



Rodolfo J. Romañach, PhD.

Professor of Chemistry at
UPR – Mayagüez Campus



PAT-Process Analytical Technology and Advanced Pharmaceutical Manufacturing



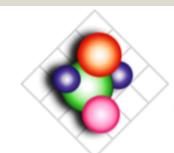
TRANSFORMA

Process Analytical Technology and Advanced Pharmaceutical Manufacturing

Rodolfo J. Romañach,
Dept. of Chemistry
rodolfoj.romanach@upr.edu



We have
Moved to
Manufacturing



NSF Engineering Research
Center for Structured Organic Particulate System (C-SOPS)



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New Jersey Institute
of Technology

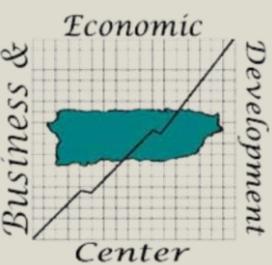




Lilly



NSF Engineering Research
Center for Structured Organic Particulate System (C-SOPS)



The National Institute for Pharmaceutical Technology & Education



SBIR
America's Seed Fund

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Why do chemists have to work in a lab?

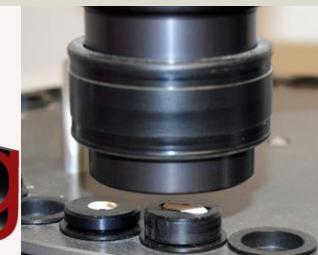


A hurricane reconnaissance plane flying inside a storm. It measures atmospheric pressure and winds in-situ.

They do not bring storm samples to the lab.



We have
**Moved to
Manufacturing**



Dr. Woodcock's presentation summary

Current Status

US Drug products are of high quality, BUT:

- Increasing trend toward manufacturing-related problems.
- Low manufacturing and QA process efficiency--cost implications.
- Innovation, modernization and adoption of new technologies slowed
 - Introduction of new technologies in facilities not for US market
- High burden on FDA resources.

From A. Hussain Presentation, May 2002, Forum for Innovation, San Juan, PR.

PAT

a Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

Scope: “The scientific, risk-based framework outlined in this guidance, Process Analytical Technology or PAT, is intended to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance.”

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)**

**Pharmaceutical CGMPs
September 2004**

FDA Mission Statement

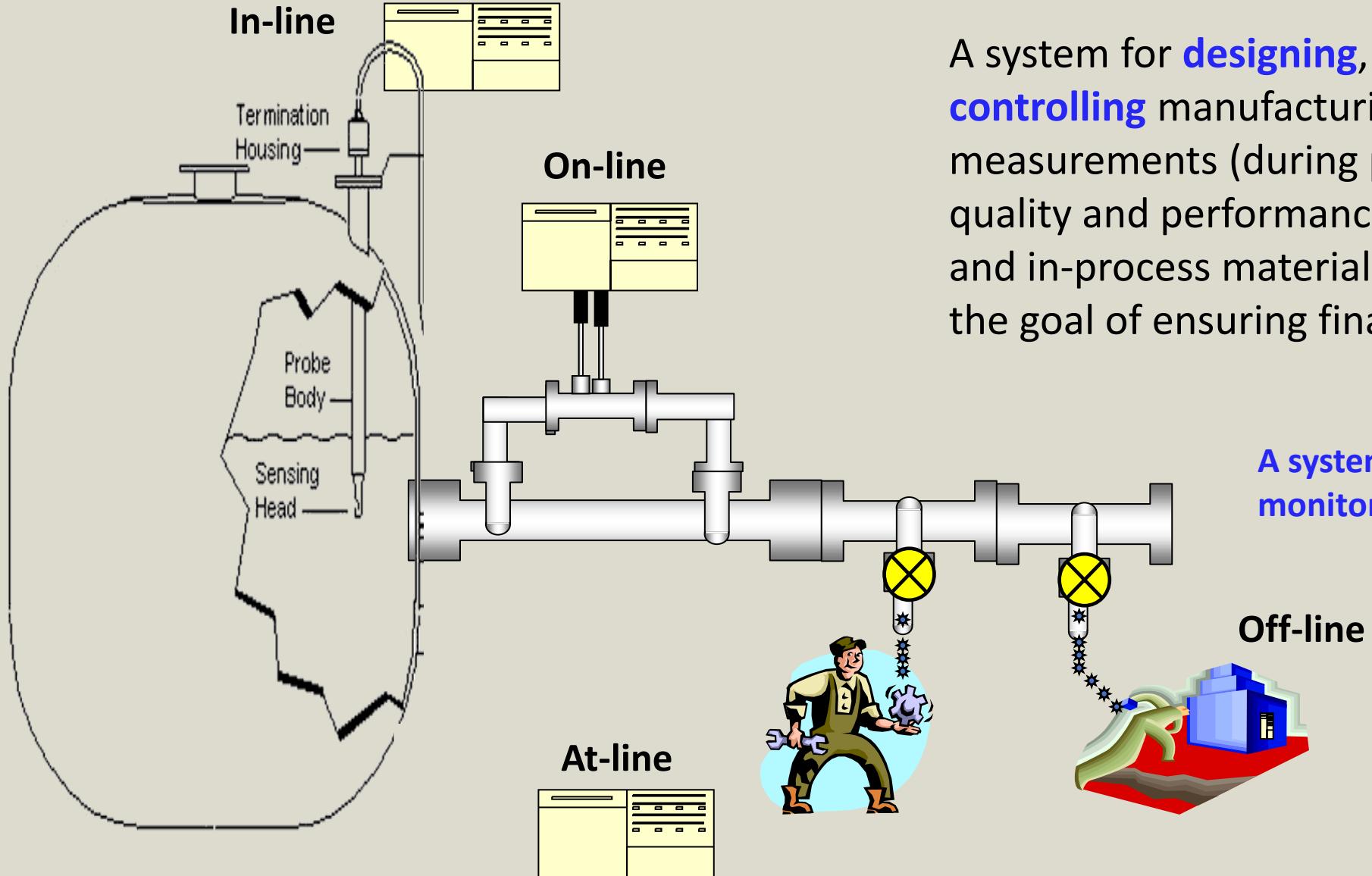
Statement of FDA Mission

FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health. FDA also has responsibility for regulating the manufacturing, marketing and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.

FDA also plays a significant role in the Nation's counterterrorism capability. FDA fulfilled this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.

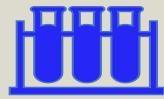
Process Analytical Technology (PAT)



A system for **designing, analyzing, and controlling** manufacturing through timely measurements (during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality.

A systematic effort to develop, monitor, and control processes.

Off-Line Analysis in the QC Lab



Samples are analyzed days after a process is completed.

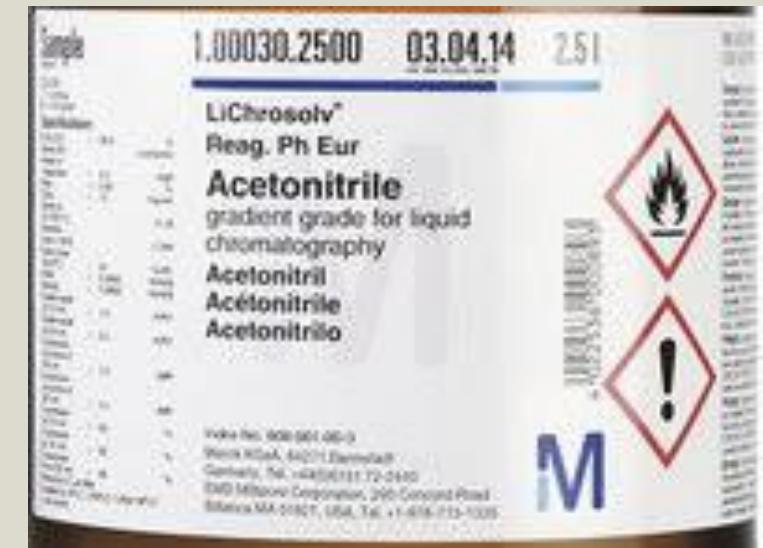
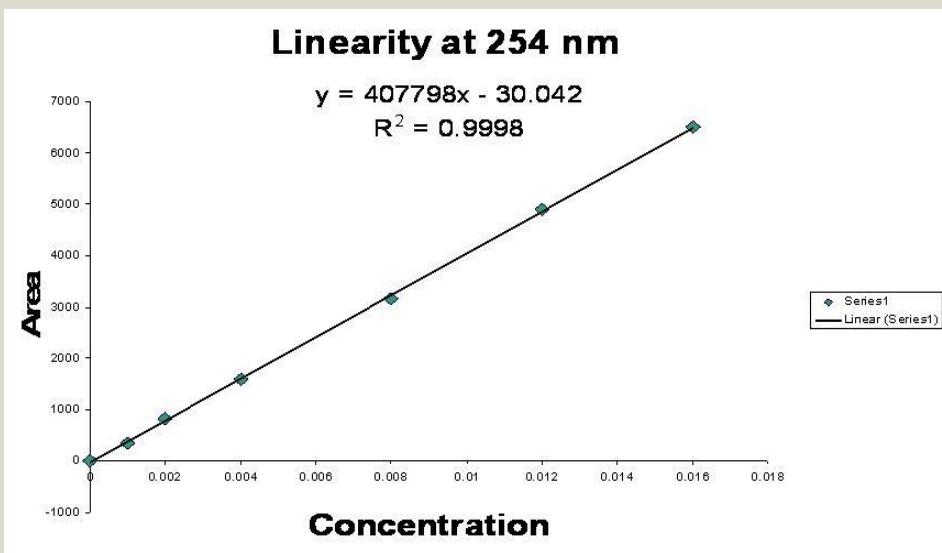


