



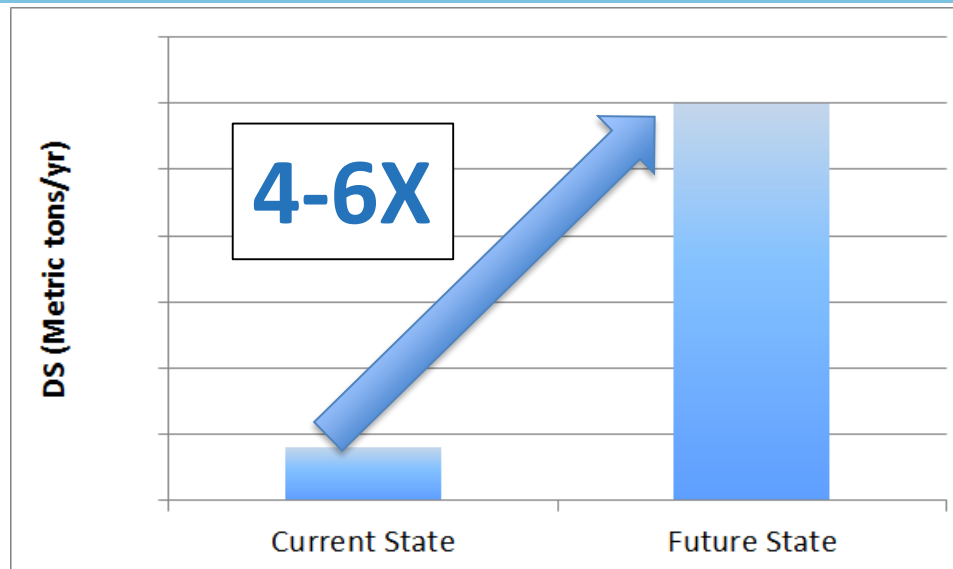
**Biogen Bioproduction for the future  
and demonstrating effective Advanced  
Process controls**

**Diane Wilkinson, Ph.D.  
Regulatory Affairs CMC, Biogen**

Bioproduction Congress, Dublin, 19Oct 2016

# Supporting Biogen's Biologic Pipeline

- Transformative drugs in clinic
  - Alzheimer's - Aducanumab (Ph.3)
- Pipeline drugs require
  - High doses
  - Large volume of product due to high unmet need (many patients)
- Forces us to rethink how we manufacture and control our processes

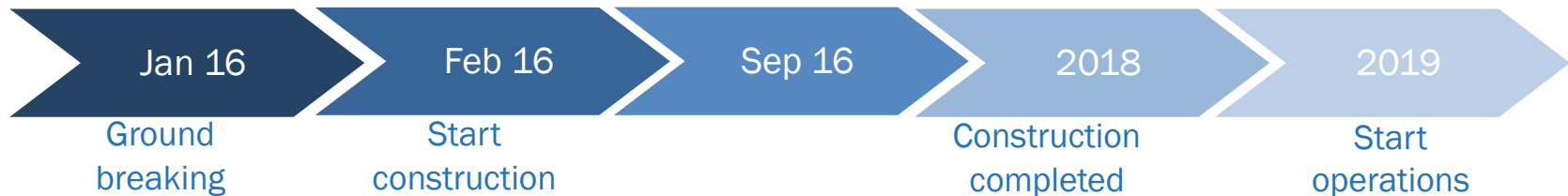


# Next-Generation Manufacturing Project

- ▶ Strong Biogen Pipeline and rising global demand for biologic products.
- ▶ Investment around CHF 1 Billion
- ▶ up to 400 new, highly qualified jobs
- ▶ next generation biologics manufacturing facility which combines Biogen's latest progress in biologics manufacturing technology
- ▶ Expected to produce 10 metric tons per year: 3-5 times more productive than existing facilities
- ▶ Provide 1 million meaningful treatments by 2020



# Timelines NGM Project



# Biogen. Now Hiring

The recruitment has begun! We are looking for people at all levels including Management, Supervisor and individual contributor + entry-level to build new team and departments within:

## Manufacturing Engineering

- Process
- Automation
- Maintenance & Maintenance Planning
- Instrumentation & Control
- Construction
- Facilities & Utility
- Validation

## Manufacturing Operations

- Upstream/Cell Culture
- Downstream/Purification
- Media/Buffer Preparation
- Tech Transfer
- Compliance

Find a life-changing role now: [Biogen.com/careers](https://www.biogen.com/careers)

Biotechnology and pharmaceutical Industry experience and related industries, at Graduate level , as well as initiating a new apprenticeship program for science and non-science students

