ENGINEERING PHARMACEUTICAL INNOVATION

Process Analytical Technology (PAT) / Quality by Design (QbD):

Integrated Systems in the Future Pharma Business Landscape

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SIEMENS

Presentation:

This presentation describes several applications of PAT and QbD approaches in bioprocess development and manufacturing for (1) monitoring, (2) controlling, (3) real-time release and (4) optimization. Examples from various cases will be presented, including new process analytic concepts for bioprocess monitoring, design of experiments, and multivariate data analysis.

Participants will gain valuable insight and a useful roadmap for leading their organizations to make the necessary changes for PAT and QbD.

Presentation Topics:

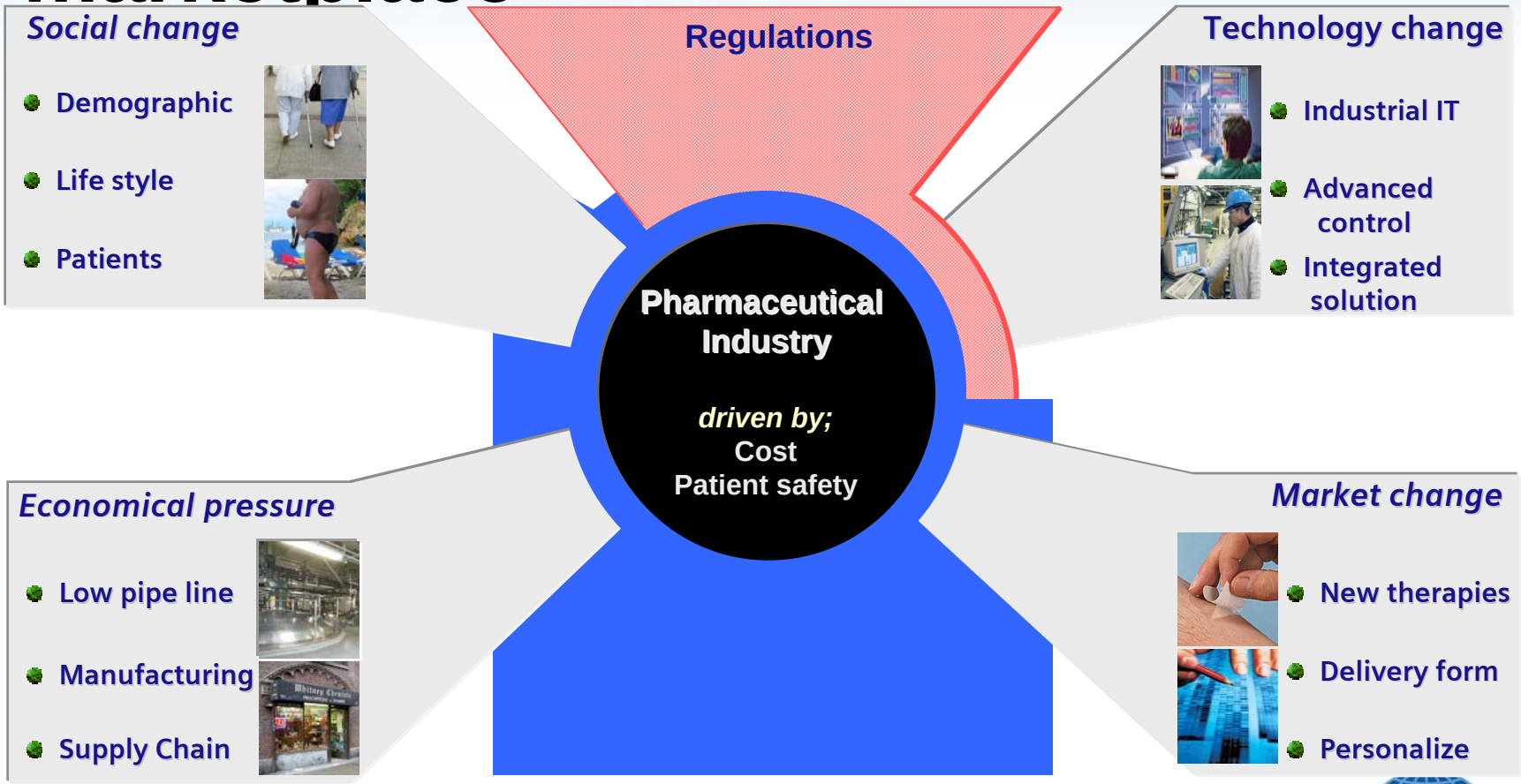
- PAT is more than just monitoring
- PAT benefits and regulatory approaches
- Measuring what and how? Some examples on new process analytic (PAT) concepts for bioprocess monitoring, design of experiments, multivariate data analysis
- Advanced Process Control and real-time product release
- PAT as part of the manufacturing and development architecture
- PAT as a continuous process understanding and improvement tool
- PAT and future manufacturing strategies