>50% of methods use solvents (methanol, acetonitrile), and separate the compounds through liquid chromatography.



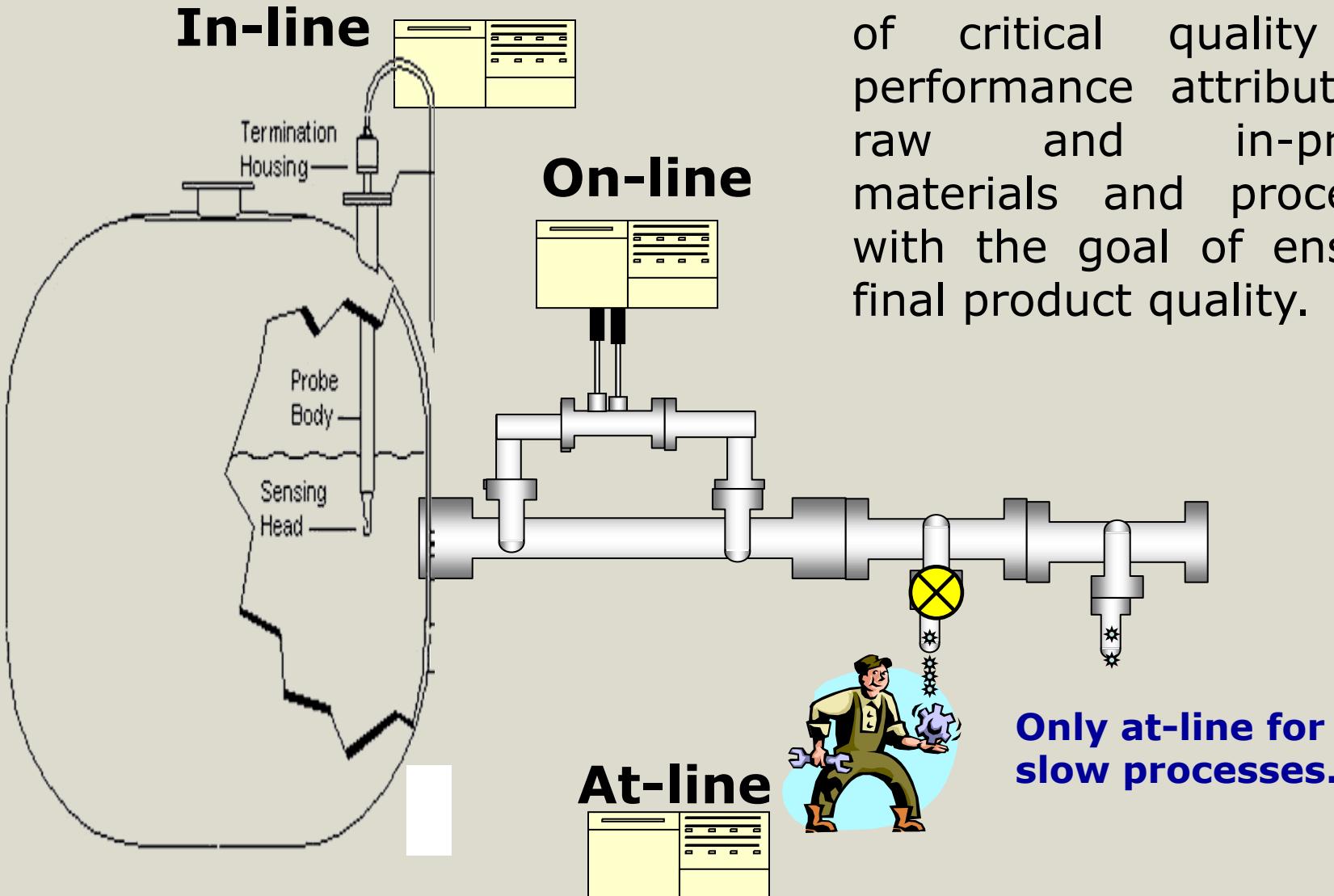
Information is generated in the QC lab, and goes to a LIMS (Laboratory Information Management System)

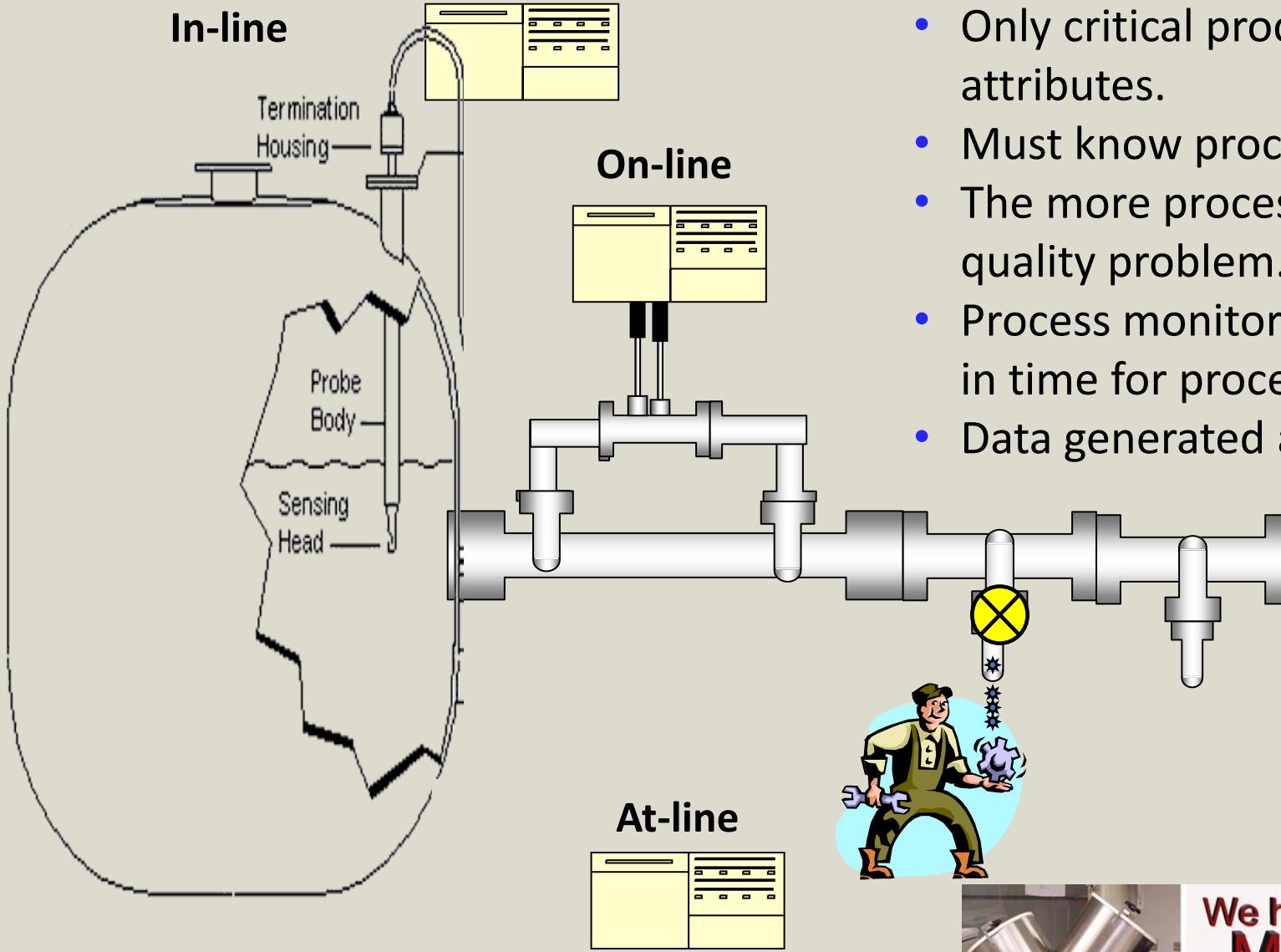
Current Univariate Methods



- HPLC used for a large number of analysis.
- Only one signal used (absorbance at one wavelength).
- A significant amount of time and solvent employed to separate everything and obtain only one component to be measured by the detector.
- Chemists love to obtain linear relationships.

