Our journey towards engineering control in Janssen Manufacturing

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Outline

1. Path covered so far
2. Our next steps
3. Internal Challenges
4. External Challenges
5. Opportunities for new process technology deployment

Where we are going in pharma manufacturing

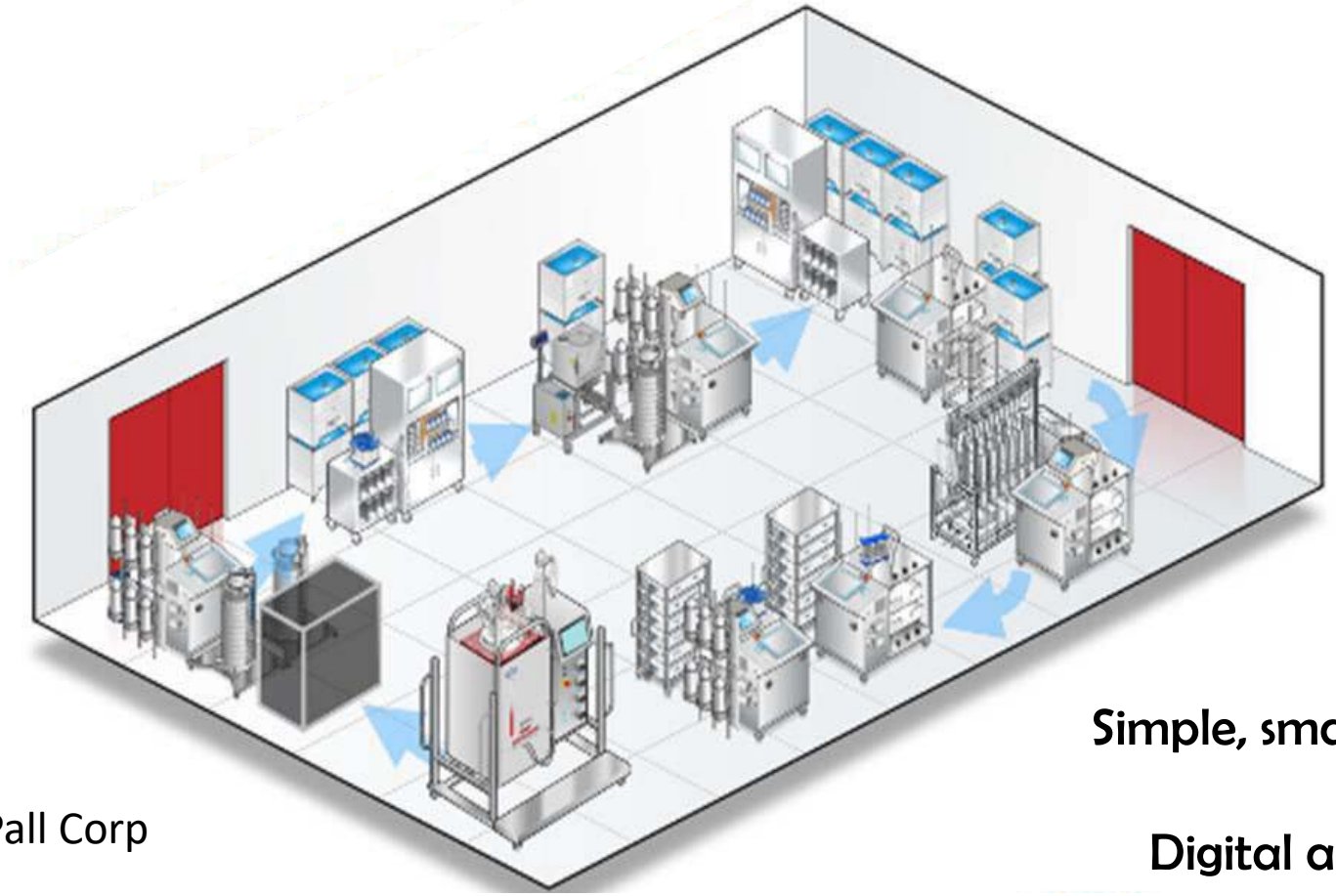

Image Curtesy of Pall Corp

Simple, small foot print, one room

Digital and real time control

Modular & flexible

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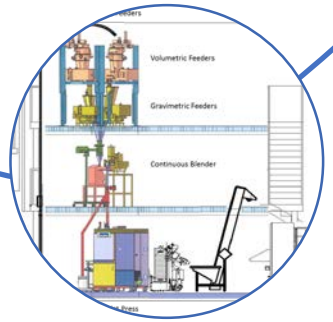
Our Journey

Solids Tech Transfer w digital twins

SM New Plant



CM in solids & RTRt

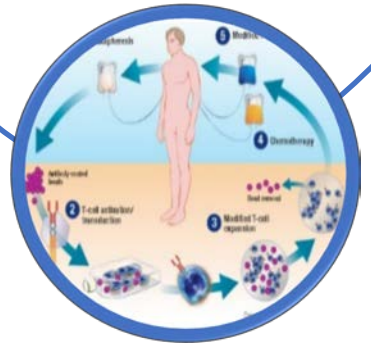
Advanced process control LM

LM Tech Transfer

Janssen

LM New Plant

Real time Quality



Real time release LM

Completed projects

Next priorities

Digital Twin Benefits for SM New Plant

- New approach to Tech Transfer
- Integrated modeling and PAT
- Results are in.
- They have been more positive than initially projected