The actual challenge:

Prices of drugs are under pressure, costs and time for development are increasing, the capacity utilization level in manufacturing has to improve, cost of quality is high, ...

How can we shorten development time, shorten production cycle time and at the same time increase operational efficiency

Changes and impacts on the pharmaceutical manufacturing marketplace



How things will change and what will be supporting technologies for the future vision?

On short, medium and long term

New technologies and alternative strategies shaping future R&D & Manuf.

- PAT/ Quality by Design
- PLM
- SPC

- Continuous Mftg. Concepts
- Miniaturized manufacturing
- PAT / real-time product release
- Condition based maintenance

- Demand driven manufacturing
- Modular plant design
- Recipe driven manufacturing
- Disposable manufacturing

- Clinical trial management
- R&D Suite (WFM, Data portals)
- E-licensing
- PLM

Built-in Quality

Increase manufacturing performance & throughput

Flexible Manufacturing concepts

Speed-up development & closing the gap

How will companies cope with the changing environment?

What will be future challenges?

- Changes due to new production technologies
- Increase operating efficiency
- Reduce product costs / achieve competitive pricing (e.g. response to biogenerics)
- Produce individual products / address niche markets (Personalized Medicine)
- Accelerate time-to-market

What is the strategic response?

What will be the implications on the way we manufacture in future?

PAT / QbD will be a key enabling technology for future manufacturing scenarios.

Manufacturing strategic leaps to the medium and long term: Future Manufacturing Strategies

Scenario 1:
Modernize within existing facility
But, essentially same approach & scale

Scenario 2:
Continuous processing, RTPR, JIT production

Scenario 3 = Specialty Niche products:
Small scale pilot centers, Integration of R&D and production: Small batches 24/7 running

Scenario 4 = Gross / mass market:
Large-scale highly flexible plants, with high throughput

Move to personalized medicines

Clinical and patient feed-back loops

Continuous optimization and improvement

5 year | 10 year | 15 year

Short term future (within 5 years)

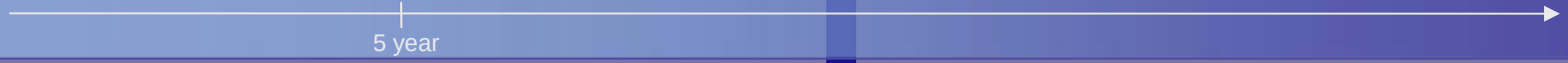
What will be future challenges?

What will be the implications on the way we manufacture in future?

What is the strategic response?