PAT = Timely Generation of Process Data Generated in Manufacturing





- Do not want to measure everything.
- Only critical process parameters and critical quality attributes.
- Must know process well.
- The more process knowledge the less risk of a quality problem.
- Process monitored in real time; response must be in time for process control to occur.
- Data generated at plant.

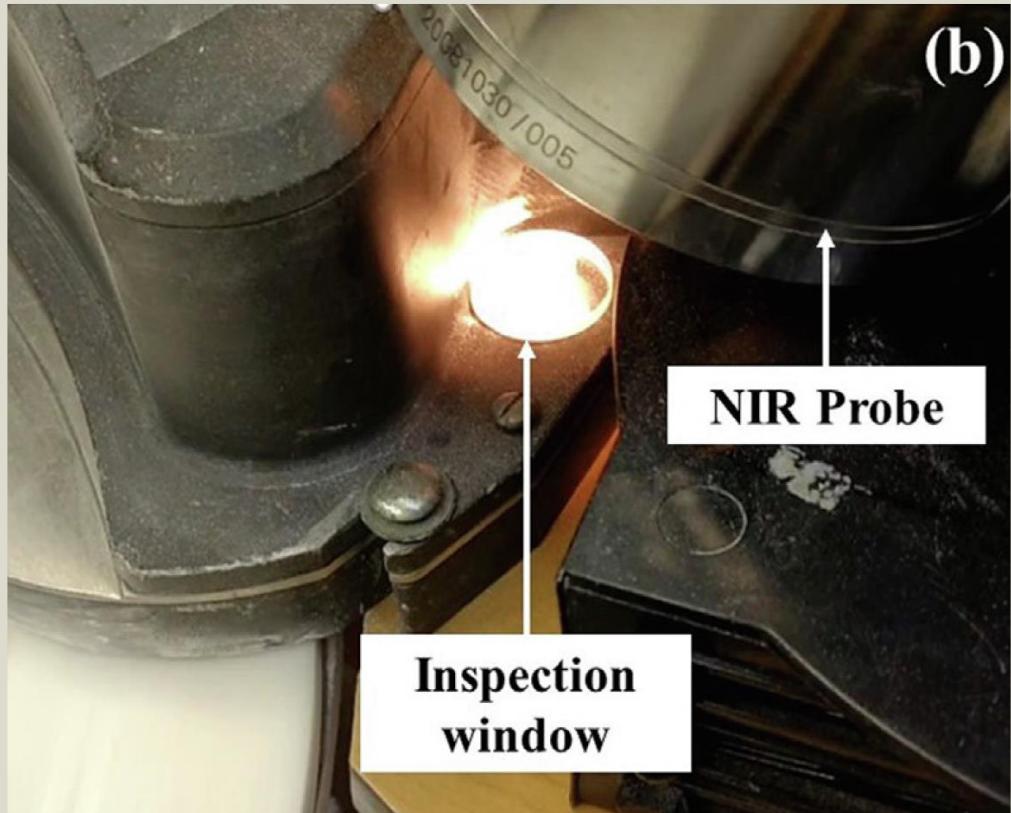


Non – destructive methods – capable of real time analysis

Raman Spectroscopy



Near Infrared Spectroscopy

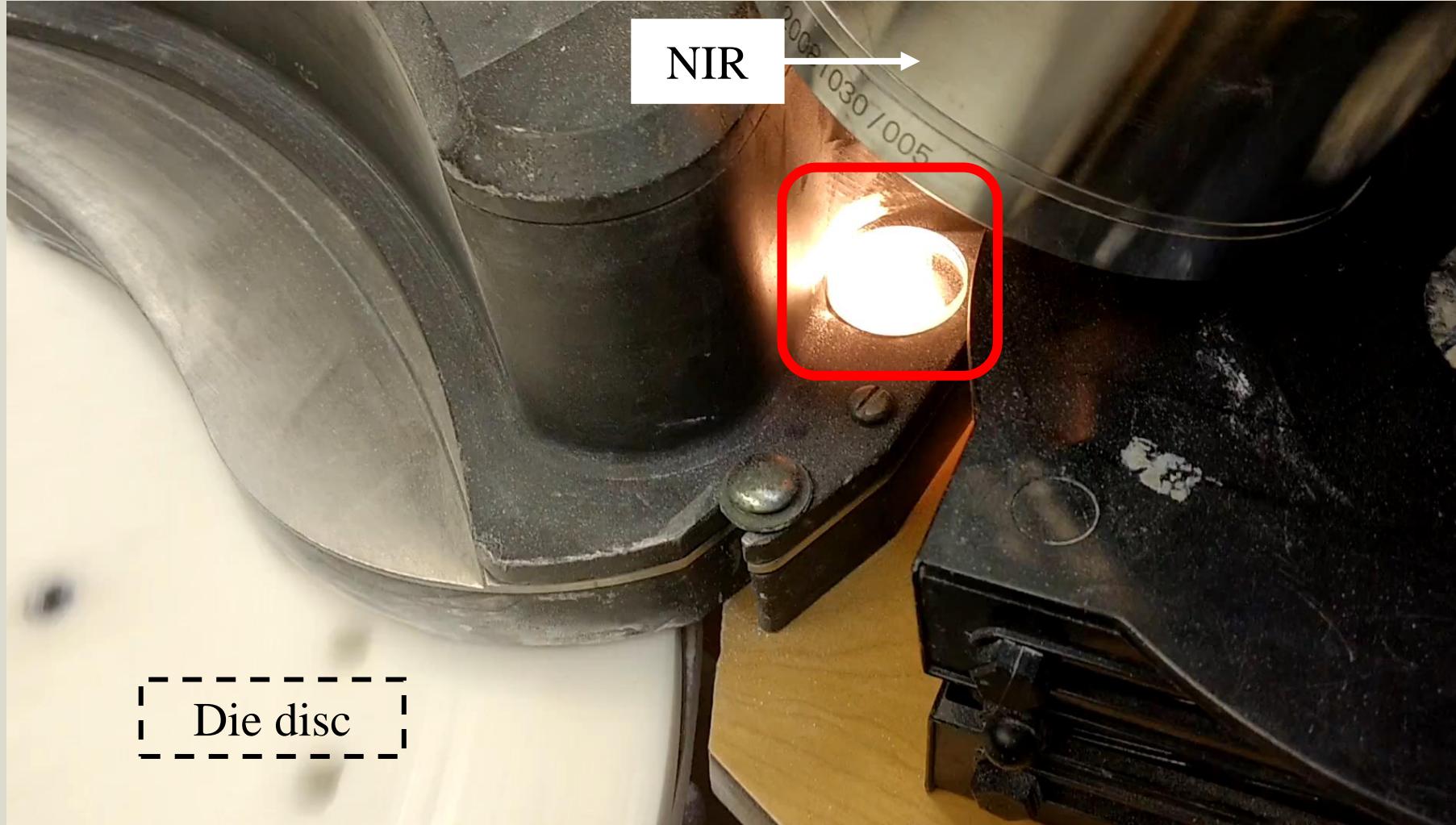


Real time monitoring

ENGINEERING RESEARCH CENTER FOR
STRUCTURED ORGANIC PARTICULATE SYSTEMS
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NEW JERSEY INSTITUTE OF TECHNOLOGY
UNIVERSITY OF PUERTO RICO AT MAYAGÜEZ



