Harnessing the Power of Analytical Sensors in Pharmaceutical Manufacturing: Past, Present, and Future Goals

Karin Balss, Ph.D.

Scientific Fellow

Advanced Technology, Technical Operations

Janssen Pharmaceuticals

Martin Freeman, Untitled
Diagnosed with AIDS in 1990, Martin lives in
San Francisco where he continues to create new pieces.

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

The goal of the workshop is to identify and discuss potential innovative technologies that could be realistically implemented in the next 5-10 years.

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (FDA 2004)

"The Agency considers PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality."

Role of Sensors in APC and Quality

Advanced Process Control: Components and outcomes

- Multivariate Monitoring & Control
- Advanced Sensors
- Mechanistic modeling:

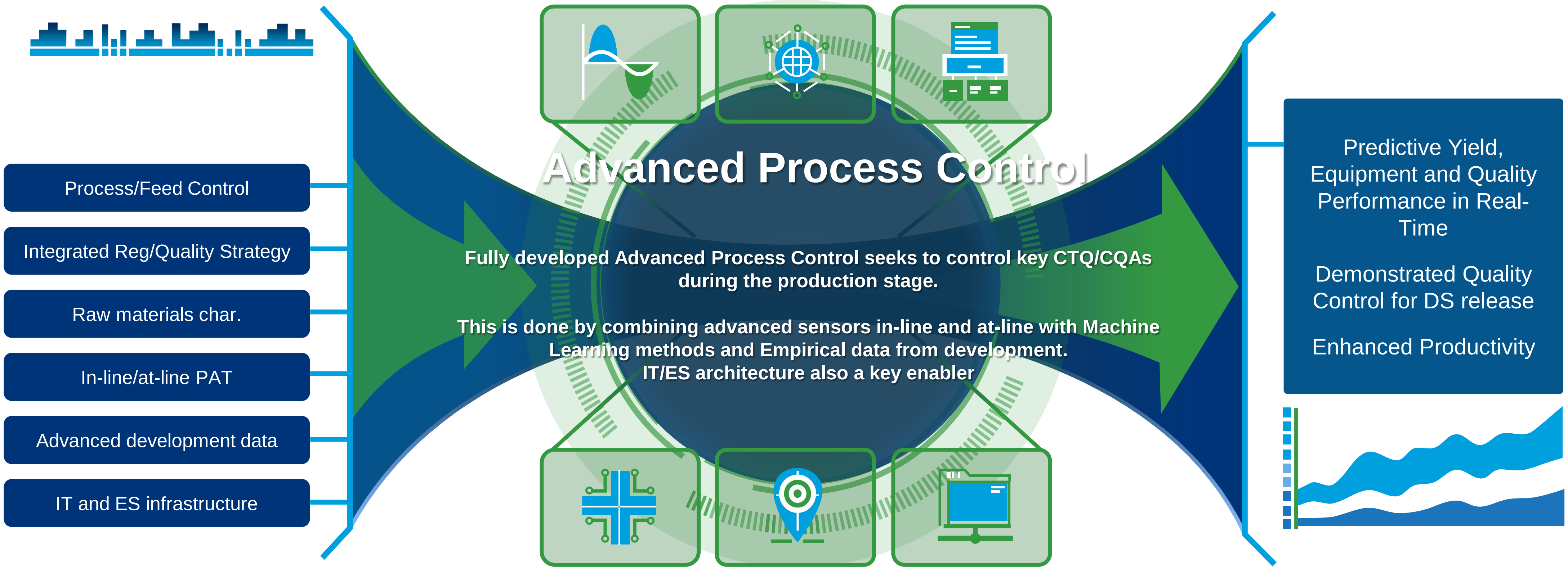
Data infrastructure

Development data & understanding

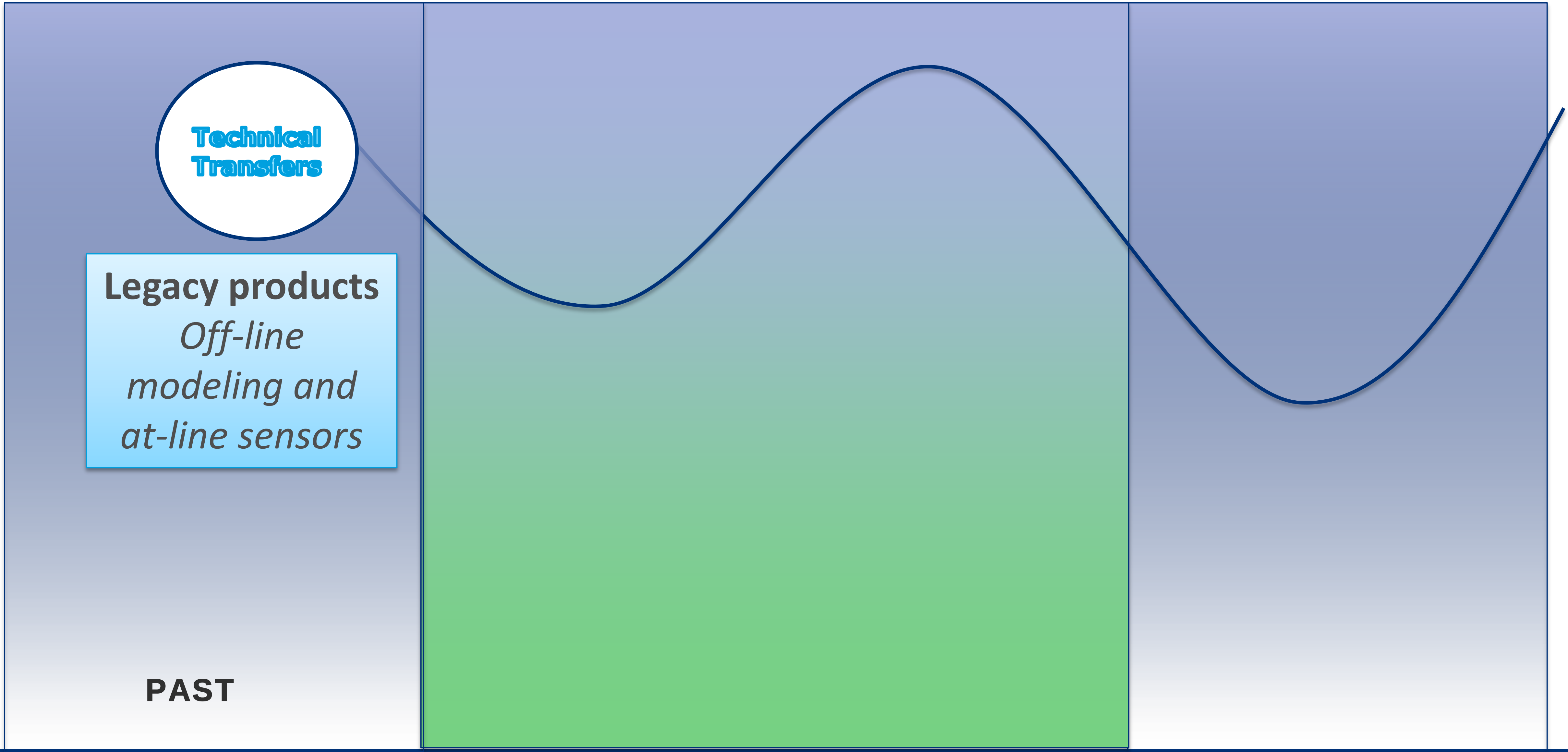
- Real Time Release
- Real time quality control
- Lean Technology Transfer
- Product digital fingerprints