- Increase operational efficiency (OEE)
- **PAT (Process Analytical Technology) / QbD**
- Electronic data acquisition and Data Management
- EBR
- MES
- PLM
- Real-time enterprise (data integration and management, dashboards / cockpits, facilitating real-time decision making)

Scenario 1:
Modernize within existing facility
But, essentially same approach & scale



The regulatory changes & PAT / QbD

New pharma regulations

The US authority FDA started an initiative to:

- **improve manufacturing quality (reduce the risk of bad quality products)**
- **accelerate development**
- **lower the regulatory burden (inspections)**

to allow process changes and optimizations throughout the product lifecycle

•FDA's new principles:

- **Process Analytical Technology (PAT)**
  Understanding + controlling the manufacturing process
- **Quality by Design and Design space**
  PAT principles for process development
- **Quality systems approach**
  Reflecting product & process understanding and knowledge

PAT / QbD definition

- Process control trough new technologies focusing on manufacturing science
- A system for designing (process development), analyzing and controlling manufacturing processes, based on timely measurements of critical Q & performance attributes
  of raw-materials, in-process materials and processes with the goal of ensuring final product Q.
- Processes to assure acceptable end-product Q at the completion of the process *(quality by design)*
- Focus on understanding

PAT / QbD is a key enabling technology for future development and manufacturing

The regulatory landscape & PAT / QbD

New regulations

FDA's new initiatives to:

- improve manufacturing quality
- accelerate development
- lower the regulatory burden

FDA's new principles:

- risk based approach
- scientific approach, based on process understanding

PAT (Process Analytical Technology)

- **PAT = Understanding + controlling the manufacturing process**
- **A process is well understood when:**
  - **All critical sources of variability are identified and explained**
  - **Variability is managed by the process**
  - **Product quality attributes can be accurately and reliably predicted**
- ***Process Understanding is inversely proportional to risk***