Substantial direct cost savings

FTE requirement reduced by 50% and peak load by 66%

6x more process data obtained

Project risk reduced by 60% at start of characterization compared to standard

QC sample reduction of 80%

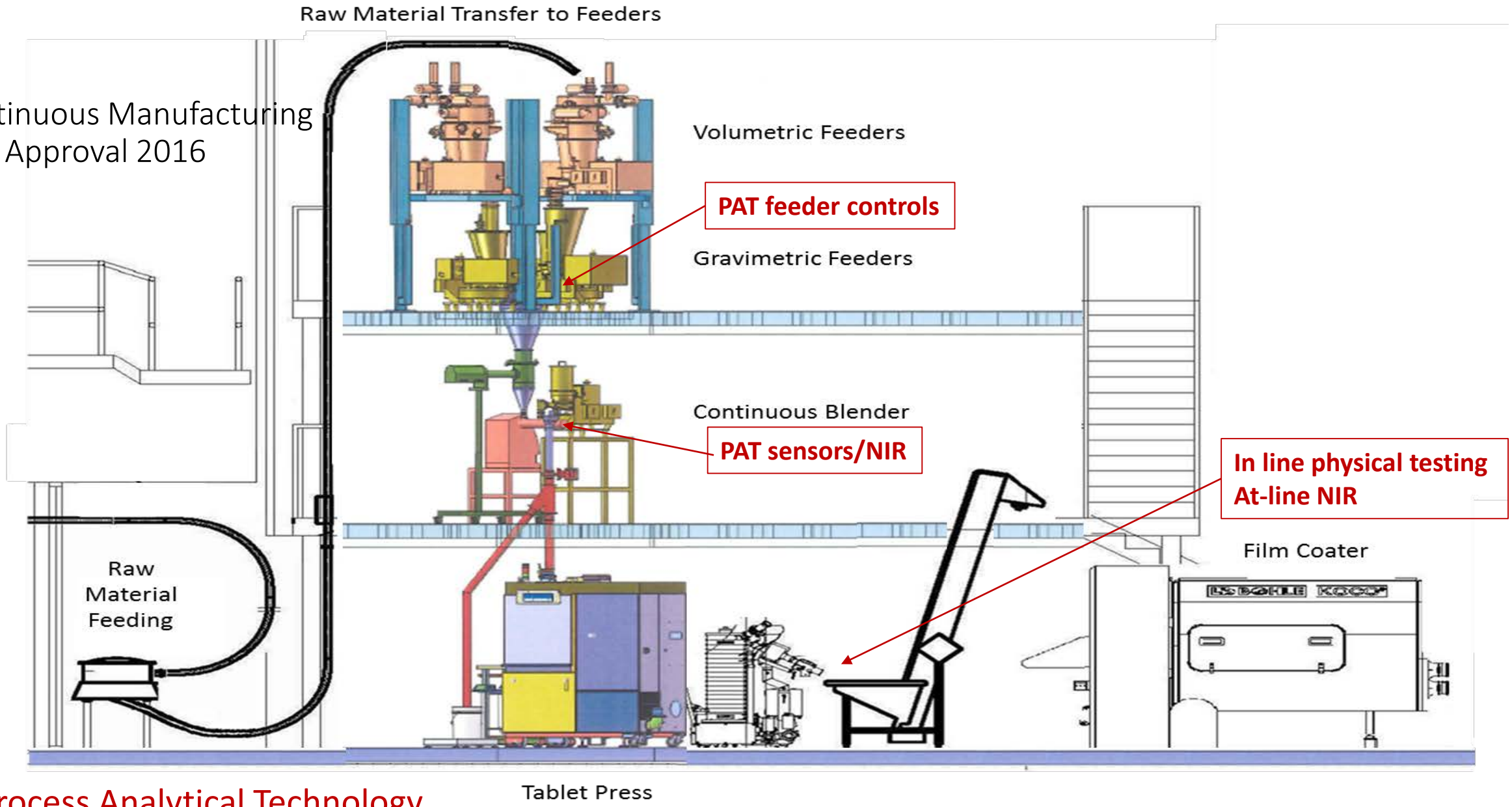
Real time process corrections were enabled through the digital twin

Reduction of 9 ton of material usage and waste

Project timeline reduced from 7 to 2.5 month

CM for Solids

Continuous Manufacturing
FDA Approval 2016

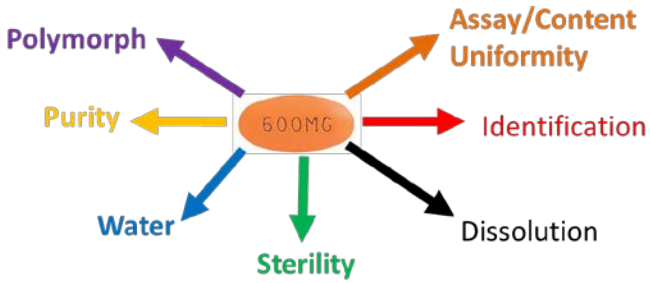


PAT = Process Analytical Technology

MANUFACTURING for the FUTURE
Enhancing customer value through innovation and digitization