- Faster more agile supply
- Enhanced Quality Assurance

One way to reduce QC testing is with the use of Advanced Process Control



Sensors in Manufacturing



janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Overall technical transfer strategy

- Granulation → mechanistic model and PAT
- Blending → PAT
- Tableting → statistical model
- Coating → mechanistic model

- Models and sensors provide process manufacturing guidance within PAR
- Offline Models, PAT At-line, in-line PAT
- Models and sensors create the digital twin of your process

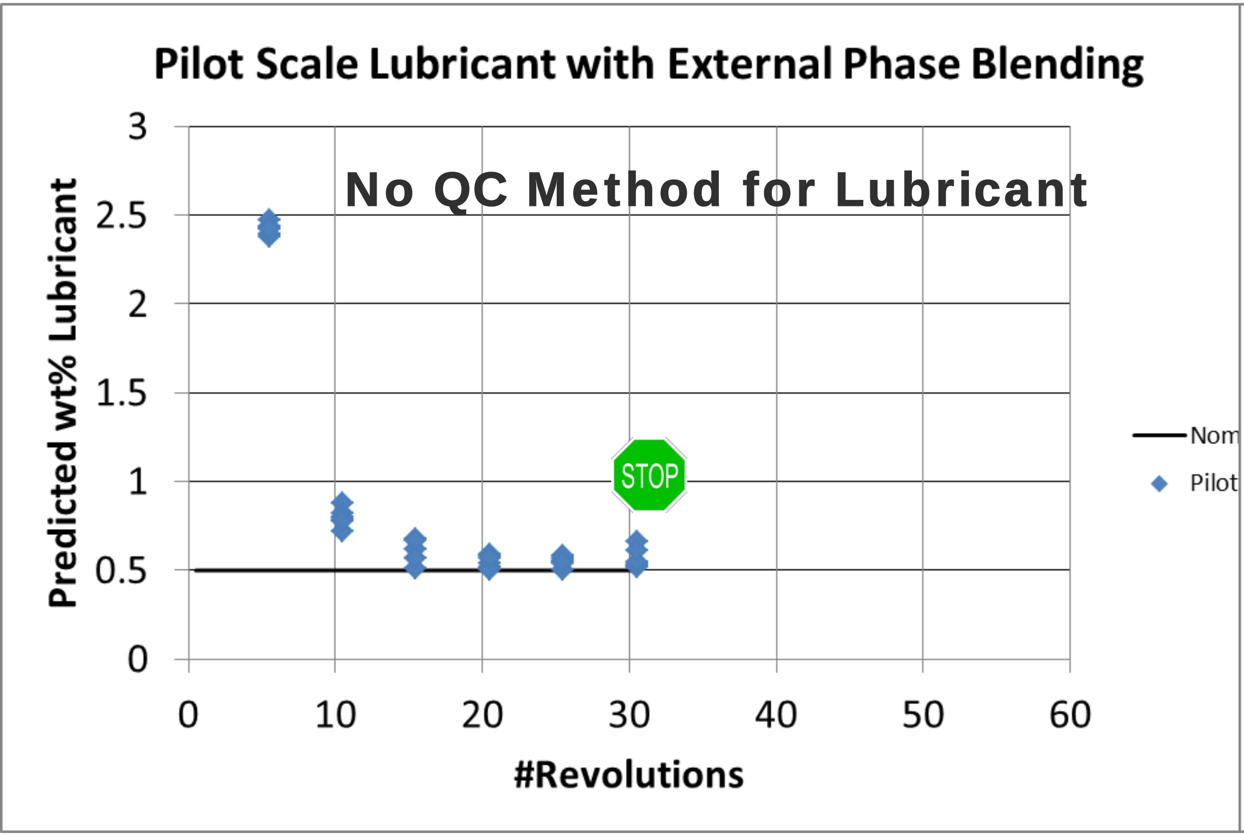
Key Opportunity:

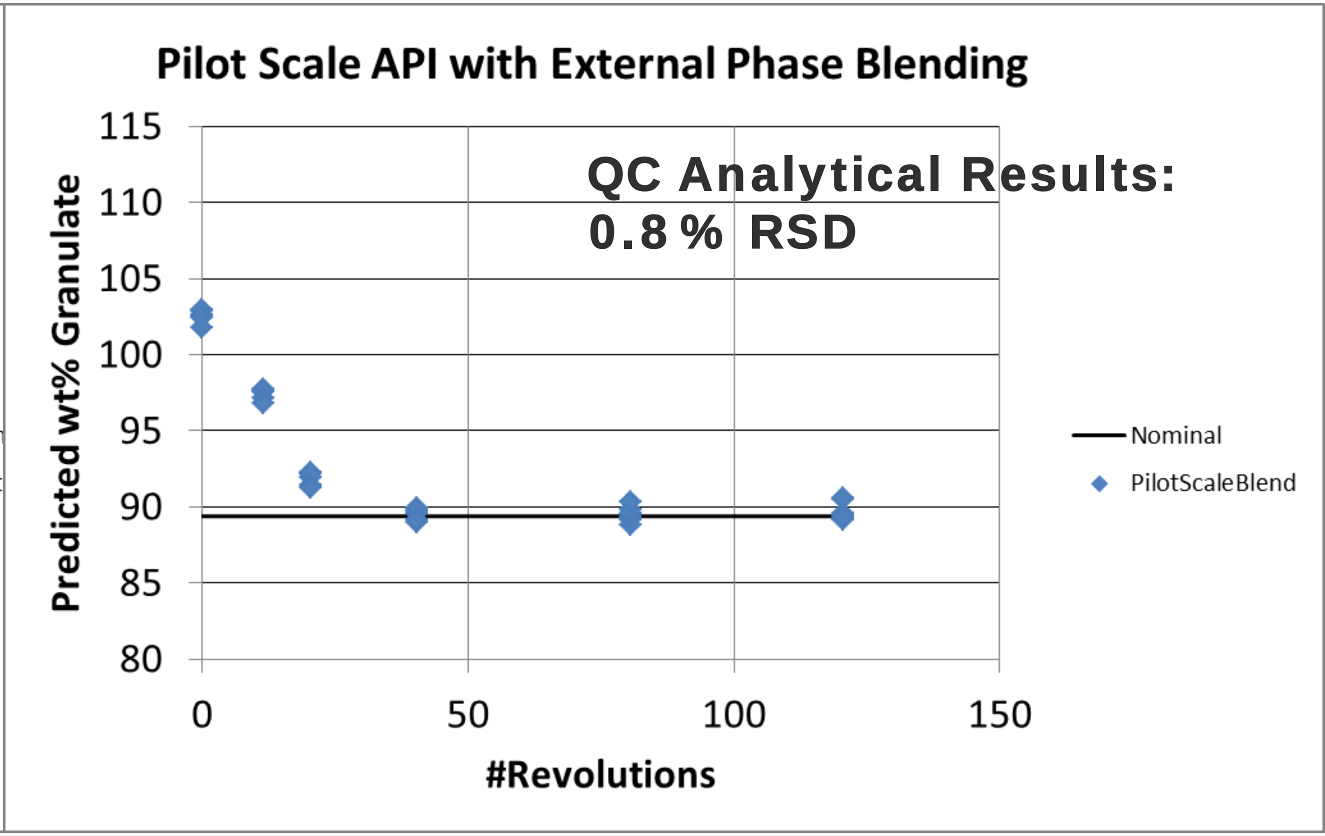
5 characterization batches

1 characterization batch

We're only as strong as the weakest link!
If 3 batches are needed for blending, we must do 3 batches of everything