FDA's new draft guidance on process validation

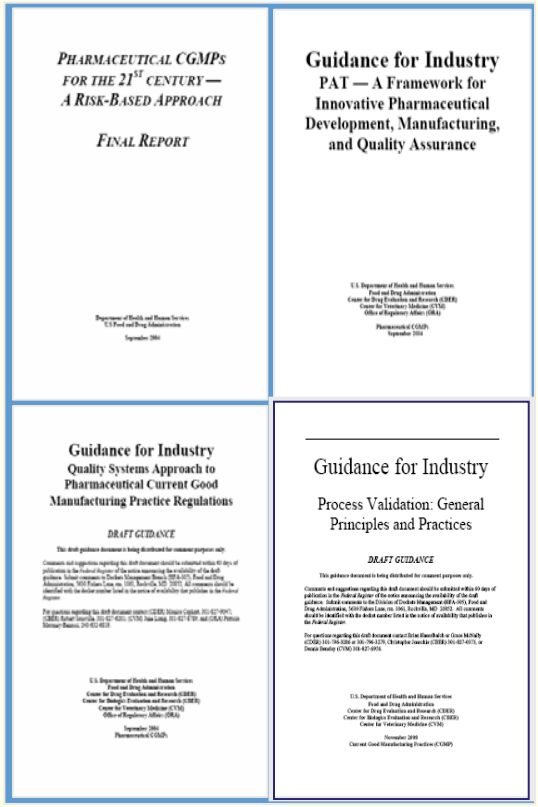
New regulations

FDA's new draft guidance on process validation: General principles and practices

Nov 2008

Mentions the concept of

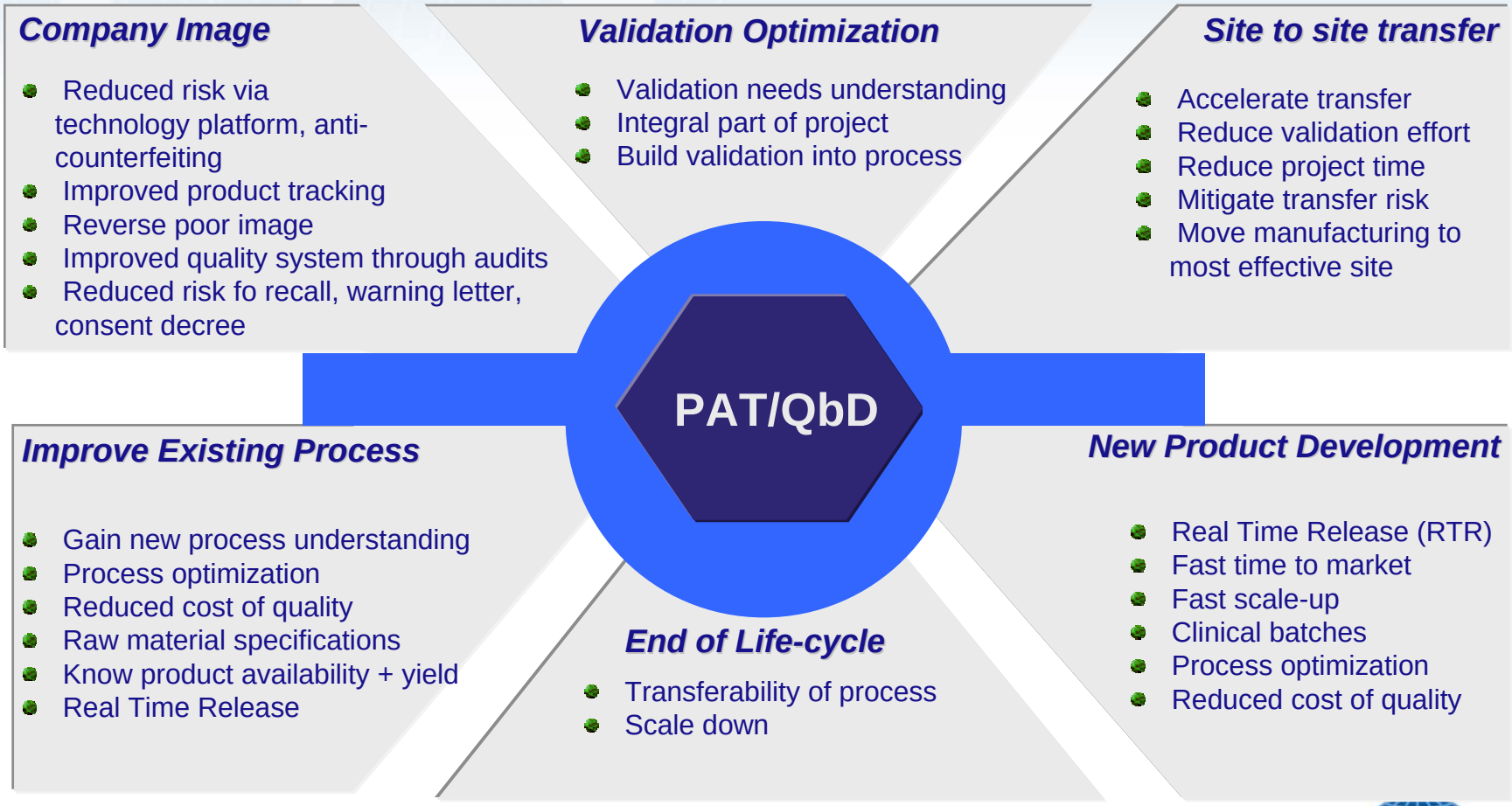
- an integrated team, requiring collaborative work
- capturing process knowledge (based on "*ensuring uniform collection and assessment of information about the process*") and understanding, and facility design and equipment selection.
- Continuous Quality Verification