# State of our current Bioproduction Processes...








- Multiple tools for analyzing raw materials
- Good understanding of critical components in the raw materials affecting product quality
- Understanding of process levers that control product quality
- Linkage of the unit operations
- Feed back/forward adaptive control
- Extensive real time monitoring systems
- Sophisticated models for predicting product quality
- Significant process history for commercial products

# General Approach -APC

- Develop a clear connection of process parameters that affect product quality attribute/s
- Predictive models that can predict product quality
- Process signatures that are indicative of product quality (growth curves, peak shapes, etc.)
- On-line measurement and control

**Use these tools to assure process and product quality consistency**

# Why use APCs

- Better understanding of your process 
- Leverage manufacturing platform data 
- Reduced overall testing 
- Minimise risk of batch failure 
- Reduced time to batch release 
- Speed up time for process development to support initial regulatory filing (MAA/BLA) 
- Reduced regulatory burden post-approval 

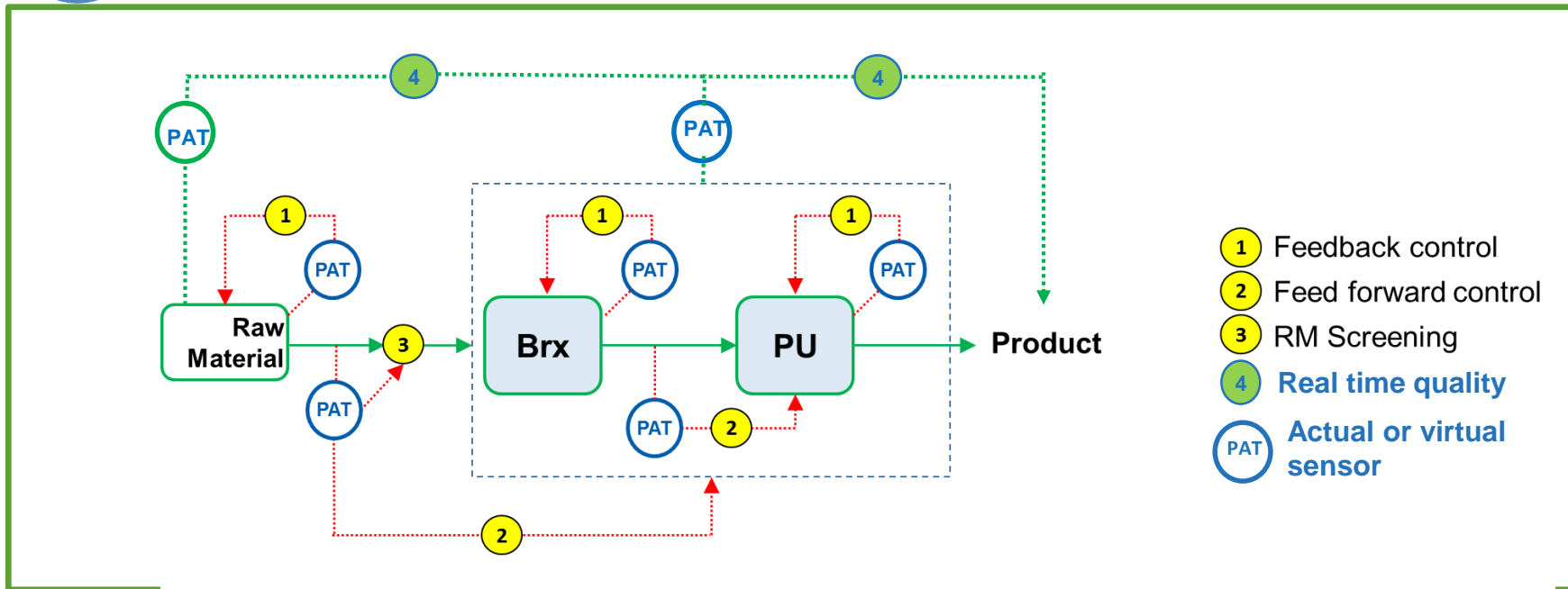
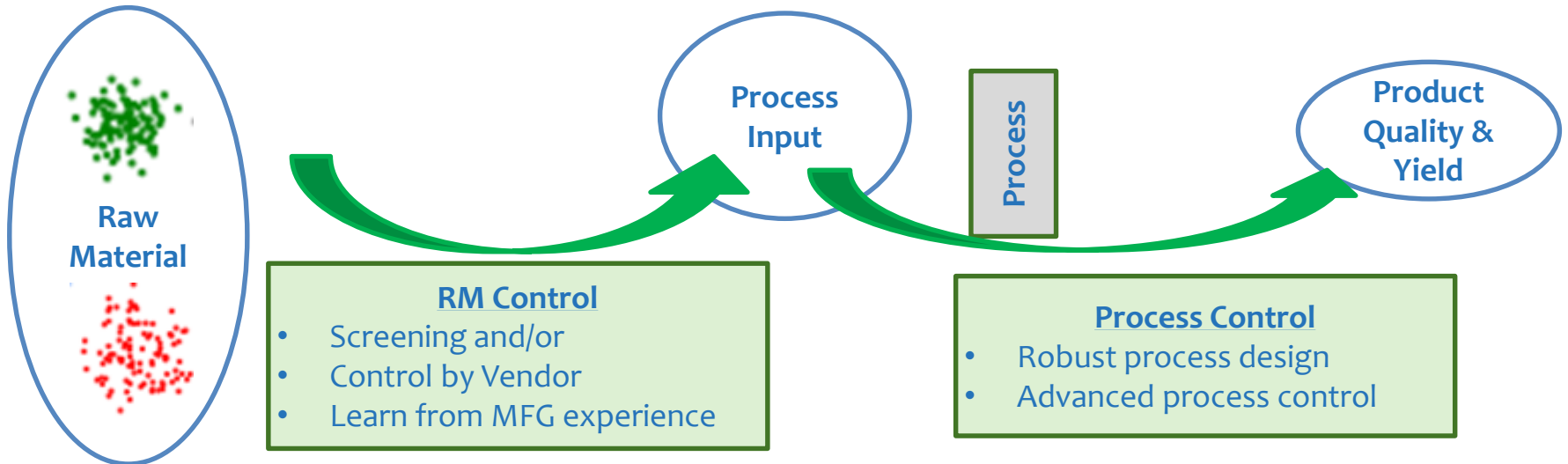
Eventually