Lean TT with PAT to Monitor Blending

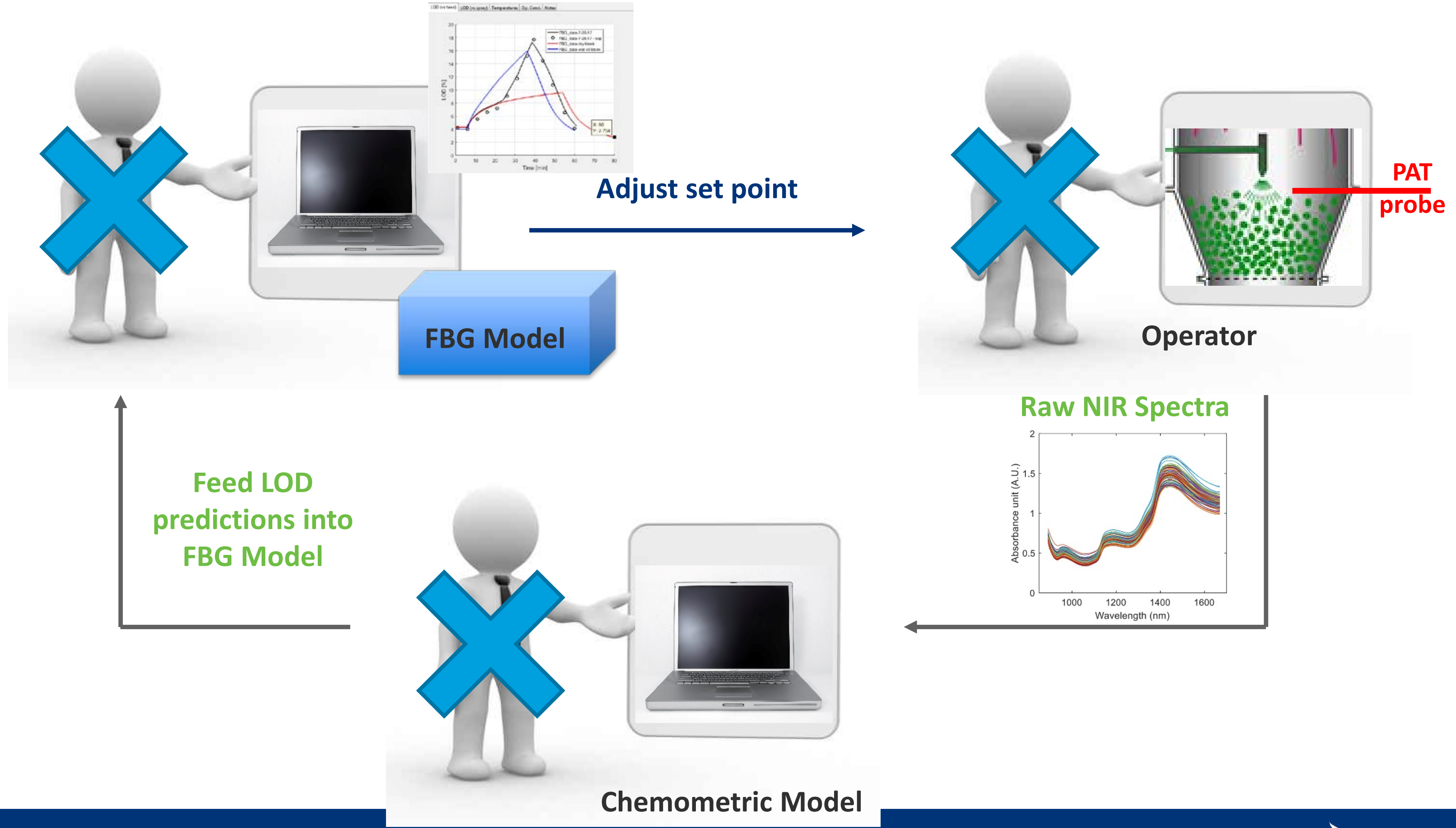




Without PAT: Guess and Compress, Compression unit operation is the first indication if lubricant not blended properly

With PAT: insight into lubrication blending

APC example: Open/Closed – Loop Feedback Control



APC (Modeling and PAT Sensors) generates value during Technical Transfers

Direct cost savings

FTE requirement reduction

QC sample reduction

Real time process corrections were enabled through the digital twin

More process data obtained

Project risk reduced

Reduction of material usage and waste

Project timeline reduced

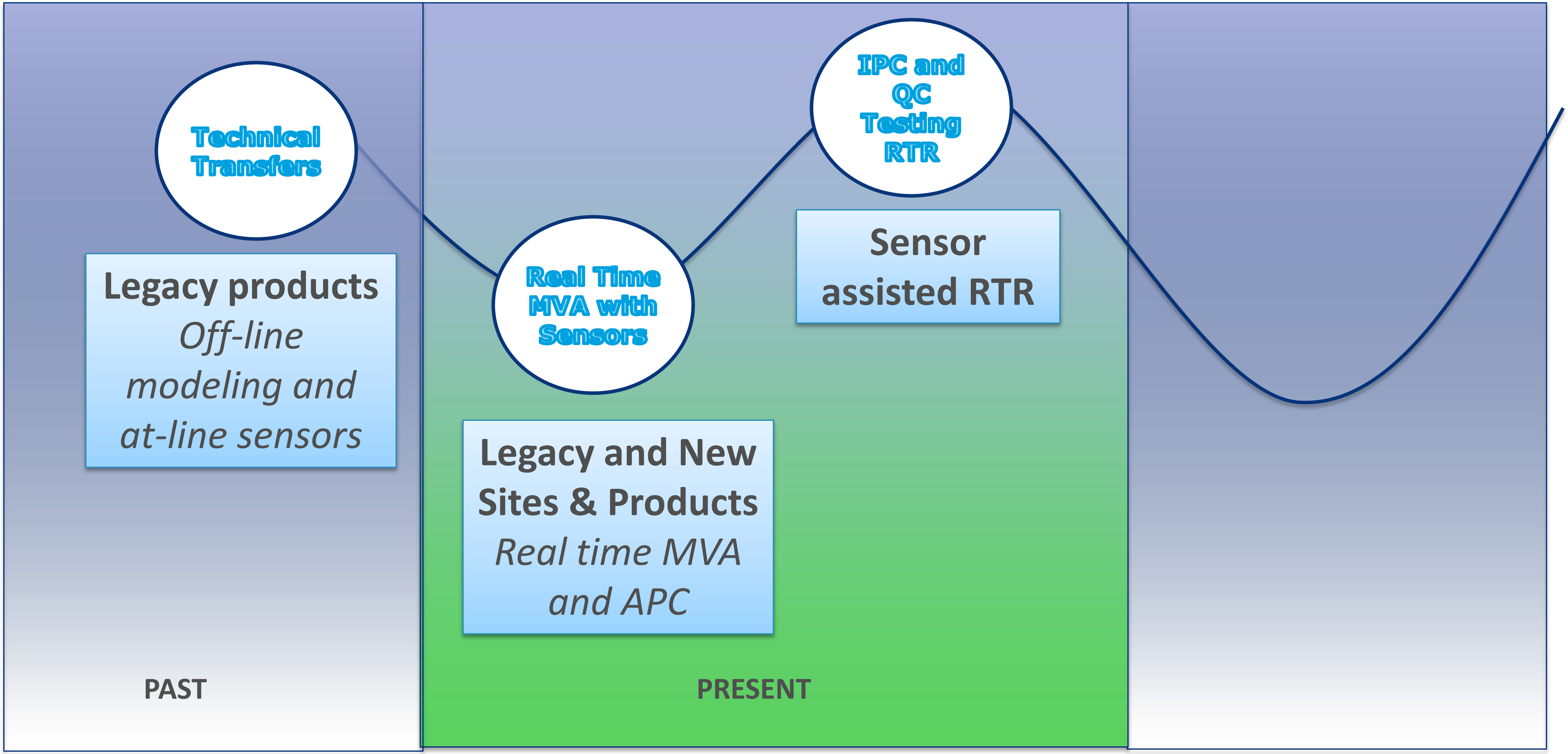
Examples of Sensor Deployment Solids Manufacturing