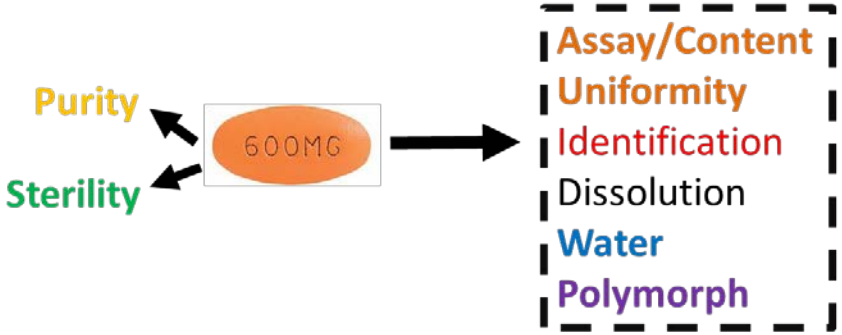
Tablet Release Testing

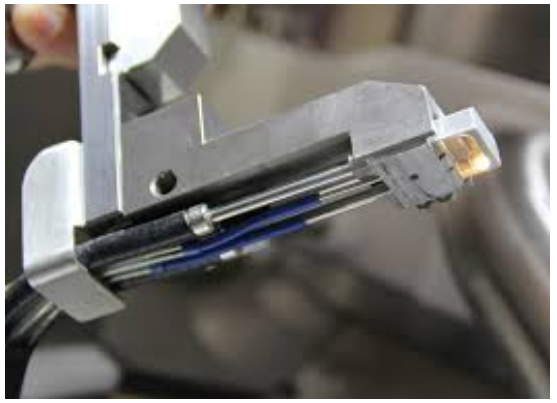
Current



7 different Instruments –
Days/Weeks/Month to release

Future





1 instrument–
Minutes/Hours to release

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CM for Solids results

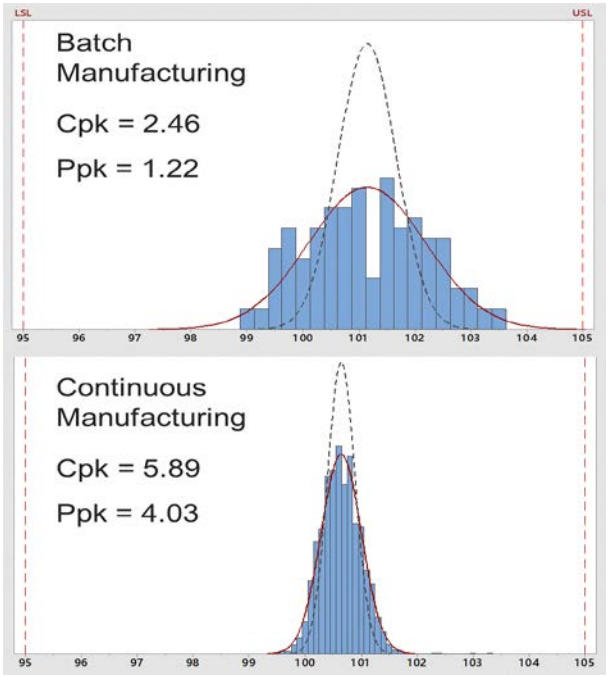
	Batch Process 2008		Continuous Manufacturing Process 2016		Continuous Manufacturing Process with Surrogate Dissolution Model 2019	
CQA	RTRt	Laboratory	RTRt	Laboratory	RTRt	Laboratory
Identification		√	√		√	
Assay		√	√		√	
Uniformity of Dosage Units		√	√		√	
Chromatographic Purity		√		√		Sunset
Dissolution		√		√	√	
	> 21 days		8 days		< 1 day	

- Cycle time from batch start to release

Batch	CM with RTR
41 ± 10.5 days	7.6 ± 1 days

- Assay Cpk & Ppk : **+ 140 %**

Batch	CM with RTR
Cpk = 2.46 (6 sigma) Ppk = 1.22	Cpk = 5.89 (>>6 sigma) Ppk = 4.03



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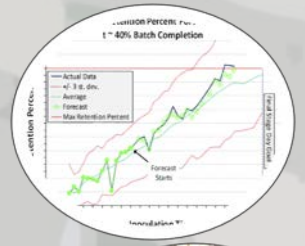
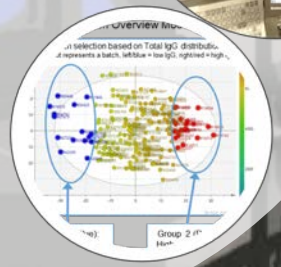
Advanced Monitoring and Process Control

- ❑ *Proactive analysis*



- ❑ *Shop floor awareness*

- ❑ *Retrospective optimization*



5-30% titer increase potentials found in sites analyzed

Control variables ID'ed & undergoing testing or implementation

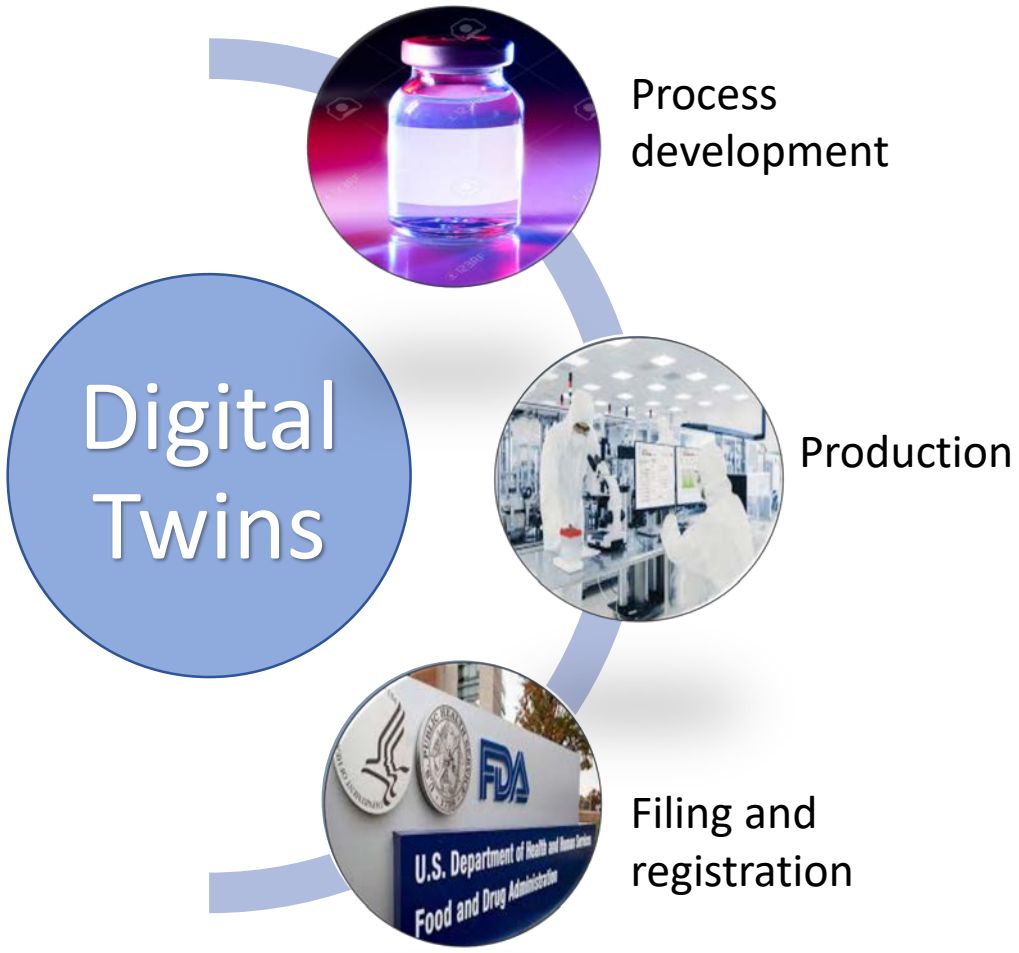
Solutions are re-usable site to site, type to type