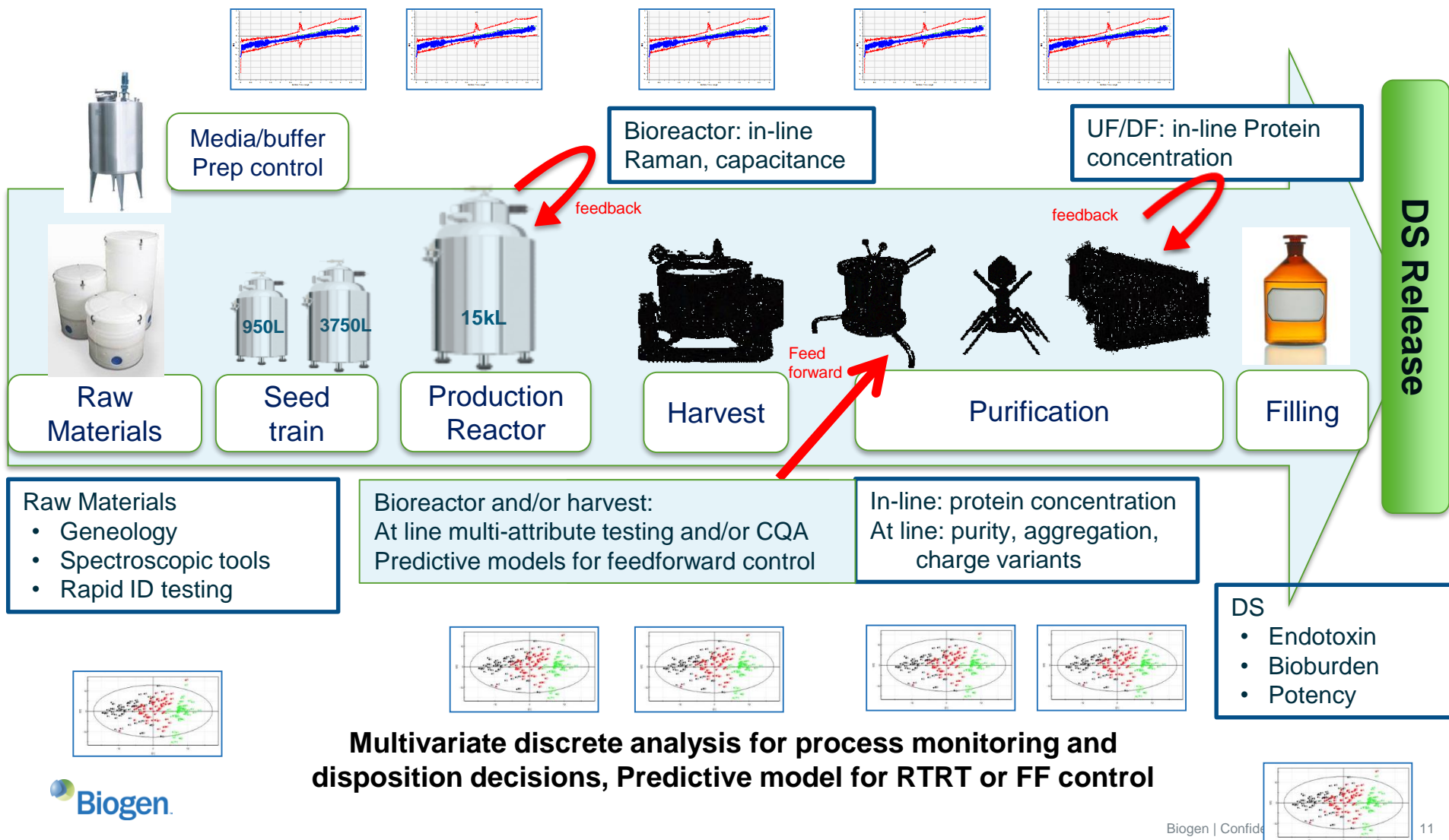
# Implementing APCs

Test	Goal
Raw Material (individual materials and whole media)	<ul style="list-style-type: none"><li>• Minimize sources of variability from raw materials (for consistency in Yield, Product Quality)</li></ul>
Product Quality in Process Intermediates	<ul style="list-style-type: none"><li>• Process understanding</li><li>• Process monitoring</li><li>• Feed back/forward control</li><li>• Real time release</li></ul>