Guidance on Process Validation

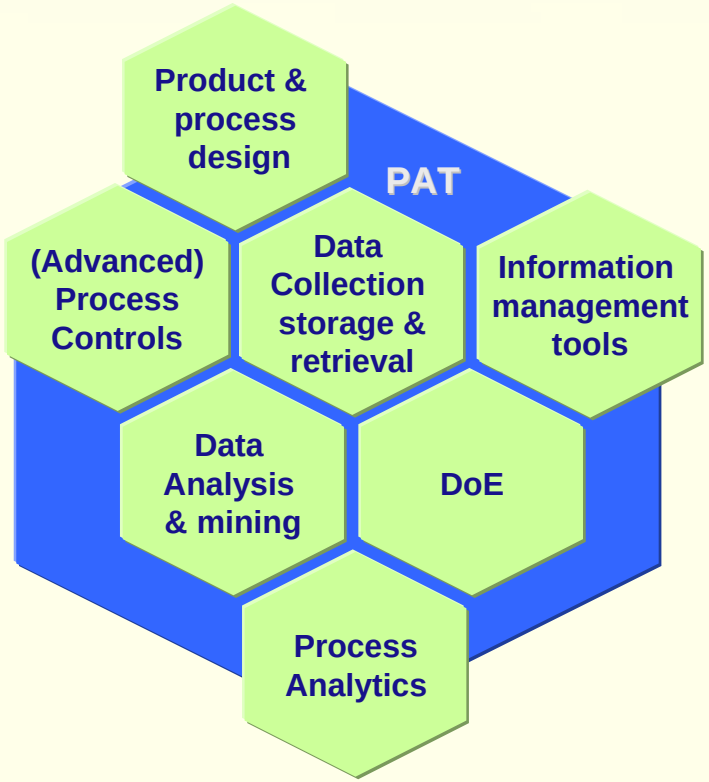
- This new guidance includes their current thinking on advances in manufacturing technology (a.o. PAT / QbD) and aligns process validation activities with the product lifecycle concept.
- Defines process validation: *"as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products."*