Value generation is accelerating

Outline

1. Path covered so far
2. **Our next steps**
3. Internal barriers
4. External barriers
5. Opportunities for new process technology deployment

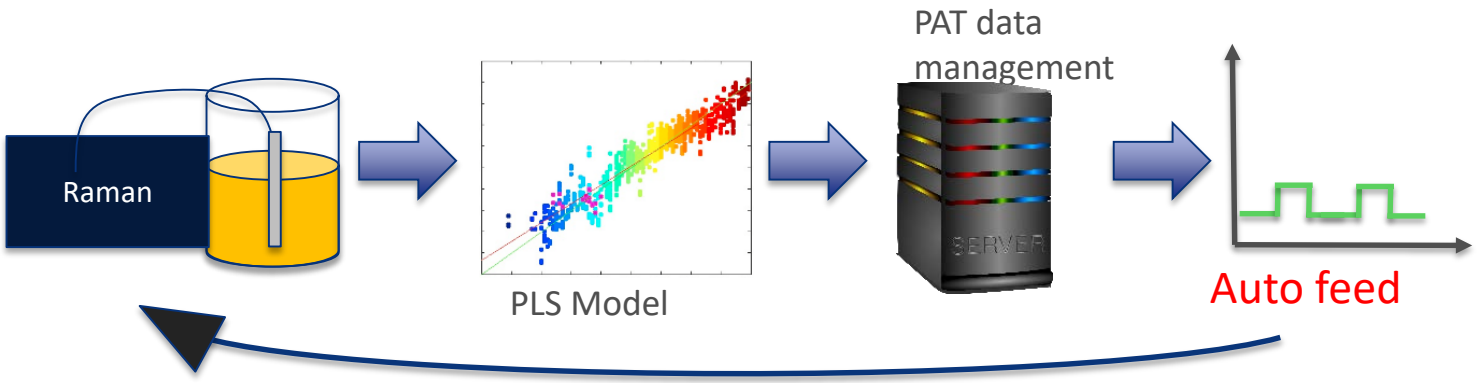
Digital Twins for API processes



Digital Twin	
Development	Production
In-Silico process design	Best in Class NPI timeline
Advanced Process control	Class leading Quality
Filing Support	Best Process at Launch
Agile plant	Flexibility

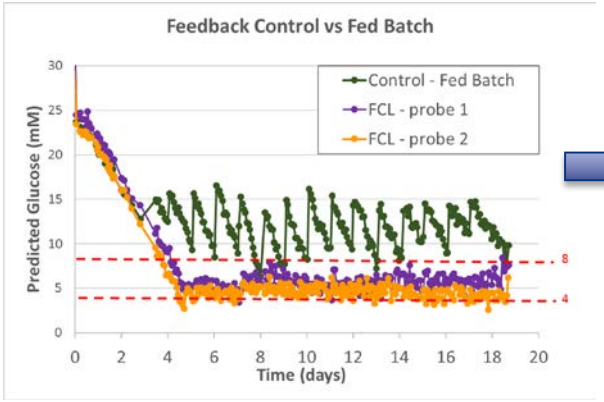
Science and data based tech transfer. Reduced risk, shorter timelines

Advanced Sensors for control in LM

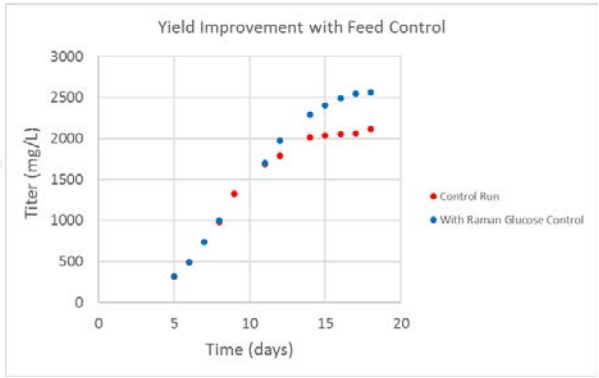


- ❑ Consistent batch profiles equals consistent product
- ❑ Consistent growth equals consistent titer
- ❑ Control feed and metabolites equals enhanced control of QAs

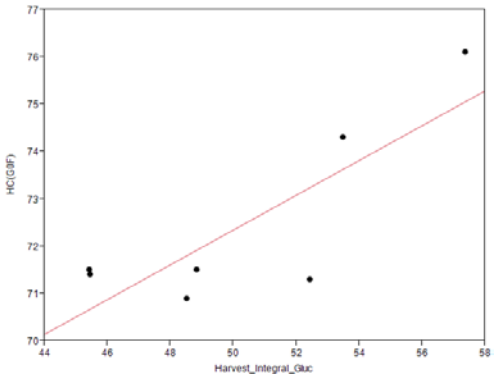
Process Control



Product Yield



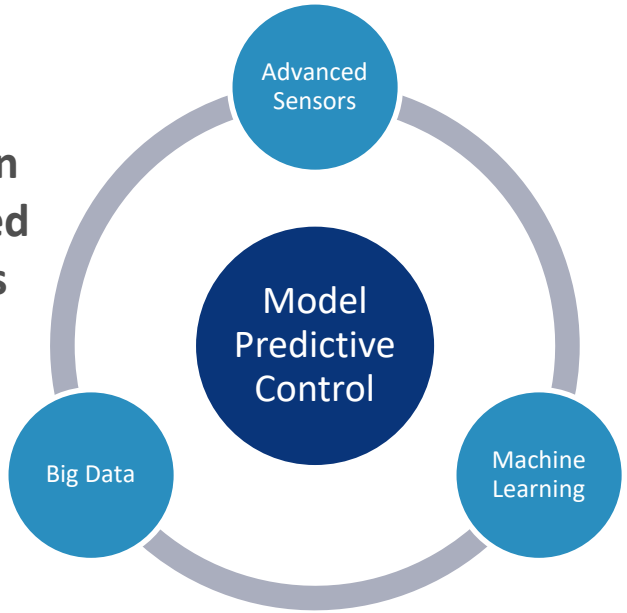
Product Quality



Accelerated Technology Transfers

Demonstrating control and reproducibility of product quality attributes from clinical through PPQ