Unit Op	Sensors	
Raw Materials	Vibrational spectroscopy/X-ray fluorescence	Release Testing
Blending	Vibrational spectroscopy/fluorescence	Monitoring
Fluid Bed Granulation	Moisture/PSD NIR/FBRM	Monitoring, APC
Roller Compaction	Vibrational spectroscopy/fluorescence	Monitoring
Compression	Vibrational spectroscopy/fluorescence	Release Testing
Coating and Printing	Visual AI, spectroscopy	Feasibility

Direct, chemically specific, quantitative measurement of product CQAs with sensors

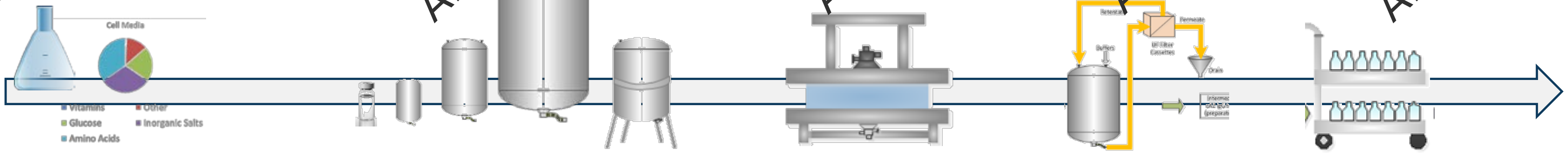
PAT technology mature, numerous vendors, established GMP implementation

Sensors in Manufacturing

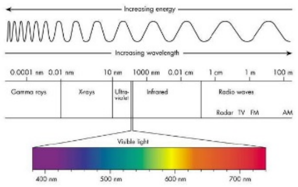


Examples of Sensor Deployment across LM API

Release Testing | IPC Testing APC | IPC Testing APC | IPC Testing APC | IPC Testing APC

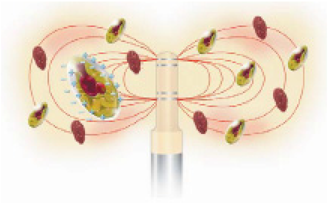


Raw Material | Pre-culture, Brx, harvest | Chrom | UF/DF | Formulation

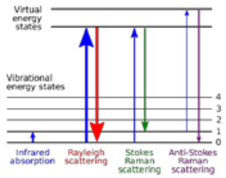


Spectroscopy

Content, finger print, raw ID

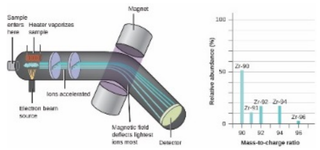


Capacitance
Biomass

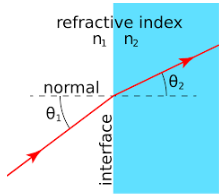


Vibrational Spectroscopy

Media comp, titer, CQAs, finger print



Mass Spec.
Media comp, titer, CQAs



Refractive index
Conductivity
UV
Media

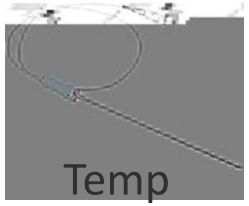
Example Bioreactor Operations: The Sensing Status Quo

Critical process parameters: Temp, pH, DO, CO2

What is typically monitored/controlled?

pH

DO



Temp

biocap

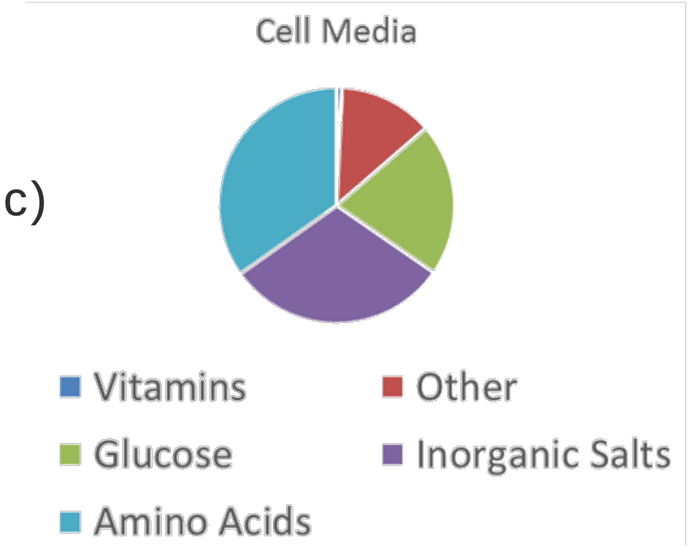
OD

CO2

mass

Sharper Image: Views into the bioreactor

IPCs for feed targets (glc)



What about feed? What if there existed a probe that could provide real time info on feed (think beyond glucose)?

What about product? What if there existed probes that could provide real time info on yield, quality?