Acquisition of NIR spectra

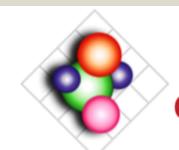
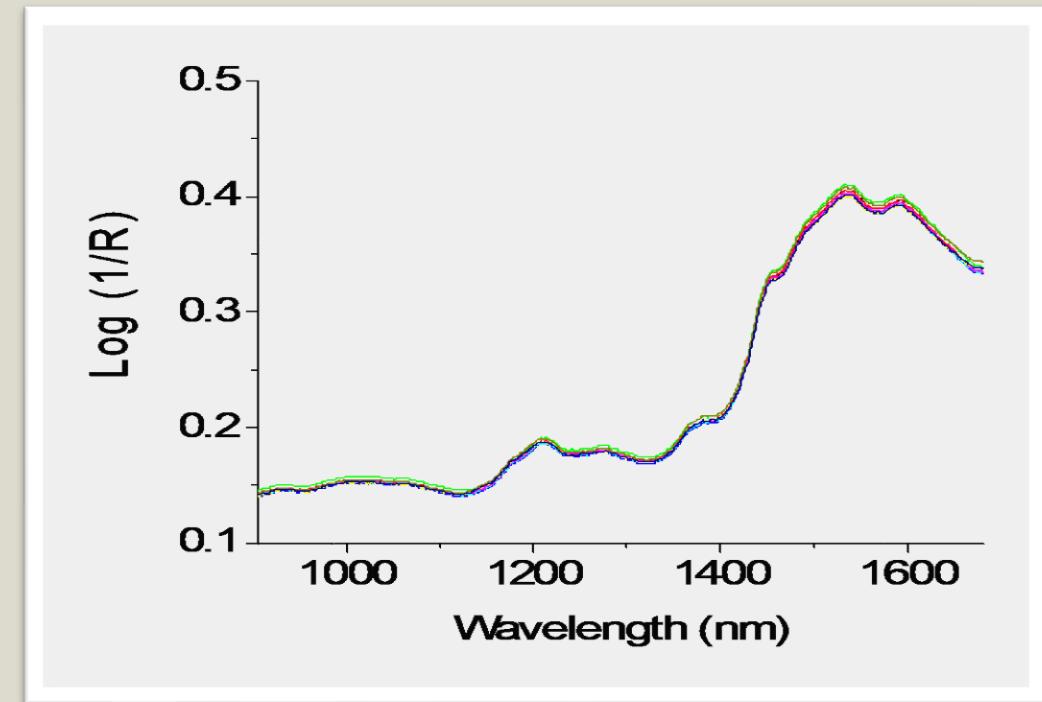


The NIR were acquired in-line as the formulations flowed through the feed frame

Working with Spectra Obtained in Real Time During Manufacturing

- Spectrum, -- a vector
- Multiple vectors – matrix
- Use Linear Algebra & Multivariate Data Analysis

Wavenumber (cm-1)					
Spectrum	6992.93	6988.536	6984.679	6980.822	6976.965
1	0.090334	0.091461	0.092569	0.093737	0.09496
2	0.060275	0.061371	0.062382	0.063514	0.064805
3	0.091242	0.092353	0.093422	0.094635	0.096002
4	0.085473	0.086502	0.087423	0.088453	0.08965
5	0.075925	0.076968	0.077925	0.079014	0.080271
6	0.049536	0.050592	0.051559	0.052627	0.053833



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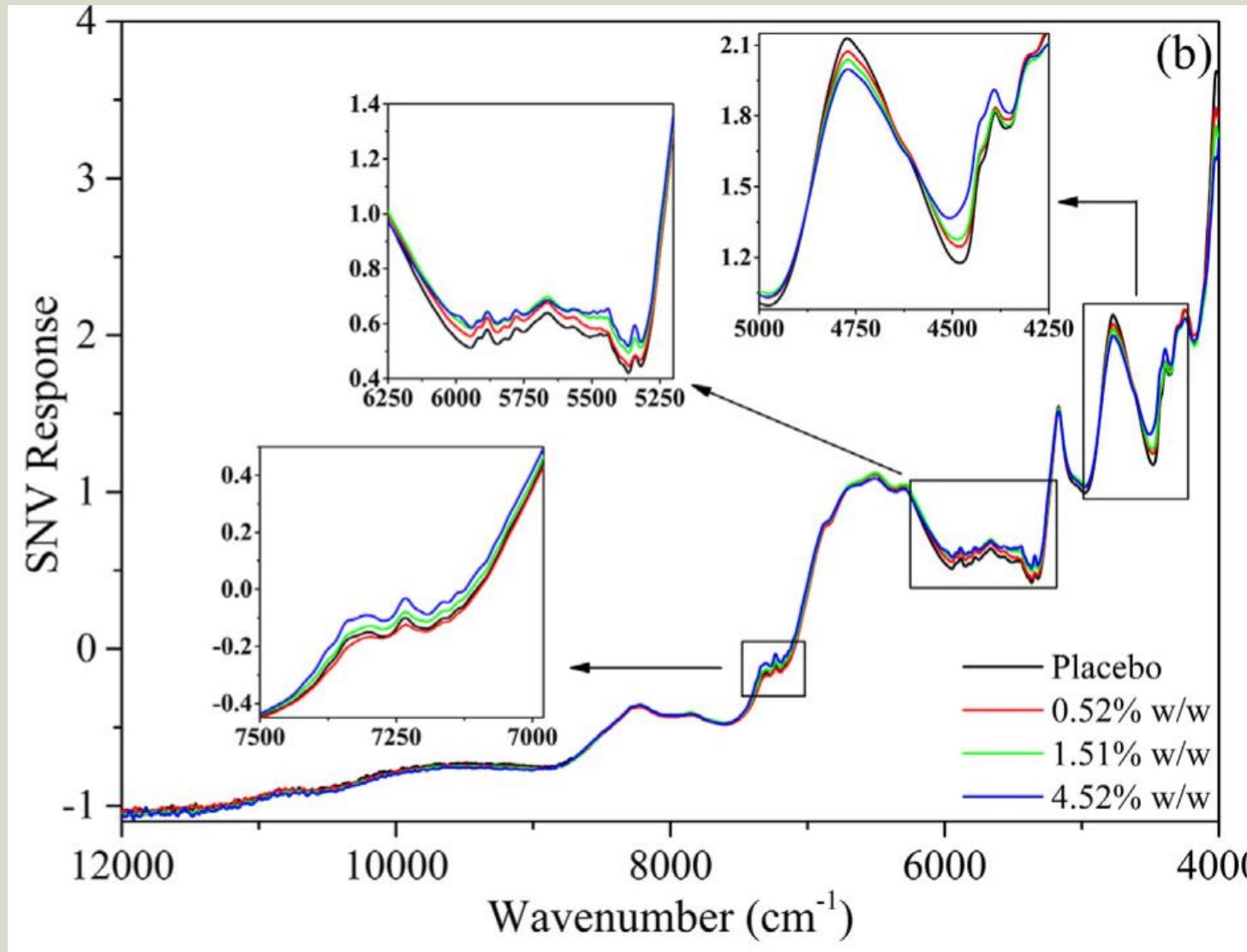
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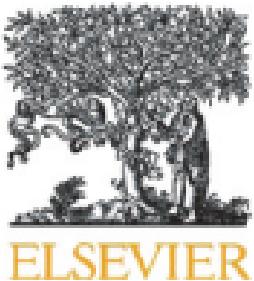
Multivariate Data Analysis



Variation Implies
Information!!