Quality awareness in real time w. advanced sensors and models



Advanced Process Control for Quality and Productivity

Development to validation data trail demonstration control and reproducibility

Modular design of software and Hardware

Because pipeline is extremely volatile: flexibility is needed

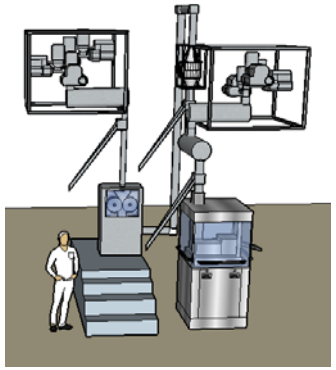
More / different feeders

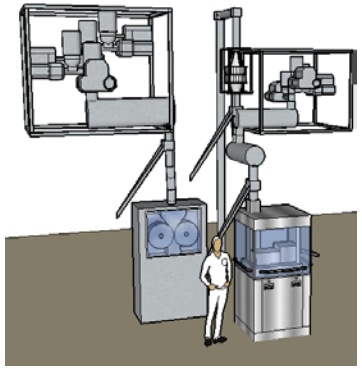
PAT tools and rejects on different locations

Replace Roller Compaction by bigger type - up to 200kg/hr

Replace Press by bigger type – up to 250kg/hr

Incorporate other technology if relevant





Start with low throughput

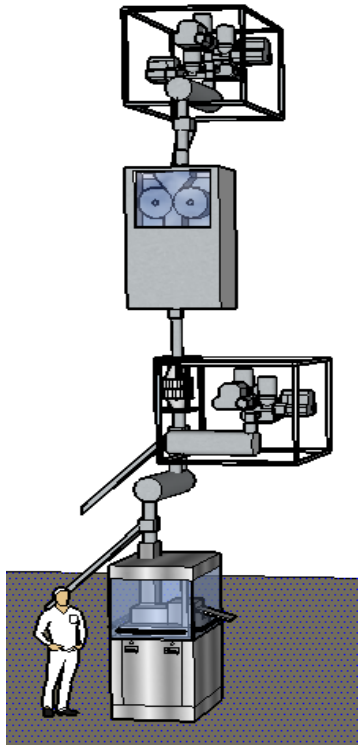
Lower cost

Only decide investment when volumes are more certain

Transform into high throughput line if volume is real

Test, qualify, easy swap

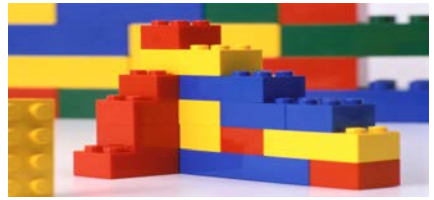
Different cofigurations possible



Flexible epuipment needs modular design:

→ Modular integration software to minimize reprogramming effort

→ Standardized software and hardware interfaces to allow different scale and brands of eqt



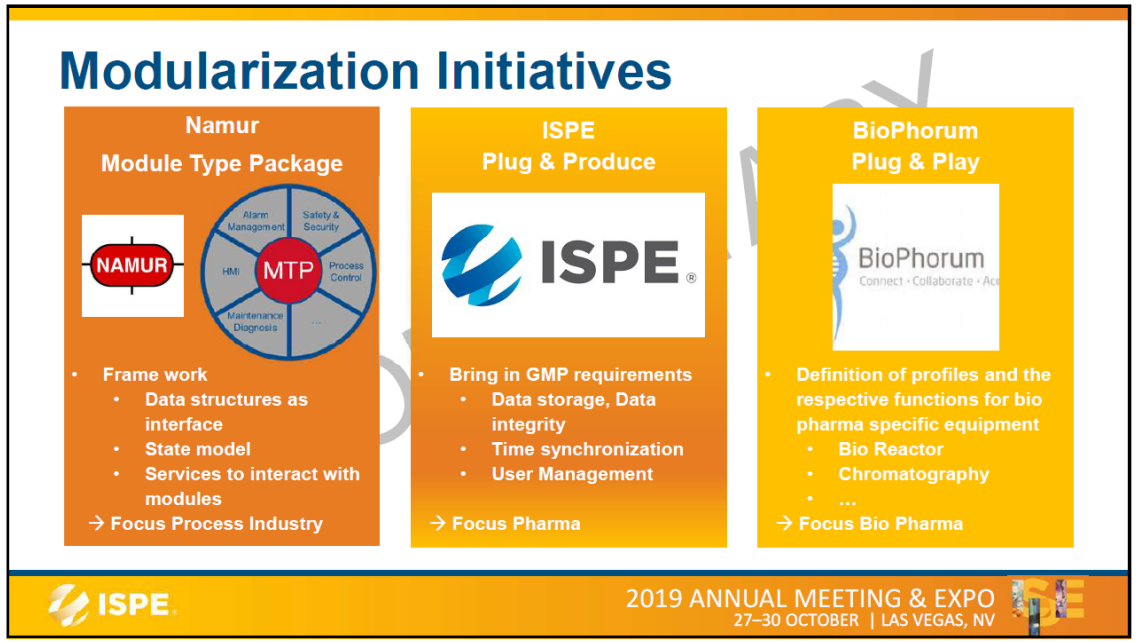
Modular concept as standard for the Industry

Industry evolution:

→ Pharma companies joining forces in ISPE to design modular lines with standardized interfaces

→ Several consortia working on interface standards: Namur, ISPE Plug & Produce, Biophorum, MMIC

→ Most Pharma companies work on standardization in their own platform – industry standardization is long term.



