation
  - More flexible and efficient post approval change process
  - Elimination of variations based on process understanding
- Eliminate waste and reduce costs

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Quality by Design - Future Outlook

- Ongoing challenges
  - Achieve clear and common understanding of QbD concept
    - Greater clarity on QbD for biological products
  - Development of regulatory processes
  - Need international harmonization and collaborative efforts
  - Need to build knowledge/experience
  - Shift “wait and see” attitude to an active participation for both industry and regulatory agencies

Desired Future State

- Industry and Regulators fully embrace QbD and integrate the concept into drug product development and commercialization
  - Agency/industry sponsored pilot programs
  - ICH Q8/Q9/Q10: common and consistent understanding and approach
  - Significant benefits realized
    - Real time release
    - Consistent product quality
    - Waste reduction
    - Elimination of variations

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Integrated QbD Approach

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