Chemometrics extracts valuable information from PAT Data

Chemometrics and Intelligent Laboratory Systems 139 (2014) 168–174



Contents lists available at ScienceDirect

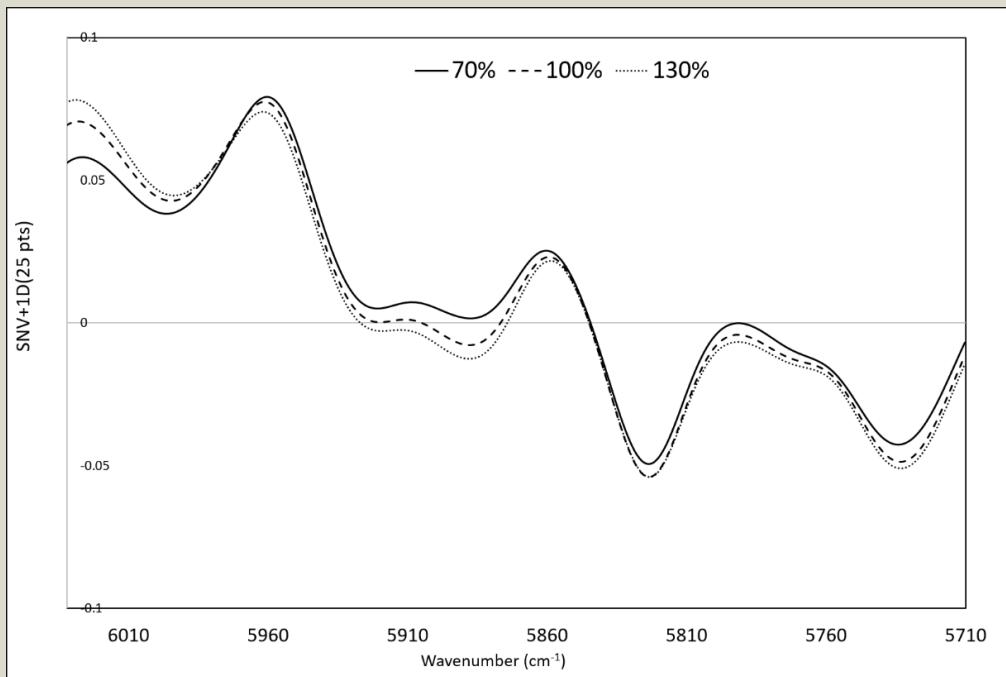
Chemometrics and Intelligent Laboratory Systems

journal homepage: www.elsevier.com/locate/chemolab

Chemometrics and
intelligent
laboratory systems

Design → Learn (Model) → Use

PLS latent variables that maximize the amount of information explained in **X** that is relevant for predicting **Y**. PLS seeks to maximize covariance between the **X** and **Y** data.



Variation Implies Information !!

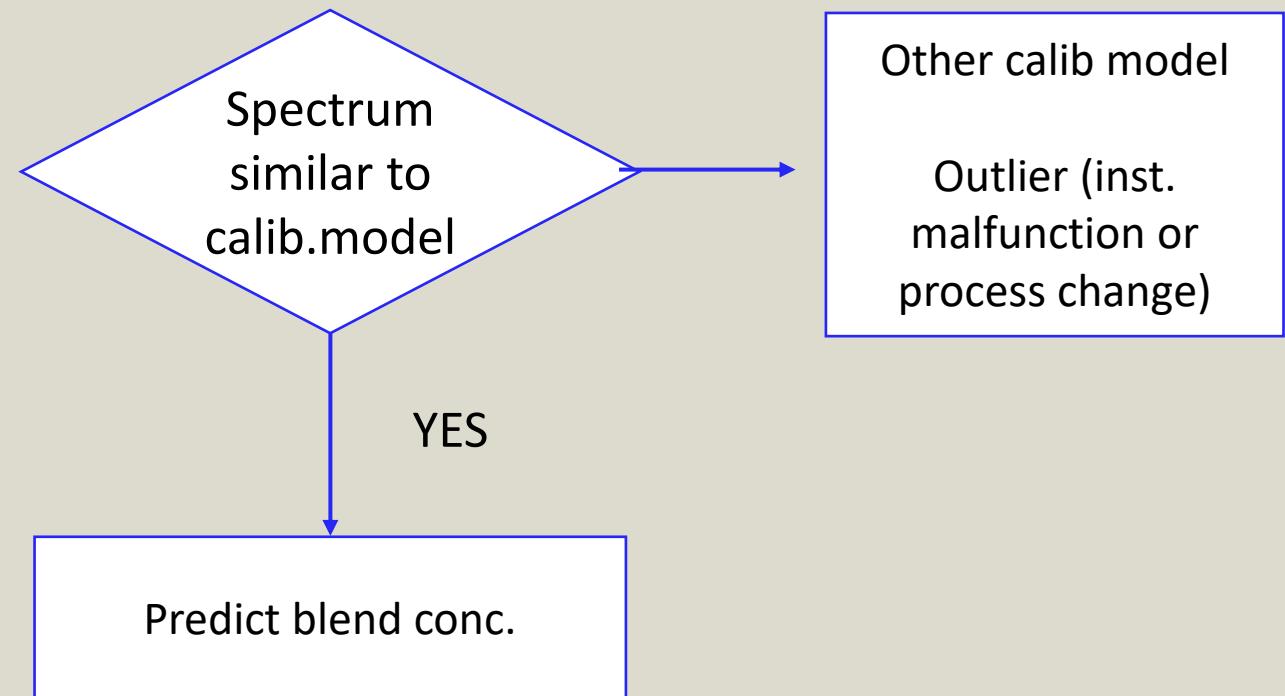
Model developed in lab, but implemented in Manufacturing

X					Y
1111	1112	1113	2200	2.15
0.2606	0.2611	0.2615	0.2619	0.2638	3.98
0.2635	0.2640	0.2644	0.2648	0.2998	5.77
0.2939	0.2943	0.2947	0.2951	0.2967	7.14
0.2828	0.2833	0.2837	0.2841	0.3009	9.90
0.2782	0.2786	0.2790	0.2794	0.3122	

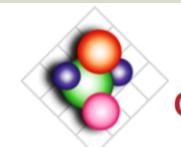
Real Time On-Line Prediction Engine

Unscrambler,
Pirouette
Vektor Direktor
SIMCA, R, MATLAB, Python used to develop model in lab.

On-line Prediction Engine used in mfg.



Analytical methods are not applicable to all materials, they are applicable to a certain formulation or product. First test with PCA determines applicability of method.



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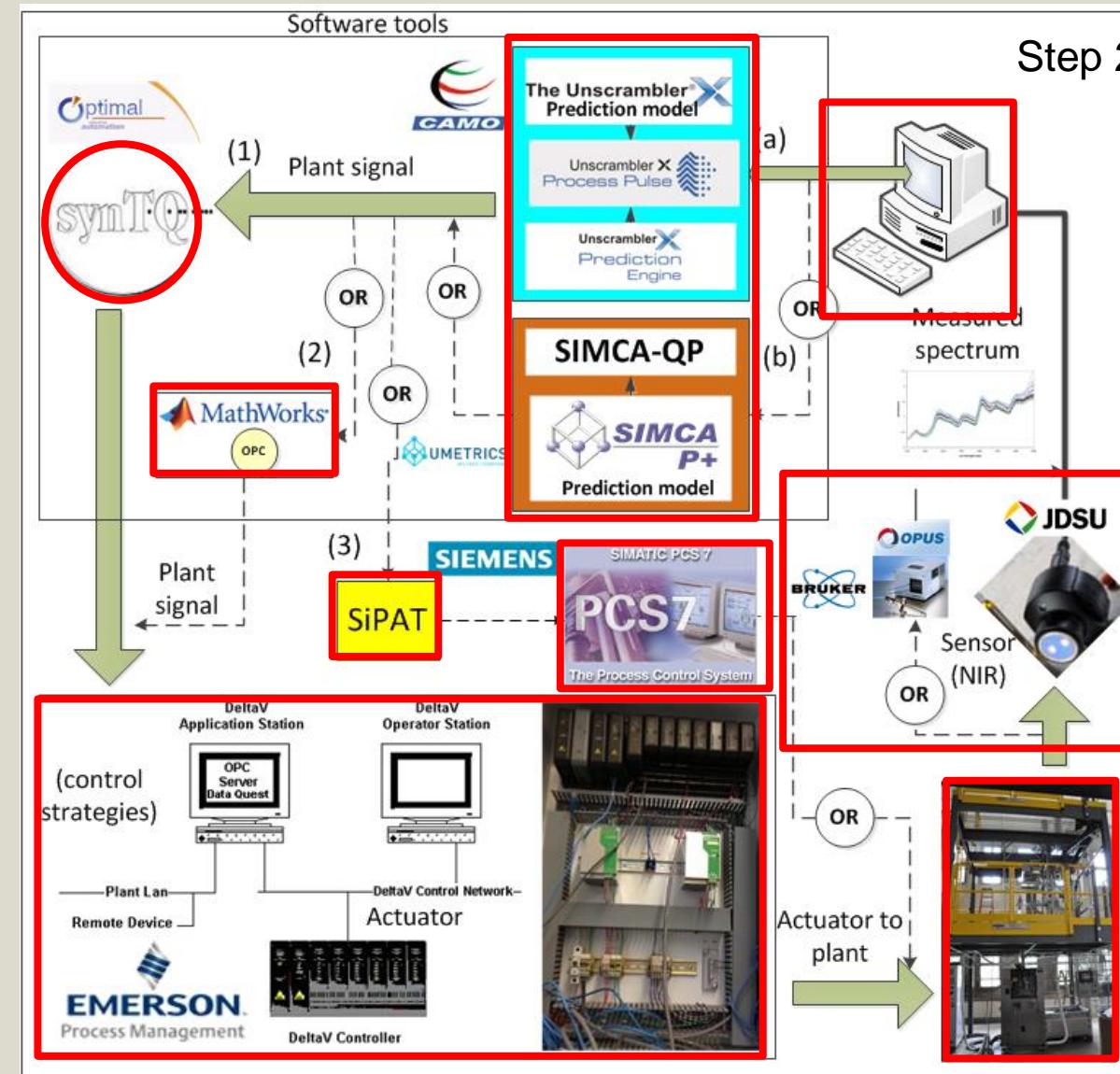
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Control hardware and software integration