BioPhorum	• Definition of profiles and the respective functions for bio pharma specific equipment • Bio Reactor • Chromatography • Normal Flow Filtration	
ISPE P&P	• Bring in GMP requirements • Data storage, Data integrity • Time synchronization • User Management	• Definition of a profile for Formulation units
Module Type Package	• Frame work • Data structures as interface • State model • Services to interact with modules	
OPC UA	• Transport of semantic data • Data Access, Alarms and Conditions, Historial Access … • Secure transport due to certificates • Services	
Ethernet, TCP/IP		

Source: ISPEAM 2019 Las Vegas (Keith Morris)

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Internal challenges

- **Can be more challenging than external**

Why

- **Uncertainty in interpretation of existing regulation**
  - **Eg. – definition of “batch” in CM**
- **Faster approval process if there are no Agency questions**
- **“Avoiding potential delays” for BLA/NDAs of critical assets**
- **Filing the “how” instead of the “what” seen as safer**

External health authorities often have avenues for advice

Adoption of new technology in existing plants

- Existing plants are often “OEE” and cost focused
  - New technology cost = upfront investment & regulatory risk & lead time
    - Reduce time to implementation from initial investment
    - Reduce risk of regulatory delay or rejection
- Need to change plant/reg culture to value a data rich environment
  - Operating staff monitors continuously and acts when needed
    - From: execute and test
    - To: Real time quality awareness and action. Continuous improvement

https://jnj.sharepoint.com/sites/PHM-GCSP/JIL

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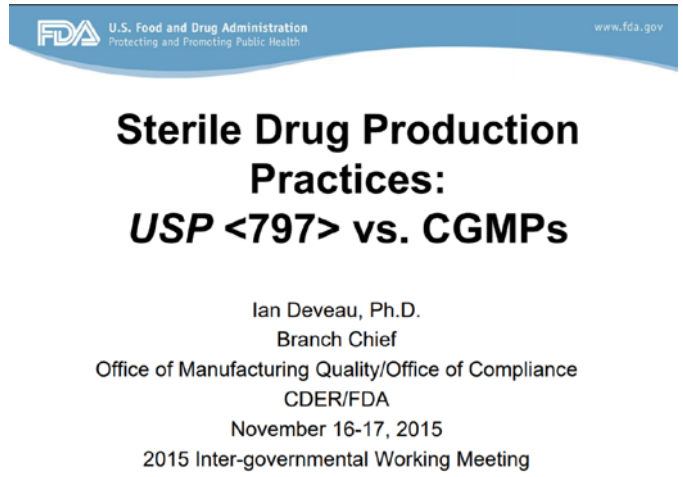
- ***Where are the regulatory challenges?***

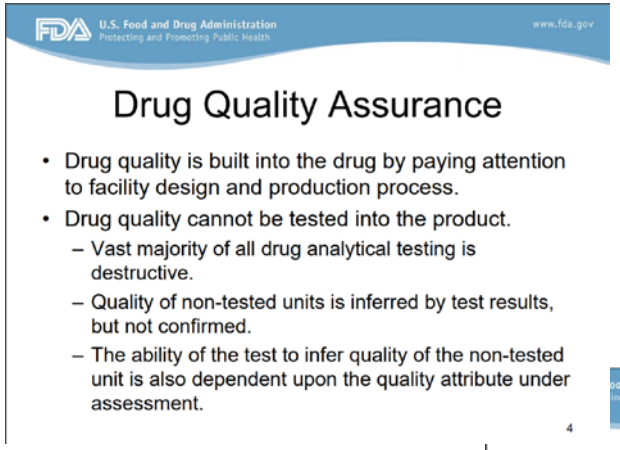
- **Some provisions made a lot of sense for our historical off-line analytical methods and limited batch to batch control capability**
  - **Fixed # of samples / batch with some statistics**
  - **Test methods needing to be discriminatory to process variation batch to batch**

- **New mfg. technology for batch and CM are leading to more varied batch sizes, inline analytics, and higher fidelity ways to detect batch to batch variation.**
  - **How do we translate these capabilities into better quality control without fitting them into the historical standards**


U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Sterile Drug Production Practices: *USP* <797> vs. CGMPs

Ian Deveau, Ph.D.
Branch Chief
Office of Manufacturing Quality/Office of Compliance
CDER/FDA
November 16-17, 2015
2015 Inter-governmental Working Meeting


U.S. Food and Drug Administration
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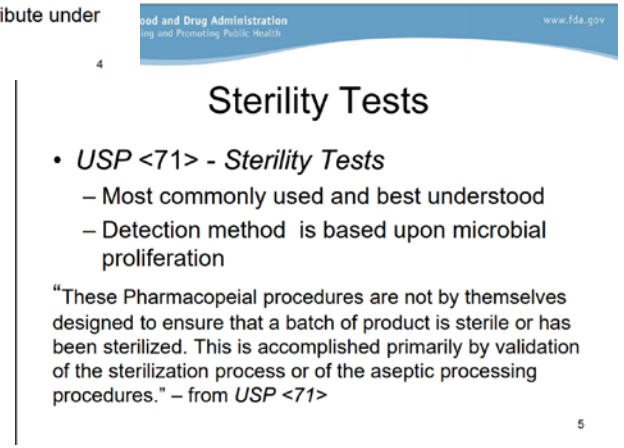
Drug Quality Assurance

- Drug quality is built into the drug by paying attention to facility design and production process.
- Drug quality cannot be tested into the product.
  - Vast majority of all drug analytical testing is destructive.
  - Quality of non-tested units is inferred by test results, but not confirmed.
  - The ability of the test to infer quality of the non-tested unit is also dependent upon the quality attribute under assessment.