Business Drivers for PAT/QbD

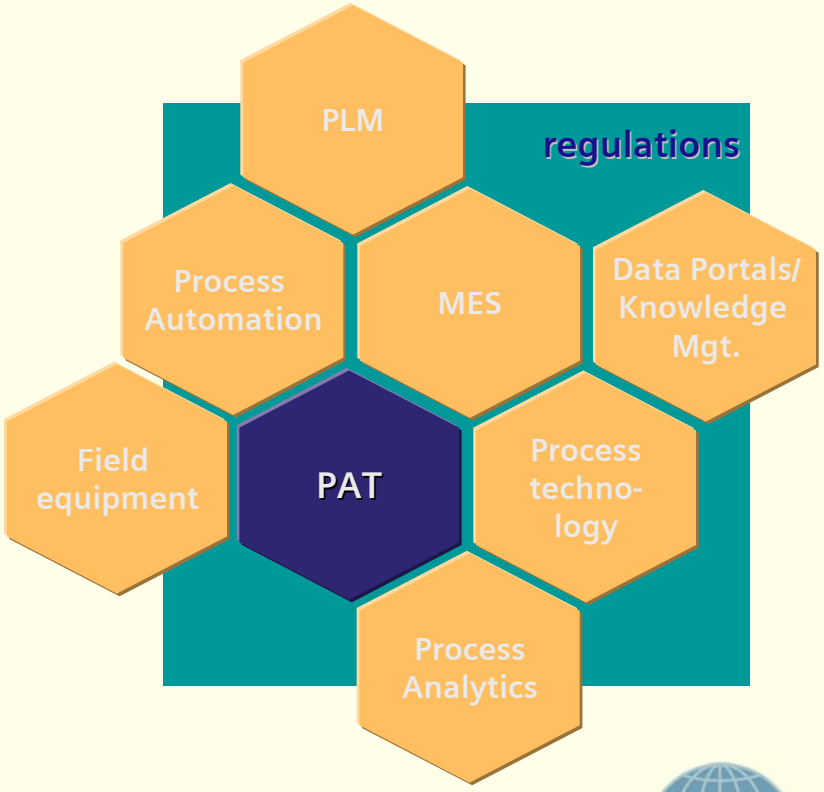


PAT / QbD the skill set and architecture fit

PAT Toolbox / Skill set

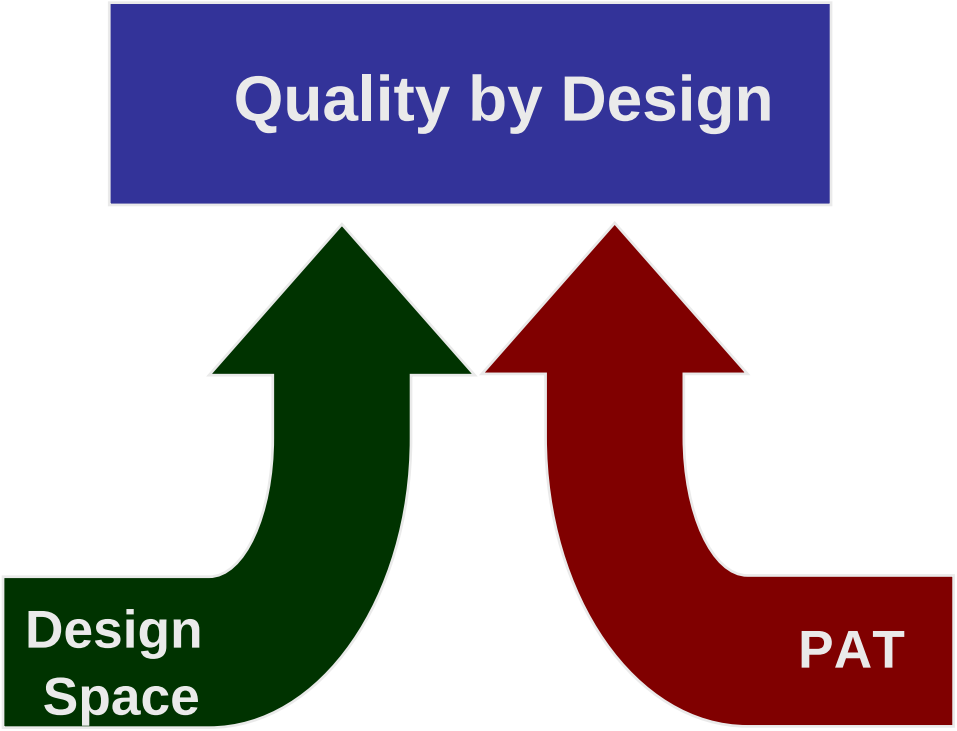


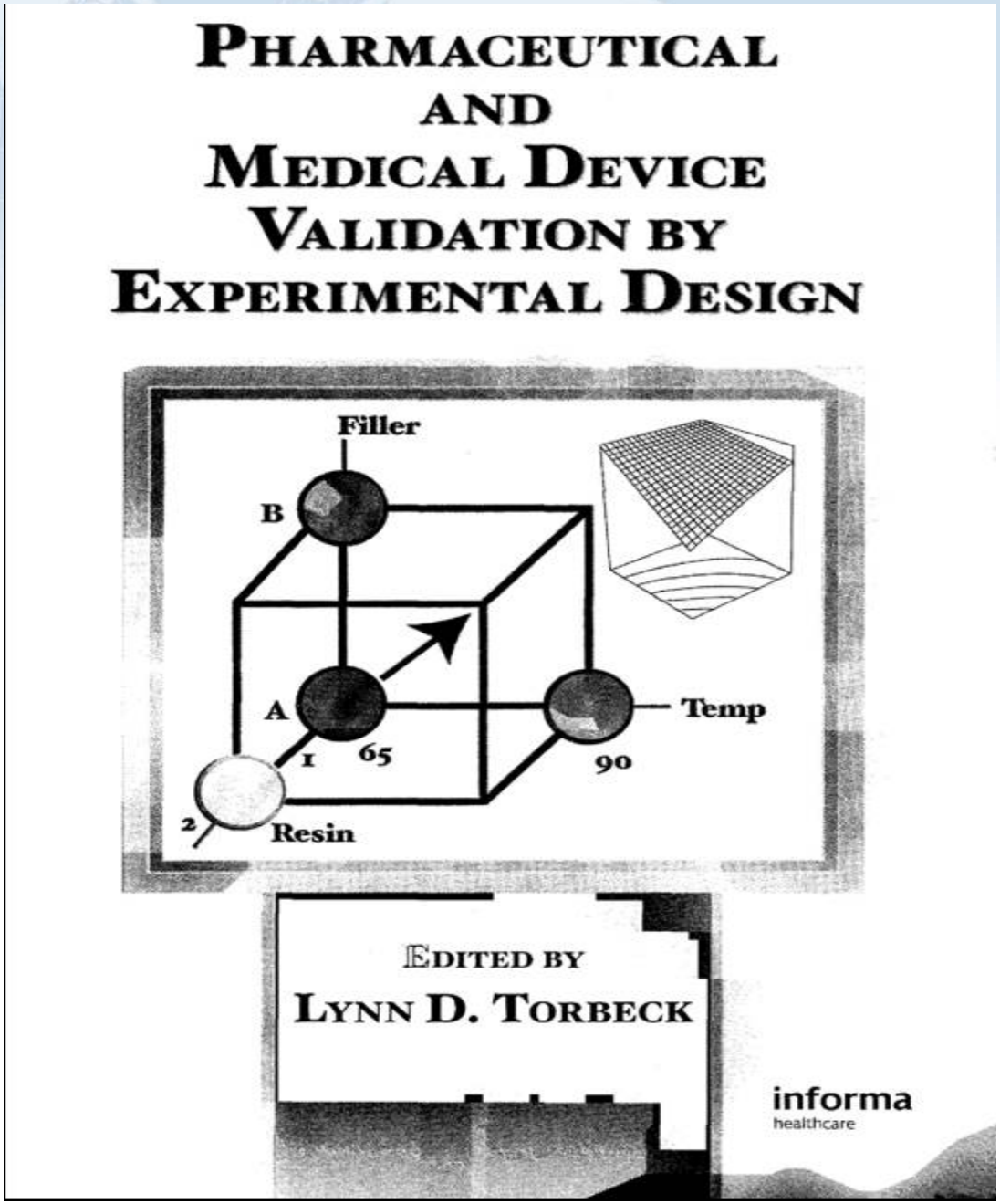
Fit in development & manufacturing landscape



PAT and QbD

“Quality by Design is the overarching paradigm and Design Space and PAT are tools to achieve this end”





Forward Summary Section:

- DOE is the fastest route to a profitable, reliable, robust, validated process.
- DOE's requirement of a rigorous design methodology that passes peer review with the scientists most knowledgeable about the process ensures scientific soundness.