Models based on virtual sensor	<ul style="list-style-type: none"><li>• Direct on-line/at-line process control</li><li>• Multivariate consistency models to assess raw material and process consistency</li><li>• Product quality prediction models to replace analytical testing</li></ul>

# Advanced Process Control



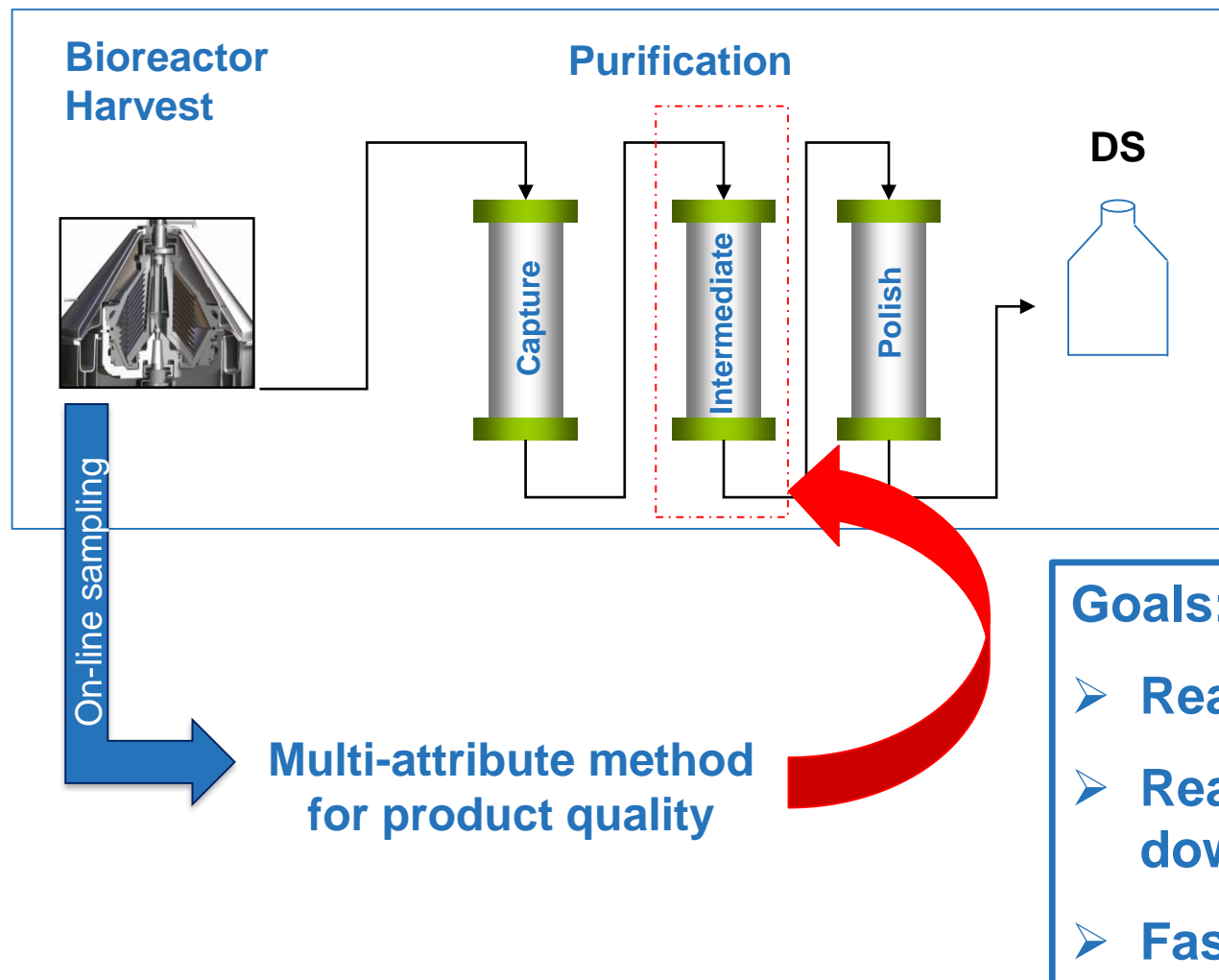
## Real-time multivariate analysis for trending, actions and disposition decisions