Computer and Chemical Engineering 66 (2014) 186-200

Step 3 – sensors integrated into plant



Step 4 – signal to Control platform

Step 1 - Design

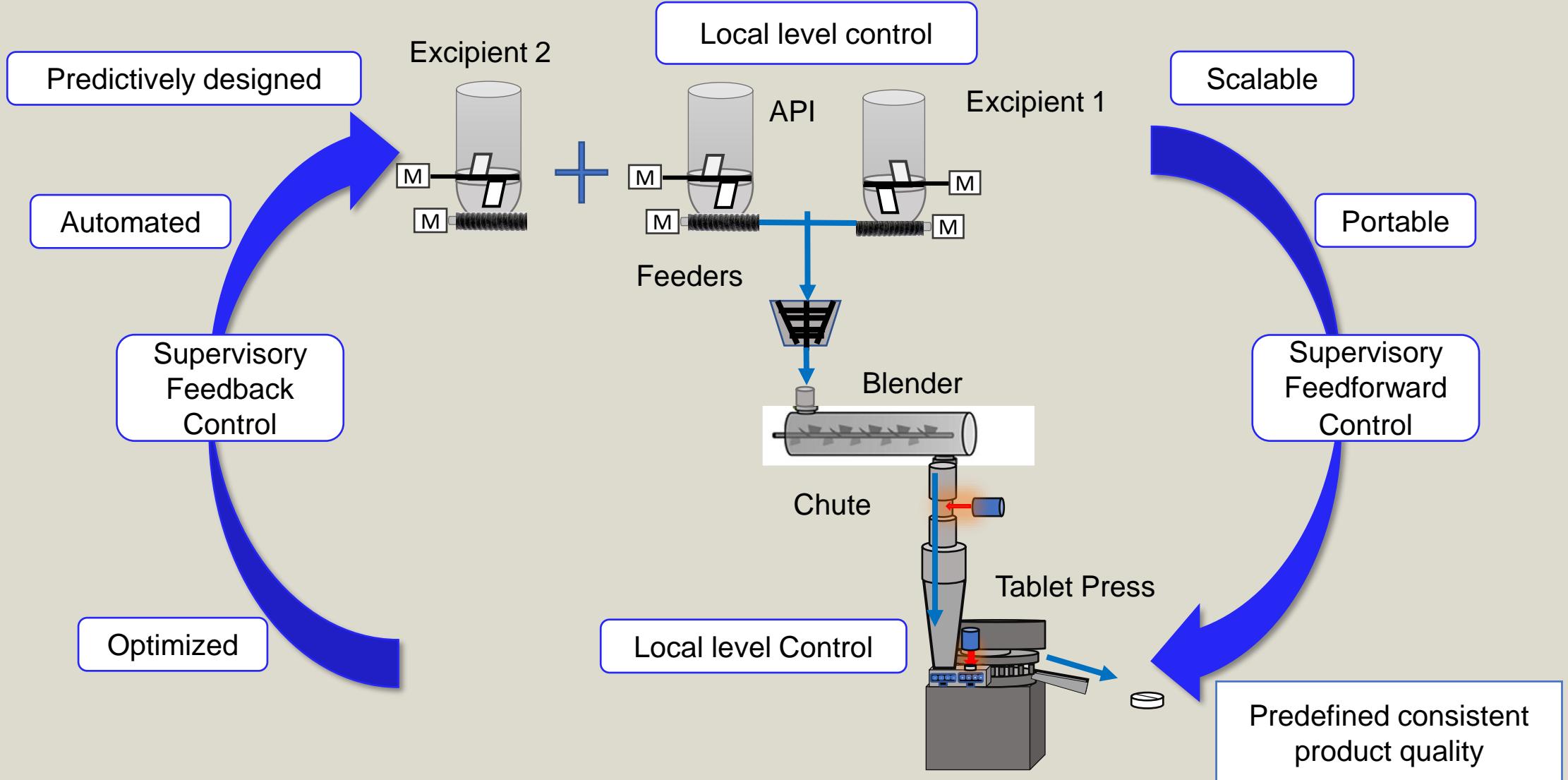
Step 2 – Method for RT analysis

**How do we recognize
Advanced Pharmaceutical Manufacturing?**

How is it different from Pharmaceutical Manufacturing?

Advanced Pharmaceutical Mfg. – A Functional Definition

A system that is designed using predictive models, where automation minimizes human intervention while enabling closed loop process control and real time quality assurance, where performance has been optimized to maximize desired process goals, where flexible amounts of product with equivalent attributes can be manufactured, and where equivalent processes can be implemented at multiple locations to manufacture products with equivalent critical quality attributes.



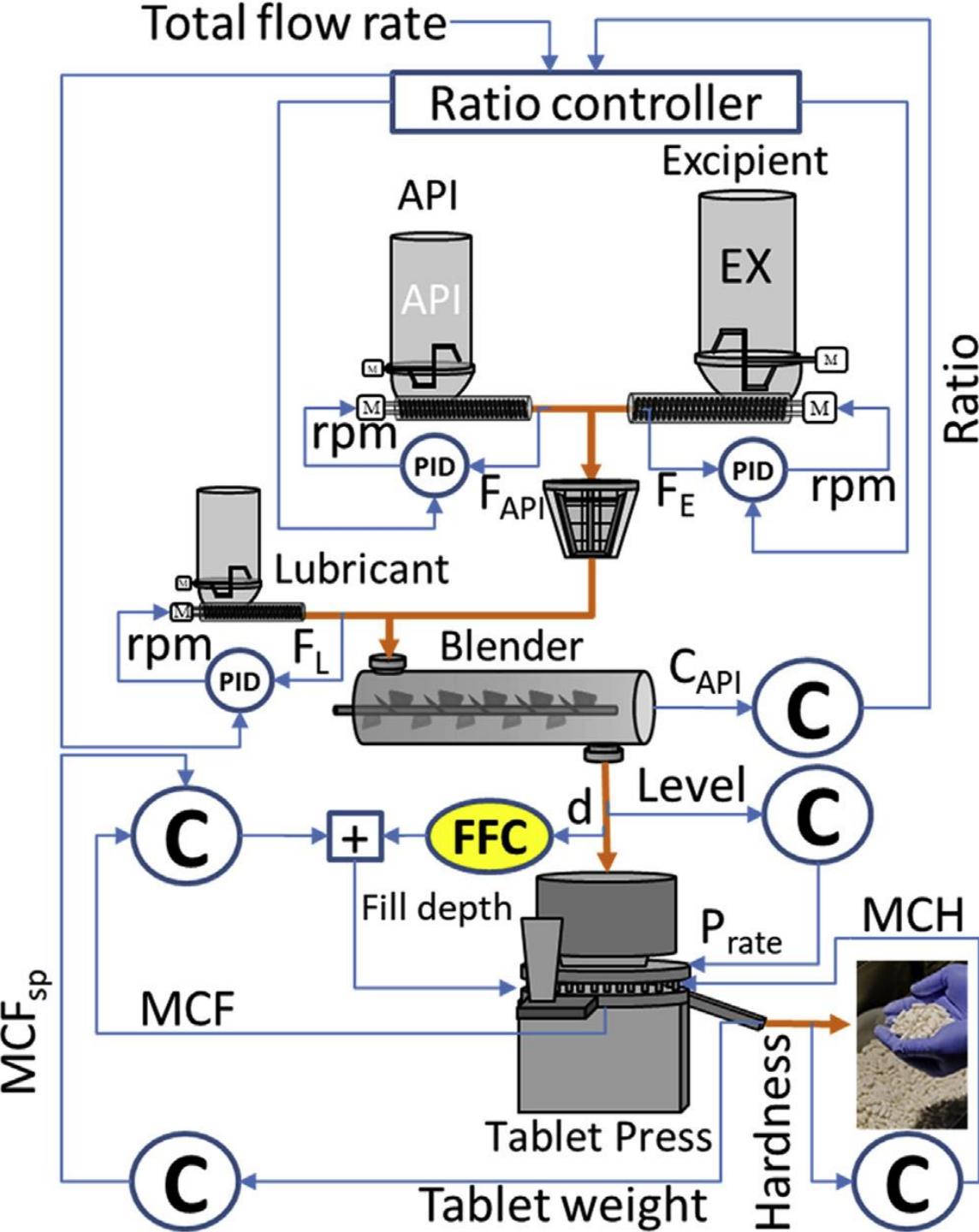
Singh R, Muzzio FJ. Chapter 12 - Integrated process control. In: Muzzio FJ, Oka S, eds. *How to Design and Implement Powder-To-Tablet Continuous Manufacturing Systems*. Academic Press; 2022:251-269.