Feed / Product Sensors

- Other
  - capsule
  - Gel based
- Mass Spectrometry
  - At-line
  - In-line
- Spectroscopy
  - NIR
  - MIR
  - Raman
  - Fluorescence

https://www.sciencedaily.com/releases/2015/10/151019123748.htm

https://pro-analytics.net/lactate-glucose-analyzer-fermentation/

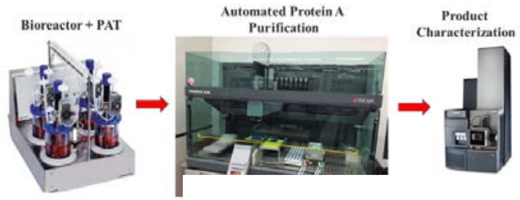
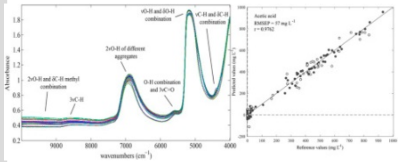
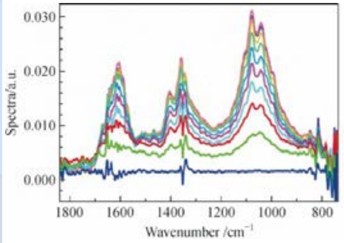
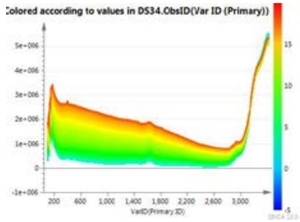


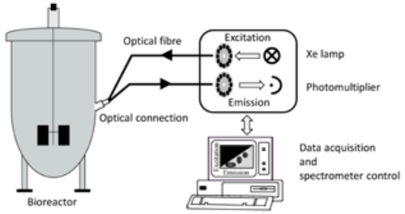
Figure 1. Automated high-throughput workflow for cell

DOI: 10.1021/acs.analchem.6b01956
Anal. Chem. 2016, 88, 8673–8679









Feed / Product Sensors

Other

- capsule
- Gel based

Mass Spectrometry

- At-line
- In-line

Spectroscopy

- Raman
- NIR
- Fluorescence
- MIR

- Limited range of analytes (Glc/Lac)
- Low cost $

- Pretreatment still required
- Destructive
- Pre-determined chemical snapshot
- Cost $$$

- Maximized range of analytes
- No sample pretreatment
- Unique fingerprint of bioreactor (chemical/physical)
- Moderate cost $$

In-Line Spectroscopy for Feed / Product

https://www.metrohm.com/en-us/products-overview/process-analyzers/applikon-nirs-xds/

https://www.sartorius.com/shop/us/en/usd/products-bioprocess-process-analysers/biopat%C2%AE-spectro/p/biopatspectro

NIR

https://resolutionspectra.com/products/procellics-raman-analyzer/

https://www.endress.com/en/Endress-Hauser-group/related-companies/kaiser-op

Raman

https://tornado-spectral.com/

https://www.sciencedaily.com/releases/2015/10/151019123748.htm

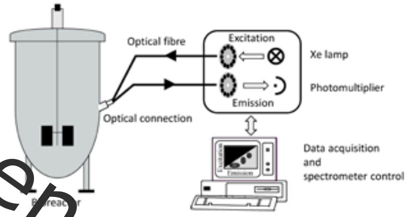
midIR

https://www.mt.com/us/en/home/products/L1_AutochemProducts/ReactIR.html#documents

High Throughput Integration

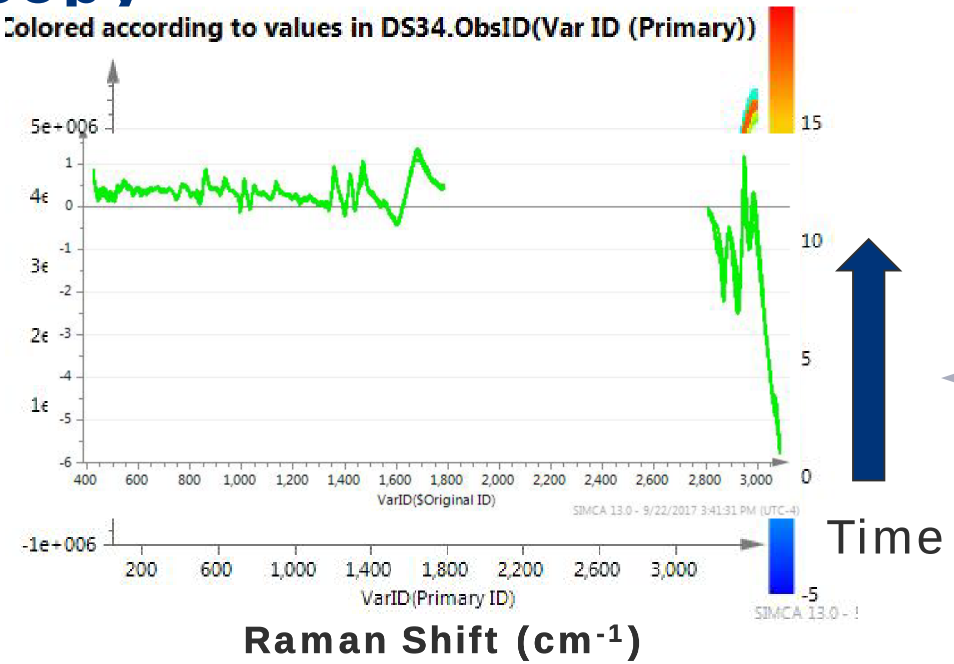
https://www.sartorius.com/us-en/products/fermentation-bioreactors/ambr-multi-parallel-bioreactors/ambr-250-high-throughput