# APC in Process Characterisation

- Using Reduced Intact Mass Spectrometry (LC-MS) for Multiple Attribute Monitoring:
  - Test for: %aglycosylated protein and specific glycoforms
  - Collect time-course data during cell culture process characterization (PC)
    - Simple, high throughput method can support the large number of PC samples
    - Data supports predictive model building (and possible control levers, if any)
  - Based on outcome of PC studies, determine if there are feedforward or feedback control opportunities
    - Define testing point(s) and target range of the product quality attributes (including method/process variability)

# APC – Downstream Control



# Feedback Control for Upstream

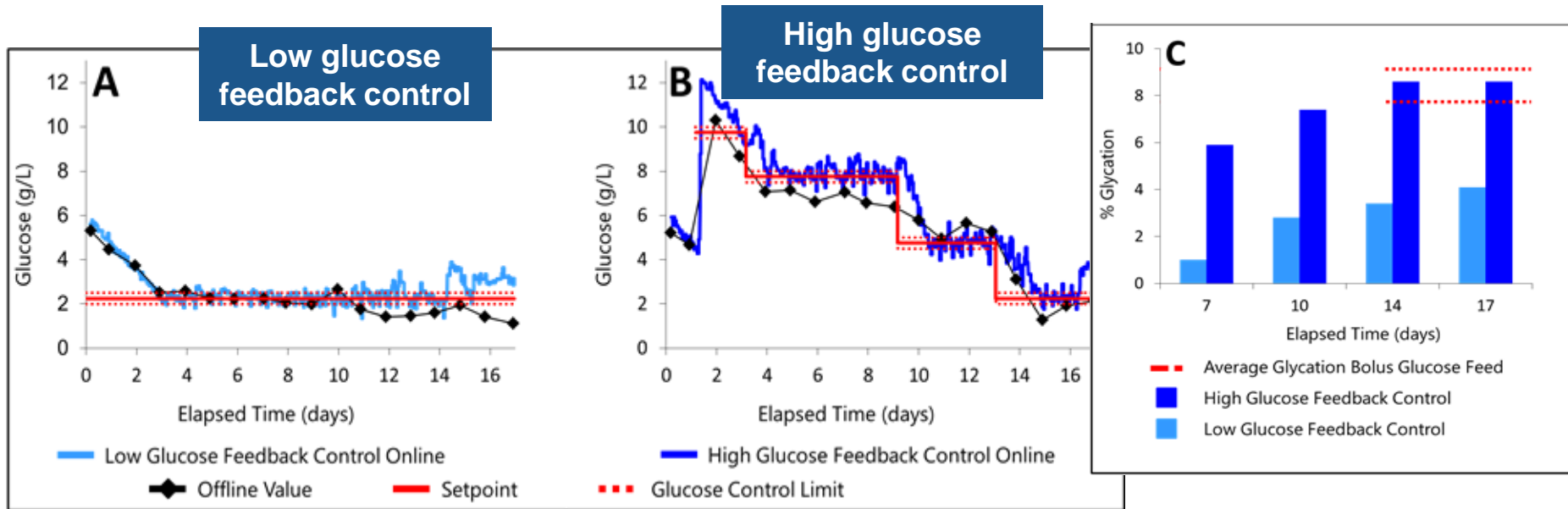
Consistent Cell Growth = Consistent Titre and Product Quality

## Feedback control – Nutrient feed based on actual biomass in the bioreactor

- Feed automation based on cell density (capacitance by dielectric spectroscopy)
- Ensures more consistent culture physiology and performance