APM is Predictively Designed: Based on Process Understanding

- A system is predictively designed when its defining parameters are selected using models that predict the system's performance.
- Based on Process Understanding
- Predictive models must guarantee the obtainment of the critical quality attributes (CQAs) expected for the pharmaceutical product.
- Example - The physical & chemical properties of excipients & API are thoroughly studied. Material property libraries developed.

APM is Optimized

- *System is optimized when a predictive model is used to select design and operating parameters of the integrated system that maximize a desired outcome or minimize an undesired one.*
- ***Minimize downtime due to equipment cleaning, process interruptions (e.g. thief sampling).***
- ***Minimize time spent on process investigations, corrective actions.***
- ***Minimize waste generated.***



Optimization

Closed loop Flowsheet modeling of integrated process.

Singh R, Muzzio FJ. Chapter 12 - Integrated process control. In: Muzzio FJ, Oka S, eds. *How to Design and Implement Powder-To-Tablet Continuous Manufacturing Systems*. Academic Press; 2022:251-269.

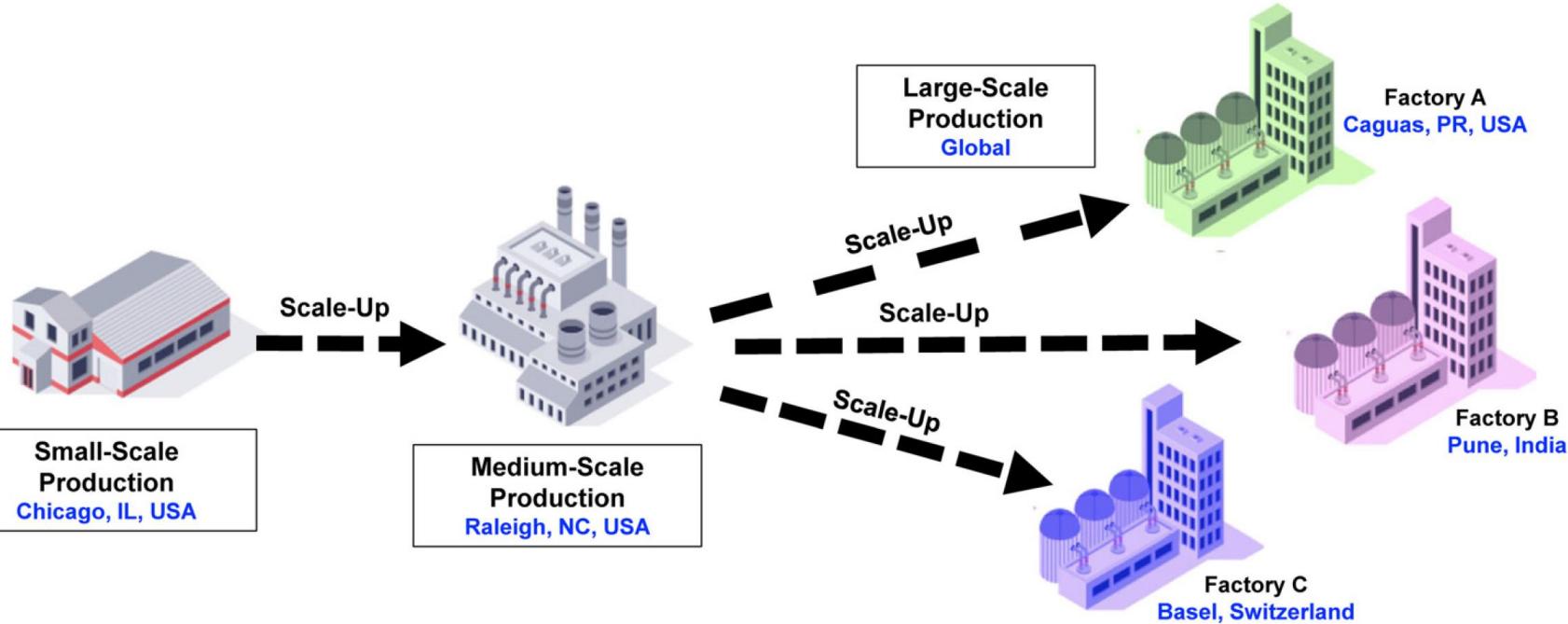
APM is Scalable

- Can be set to manufacture different amounts of a product with equivalent results.
- The outcome is assured to be the same because of the system's design.

APM is Portable

- can be implemented at different locations with similar results (e.g., distributed manufacturing).
- Process knowledge is transferred from development to manufacturing.