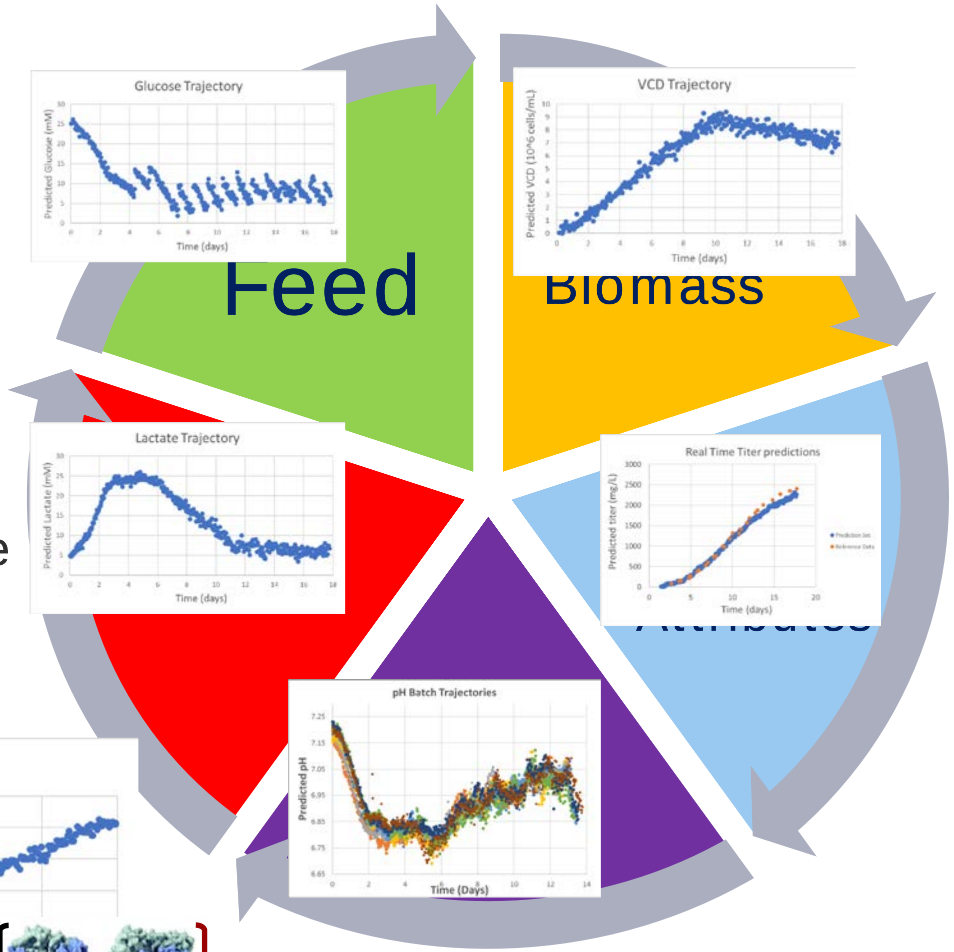
Fluorescence



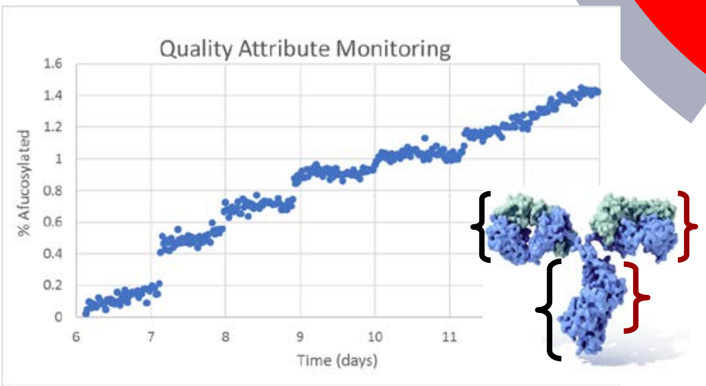
Sensors **2015**, *15*(5), 10271-10291; https://doi.org/10.3390/s150510271

Example: Real Time Monitoring Capabilities with Raman Spectroscopy



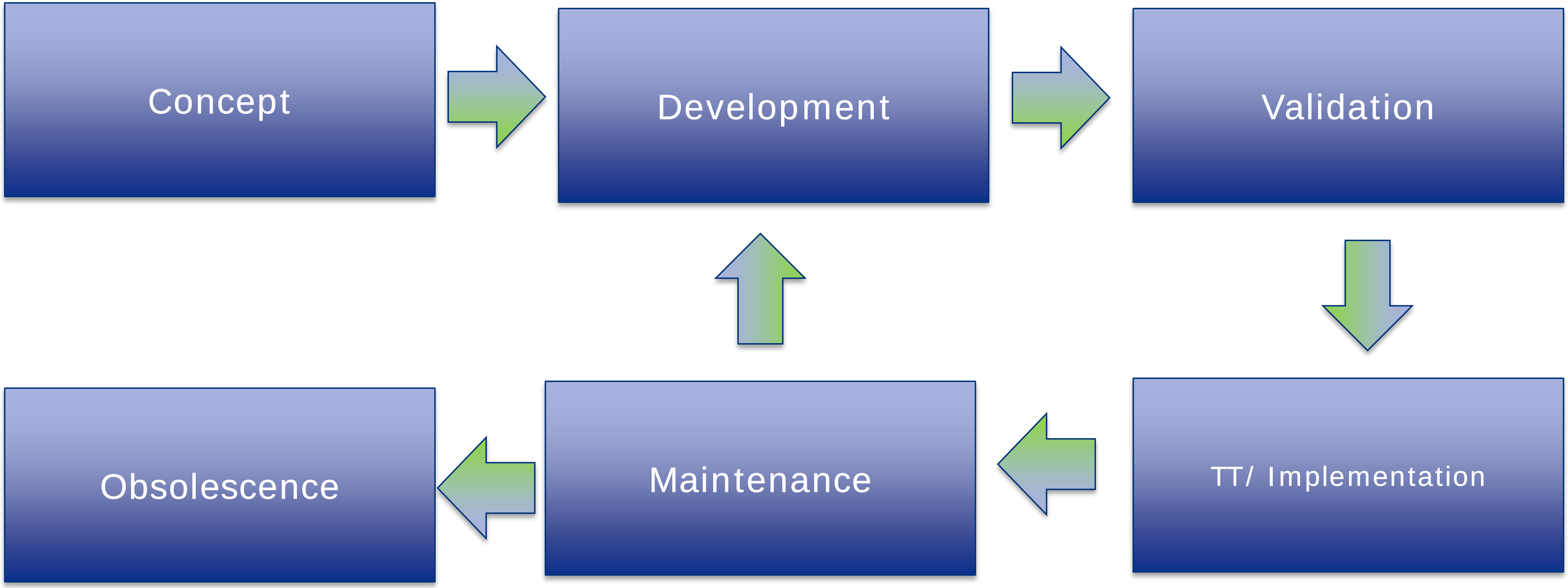


The next frontier
Product attributes!



janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Lifecycle Management of Sensors Deploying Chemometric Models



New Sensing Opportunities

https://908devices.com/news/908-devices-launches-the-rebel-the-first-at-line-spent-cell-media-analyzer-for-bioprocess-labs/

Rapid Media Analysis: At-line CE-MS

Product CQAs Multi Attribute MS

Product Stability and ID: Nano Differential Scanning Fluorimetry

https://resources.nanotempertech.com/prometheus

Product CQAs QCL-IR

https://www.daylightsolutions.com/home/applications/sensors-analyzers-spectrometers/

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Sensors in Manufacturing

Technical Transfers

Legacy products
Off-line modeling and at-line sensors

PAST

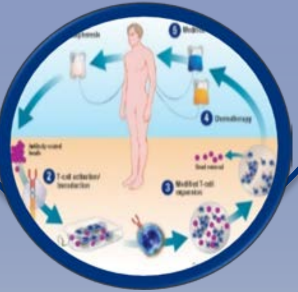
Real Time MVA with Sensors

Legacy and New Sites & Products
Real time MVA and APC

IPC and QC Testing RTR

Sensor assisted RTR

PRESENT



Integrated Quality
Extend APC to Quality Control for RTRt and PPQ

FUTURE

Typical Advanced Process Control Pathway

Advanced Process Monitoring

Early event detection and response

Enhanced process knowledge and understanding

Reduced non-conformance

Increased process knowledge and understanding

Advanced Process Prediction

Predict batch endpoints like yield or quality attributes

Discrete performance prediction

Advanced Process Forecasting

Forecast process variables in real time

Predict yield and quality attributes in real time

Preemptively avoid process issues

Continuous performance prediction

Advanced Process Optimization

Process changes recommended to operator using machine learning algorithms

PAT can provide enhanced models

Run "Golden Batch"

Increase Yield

Stabilize CQAs

Advanced Process Control

Feedback control on processes using, PAT, QbD, machine learning

Real Time Quality

Maximized performance

Feed Control Based on Machine Learning

Background and Example

An advised future model provides recommendations for "manipulated variable" setpoints to achieve optimal process performance:

Model Development:

- Historic dataset of batches with a range of process variability
- Selection of "manipulated variables"

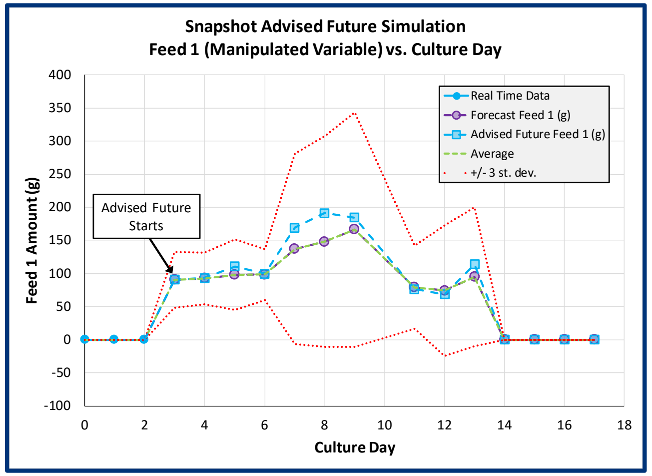
Real-Time Data Requirements and Configuration Specifications:

- Real-time data for active batches
- Optimizer configuration (what variables or batch level conditions to target, maximize or minimize)

Model Outputs:

- Predicted y-values for all batch conditions (titer, purity, etc.):

Culture Day	Projected Yield Increase if Advised Future Model Followed
3	10.7%

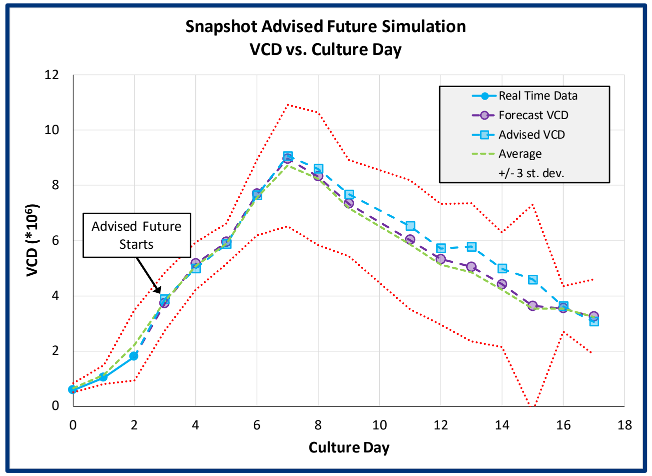


Model Outputs:

- Recommended setpoints for "**manipulated variables**" for each maturity interval

Model Outputs:

- Forecast trajectories for all variables at all future maturities (to compare what variable profiles to expect if advised future is/is not followed)



Closing Thoughts

- Lower cost, accurate, and robust sensors will continue to drive innovation in APC and Quality Applications
  - Untapped potential in Lg API
  - Historically more applications in solids with demonstrated filings for IPC, QC Release and RTR
- Multiplexed sensors in-line, at-line key for achieving real time product quality
  - Spectroscopy based
  - Mass spectrometry based
- Sensors extend and enhance capabilities of MVA, Machine Learning