4


www.fda.gov

Sterility Tests

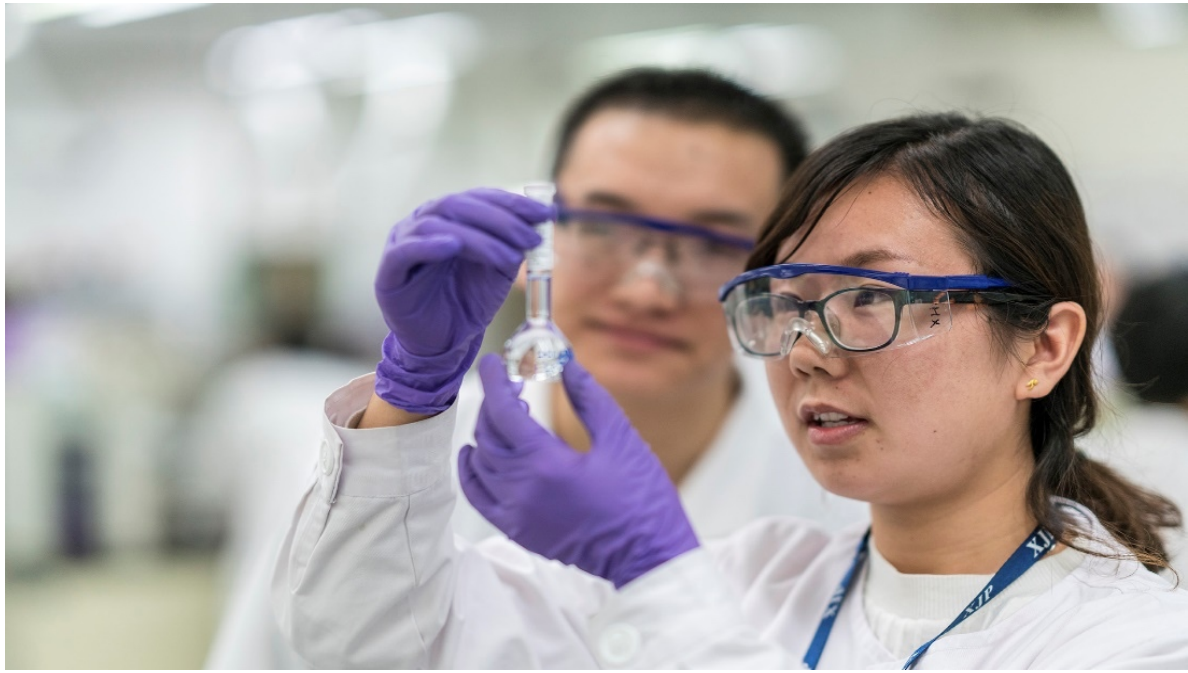
- *USP* <71> - *Sterility Tests*
  - Most commonly used and best understood
  - Detection method is based upon microbial proliferation

"These Pharmacopeial procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by validation of the sterilization process or of the aseptic processing procedures." – from *USP <71>*

5

• *Where are the regulatory challenges?*

- **Inline testing**
  - **Not a sensitive and capable as offline testing and may never get there**
  - **Is generally on the full batch in flow systems or gives a “finger print” of the batch trajectory**
  - **Often saves money, if not requiring significant redevelopment of process or test**
  - **Can increase agility and flexibility of supply**
- **How to best compare the value of offline tests with inline test for total patient value**
  - **Supply agility, lead time, quality, cost**
- **Real time predictive analytics, process health check models supplemented by selective, multi-attribute testing is superior approach to control**



Digital Twins and Advanced Process control for Process Validation

- *Where are the regulatory challenges?*

- All products go through a set of technology Transfers
  - Lab to clinical supplies, first commercial supplies, business continuity, localization, capacity build-out
- Historically TTs have been treated individually one site to another, but data analytics, APC, Digital Twins and PAT allow holistic comparison of all processes in real time
- There is a great desire to reduce the TT timelines and cost as these negatively impact supply chain agility.
- DT/APC/PAT technologies enable rapid and safe Tech transfers. Should reduce timeline from years to months

Regulatory barriers?

Best practice for innovation: Agency interaction is a fruitful process, not a barrier. Need to discuss how to interpret old regulations. Need to have honest, perhaps intense scientific discussions to bridge perspectives and interpretations

A Couple of examples

- FDA approved replacing daily off line testing of a clinical production bioreactor with real time advanced inline monitoring, since lab capacity was reduced by COVID-19

- We are exploring using an inline probe to detect bioburden in real time. Will not replace bioburden/sterility testing at the end but should allow us to proceed between operations without off-line testing and with real time assurance of quality