## Feedback control – Glucose levels in real time

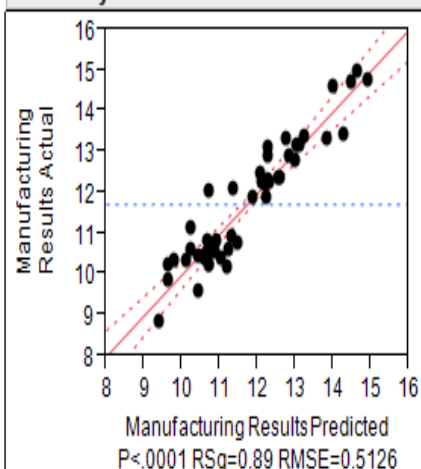
- Feed automation using Raman Spectroscopy
- Maintain glucose at low levels to minimize glycation and restrict lactate formation



# CQA Predictive Modeling for FF Control and RTRT

## Whole Model

### Actual by Predicted Plot



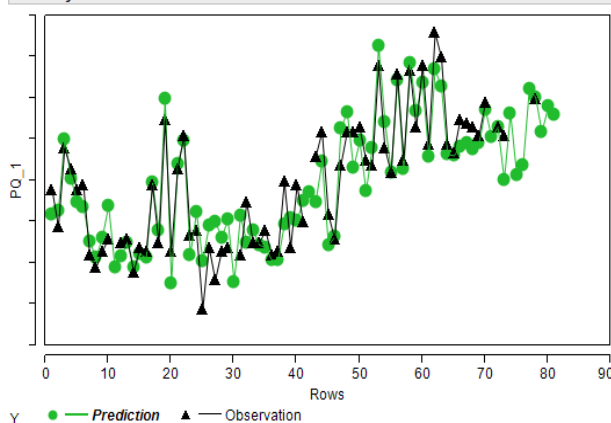
### Summary of Fit

RSquare 0.893083  
 RSquare Adj 0.883364  
 Root Mean Square Error 0.512561  
 Mean of Response 11.72495  
 Observations (or Sum Wgts) 49

### Prediction Expression

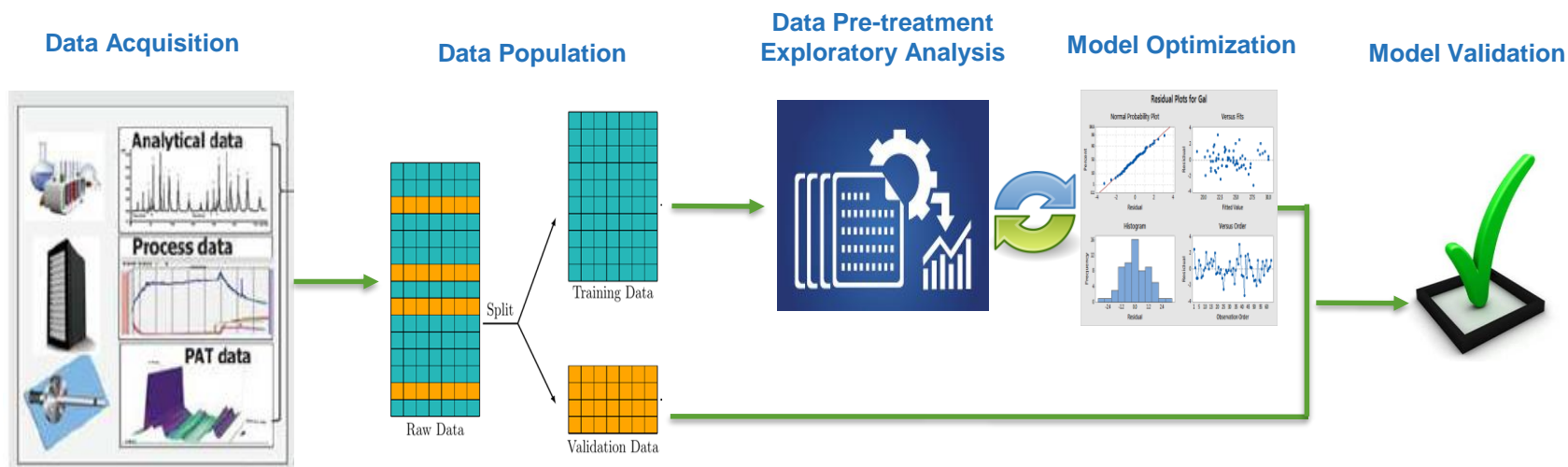
8.50183996558396  
 +2.75376385103244 \*BRX.d2.Lac  
 +4.76311979700429 \*BRX.d3.Lac  
 +1.35125413707671 \*BRX.d4.Lac  
 +0.5480234473038 \*BRX.d2.Glu