Centralized Approach to Manufacturing Scale-Up

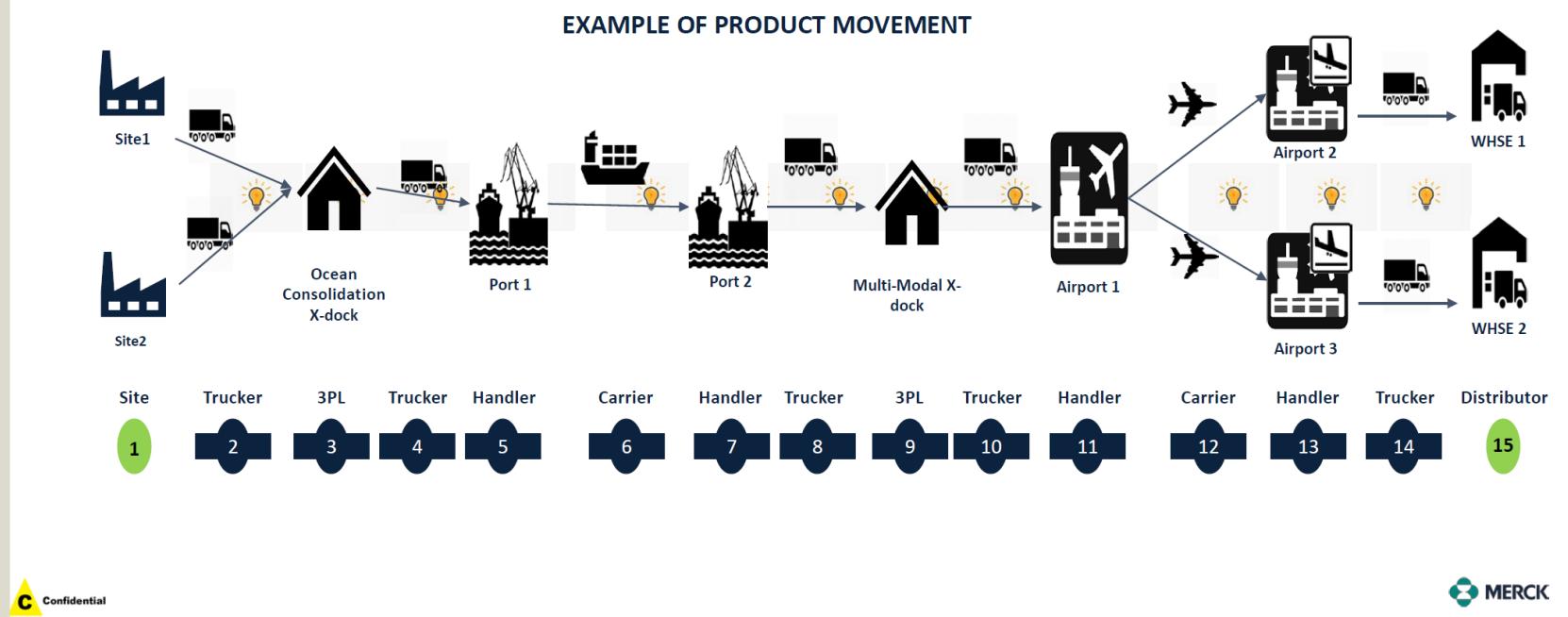


Adapted from: Algorri M, Abernathy MJ, Cauchon NS, Christian TR, Lamm CF, Moore CMV. Re-Envisioning Pharmaceutical Manufacturing: Increasing Agility for Global Patient Access. *J Pharm Sci.* 2022;111(3):593-607.

Journey of a dose, after packaging, to the patient

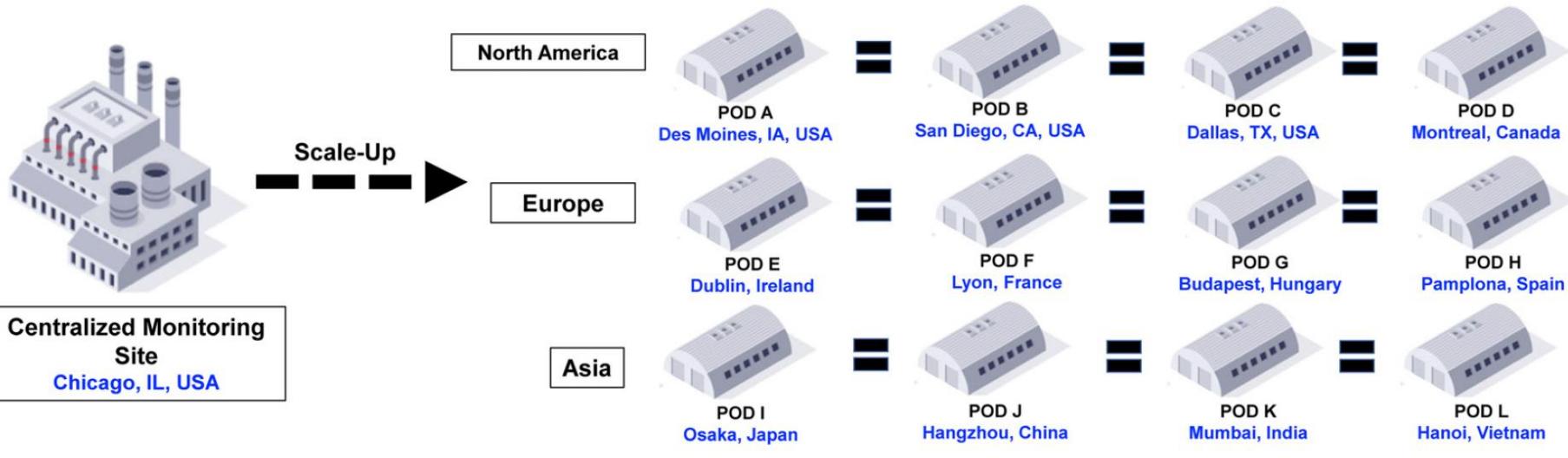
International shipments in the industry can have anywhere between 5 to 15 touch points

As the industry's cold chain portfolio increases, this will pose increased challenges



Adapted from: Sreenivasan B. Supply Chains of the Future, Embracing Technology to Enable Accessibility and Affordability of Medicines Across the Globe. . International Foundation for Process Analytical Chemistry (IFPAC). North Bethesda, MD, 2020.

Decentralized Approach to Manufacturing Scale-Up



Adapted from: Algorri M, Abernathy MJ, Cauchon NS, Christian TR, Lamm CF, Moore CMV. Re-Envisioning Pharmaceutical Manufacturing: Increasing Agility for Global Patient Access. *J Pharm Sci.* 2022;111(3):593-607.

Transforming Pharmaceutical Mfg

- “We will use all the science and technology available to provide a quality product to patients in the least amount of time”



Key Economic Analysis Tools for PAT Implementation

BUSINESS CASE			
Associated Cost	Risk Analysis	Benefits	Project Performance
<ul style="list-style-type: none">• Investments.• Bringing the methods from R&D to manufacturing.• Modifying and/or creating new procedures.	<ul style="list-style-type: none">• What is the probability of the Project occurring successfully? On time, and without exceeding the cost estimates.	<ul style="list-style-type: none">• The gains from PAT depend on its integration into the Quality System and Lean Manufacturing.• Include a reduction of QC Laboratory testing costs, and product release could be accelerated.	<p>As a function of the return on the investment.</p> <ul style="list-style-type: none">• Net Present Value (NPV).• Internal Rate of Return (IRR).• Return of Investment (ROI).

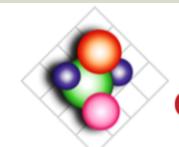
Journal of Pharmaceutical Innovation
<https://doi.org/10.1007/s12247-022-09634-0>

Development and Application of a Business Case Model for a Stream Sampler in the Pharmaceutical Industry

María A. Fontalvo-Lascano¹ · Bárbara B. Alvarado-Hernández² · Carlo Conde³ · Eric J. Sánchez⁴ ·
Mayra I. Méndez-Piñero¹ · Rodolfo J. Romañach² 

$$NPV = \sum_{j=1}^n \frac{CF_j}{(1+i)^j} - \text{Initial Investment} \quad (1)$$

Tax Incentives and PAT



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Front view of Mobile Training Unit in our lab.

Top level - feeders and control unit.

- Two **Ktron QT-20** (Max: 18.5kg/h)
- One **MT-16** (Max: 18.8kg/h)

Middle - blender

- **MODCOS Dry Mixer 70**
Modular continuous system. (10-30kg/h)

Stream sampler would be on the bottom.



Mobile Training Unit in our lab-

- We would like to deploy this system to pharma companies for training and collaboration projects.
- This system has the necessary equipment for continuous blend preparation.
- Tablet Press not available but companies can use their tablet press available.
- The stream sampler has been further improved, would connect this unit to a tablet compressing machine.



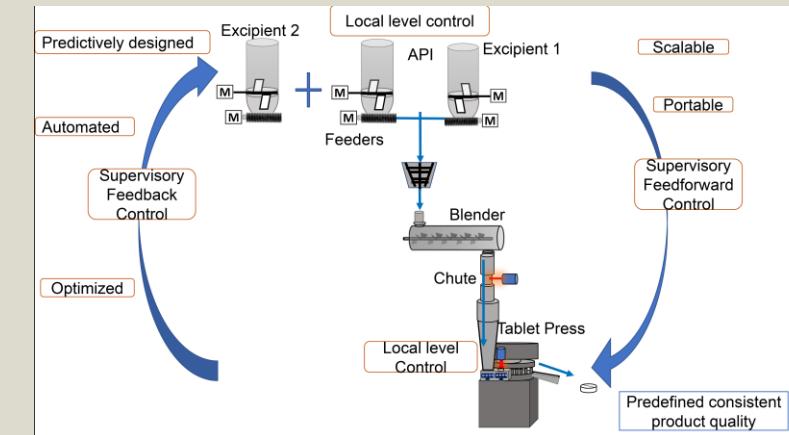
Award #01-70-14889

37



Advanced Pharmaceutical Mfg

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R.J Romañach, F.J. Muzzio, T. Stelzer, E. Sanchez Rolón, submitted to Journal of Advanced Manufacturing and Processing, October 11, 2022.

Rodolfoj.romanach@upr.edu