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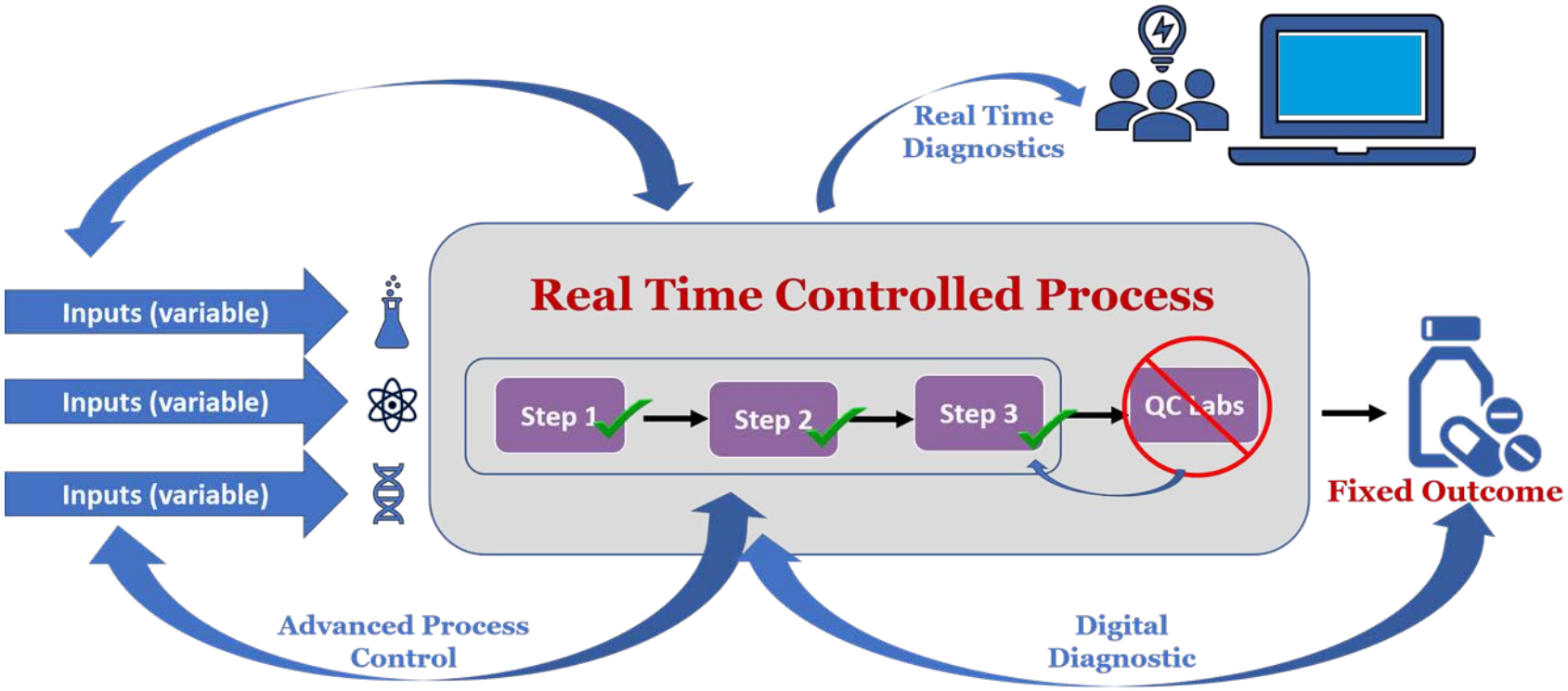
Moving from procedural control to engineering controls



This represents a fundamental shift for ensuring process control and reliability. Move from sample and test to real time awareness

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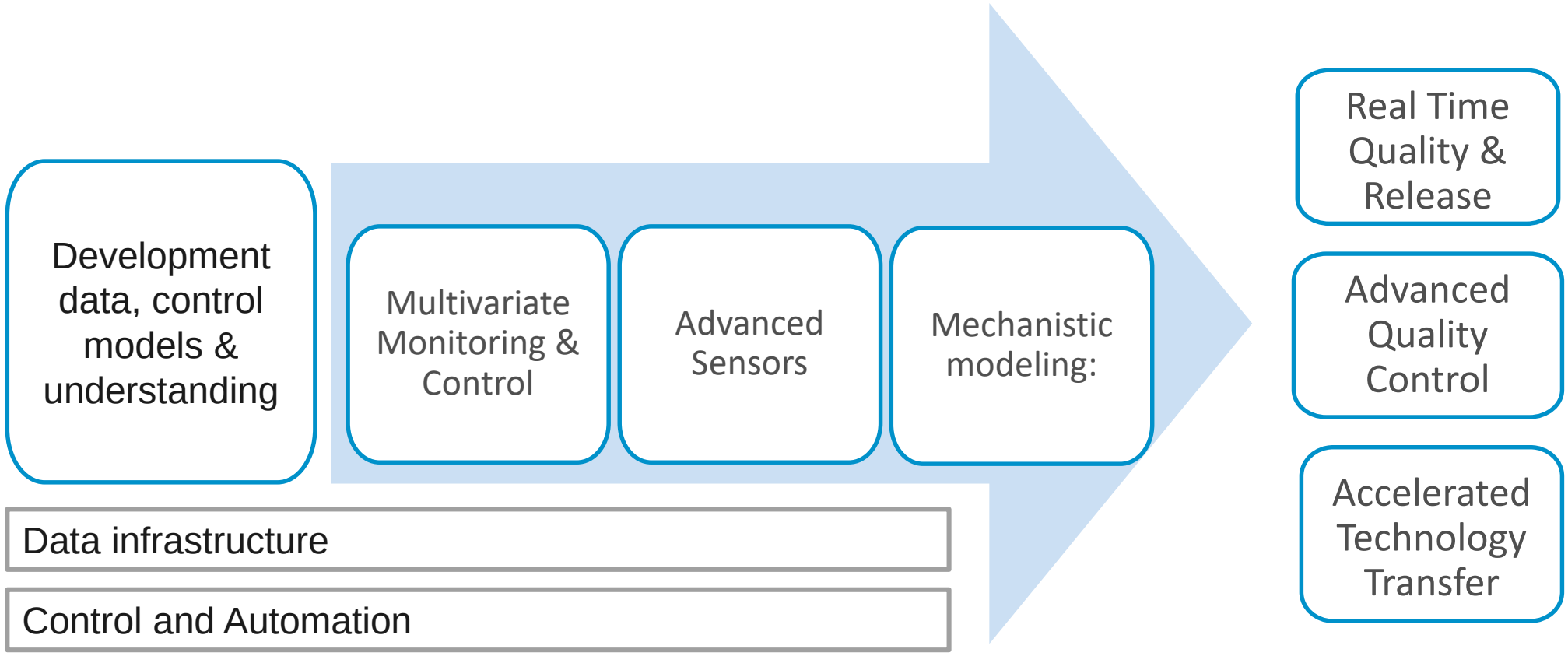
Digital Twin & APC Components



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Digital Twin & APC Components

Real Time Quality & Release	Advanced Process Control	Accelerated Technology Transfer
Opportunities		
Inline and real time data technologies are maturing Framework for RTRt by use of process fingerprinting, real time data and advanced multi-attribute methods	Real time process data and APC has significant potential for legacy products How to implement APC to further enhance quality and reliability	TT based on real time comparability Framework for TT away from the traditional set of batches to real time performance approach.

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"There is nothing more difficult to take in hand, more perilous to conduct, or more uncertain in its success, than to take the lead in the introduction of a new order of things."
— Niccolo Machiavelli
The Prince (1532)

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