### Overlay Plot



Purpose	Traditional	Future State
Product quality prediction in near real time	Release based on CQA test	Release based on Predictive Model

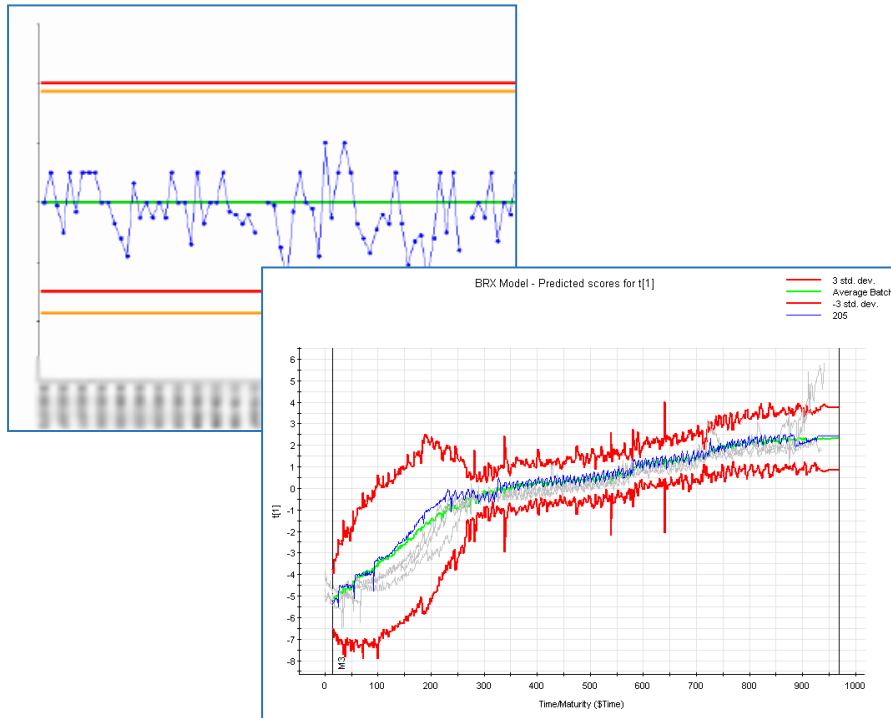
# Predictive Model Development Strategy



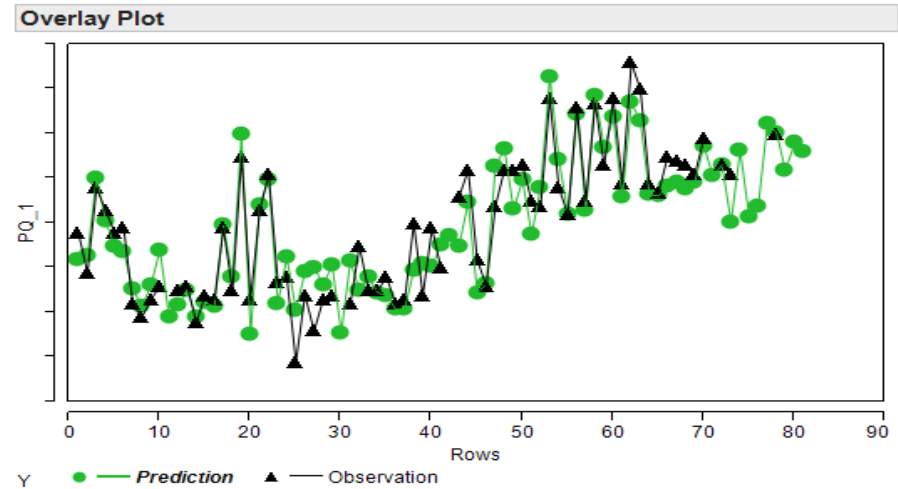
- Model impact on Critical Quality Attributes (CQA) using advanced informatics tools
- Modelability is assessed based on:
  - CQA variability in development/manufacturing experience
  - Assay variability
  - Simple or complex source of variability



# APC – Informatics



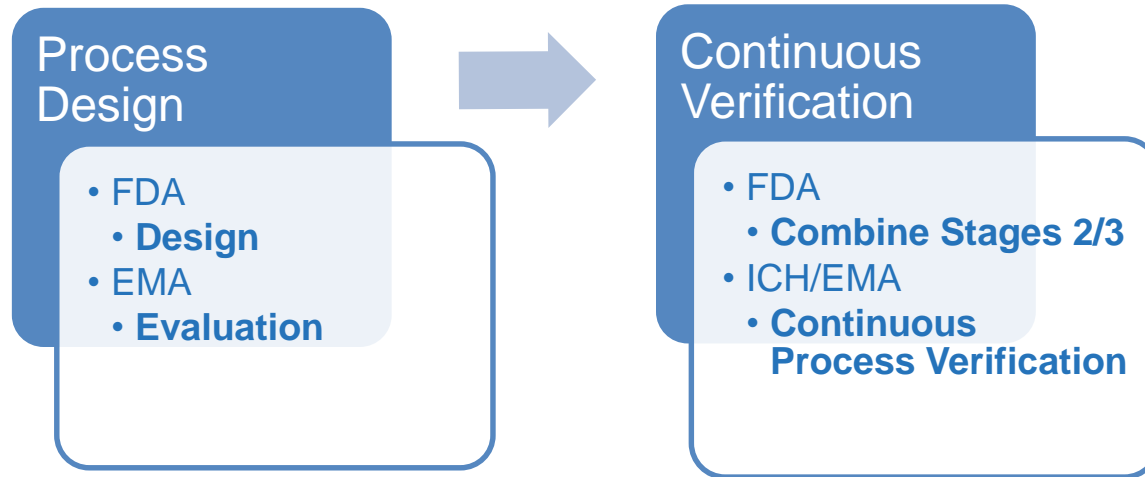
Real Time Univariate and Multivariate  
Statistical Process Monitoring



Advanced Analytics for Predictive  
Modeling of Product Quality

## Real Time Quality

# PV for Advanced Process Control



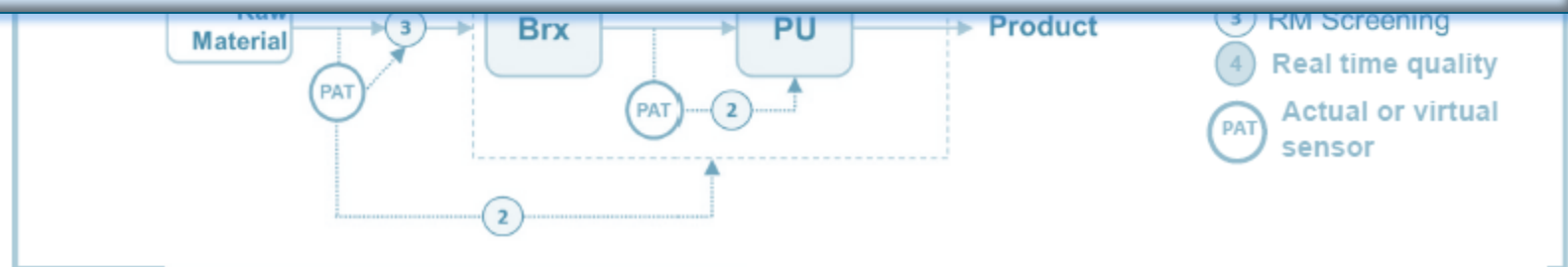
- Performance qualification applied to all batches
- Employs continuous measurement on every batch produced
- Data trending is an integral part of the approach
- Validation based on development knowledge and on-going manufacturing performance confirmed on every batch
- Combining stages 2/3 builds upon established examples (e.g. reprocessing)
- Scientific knowledge and risk assessment reduce the need for discrete re-validation exercises

# Process Validation for APC

- **ICH Q8 “Continuous process verification: An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated”.**
- Performance qualification applied to all batches
- Employs continuous measurement on every batch produced
- Data trending is an integral part of the approach
- Validation based on development knowledge and on-going manufacturing performance confirmed on every batch
- Scientific knowledge and risk assessment reduce the need for discrete re-validation exercises

# What is the future...

- ❑ Much greater level of process understanding and control
- ❑ Process signatures will help predict product quality
- ❑ Adaptive control will be a critical element of process consistency
- ❑ RTRT will be the new norm
- ❑ Process validation through continuous process verification



# Acknowledgements

- ▶ Eliana Clark – Manufacturing Sciences
  - Sarah Yuan, Rob Guenard, Gregory Stromberg,
  - Steve Doares, Canping Jiang
- ▶ Valerie Tsang – Technical Development
- ▶ Rashmi Kshirsagar - Cell Culture Development
  - John Paul Smelko
  - Alan Gilbert
- ▶ John Pieracci – Process Biochemistry
  - Brad Stanley
- ▶ Li Zang – Analytical Development
  
- ▶ Patrick Swann – Regulatory Affairs