- The depth of DOE's statistical foundation enables measurement of multiple effects & interactions in a single set of experiments proves DOE's statistical validity.
- DOE is also a resource conservator, since it requires less time and provides data quicker than single factor at a time experiments.
- The proven statistical validity of the DOE technique guarantees accurate analysis of the data and valuable information for management to turn data analysis and interpretation into action.

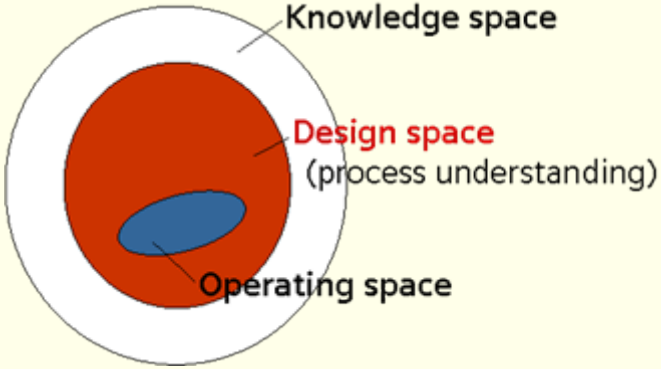
Ronald C. Branning
Genentech, Inc.
South San Francisco, California, U.S.A.

Design space

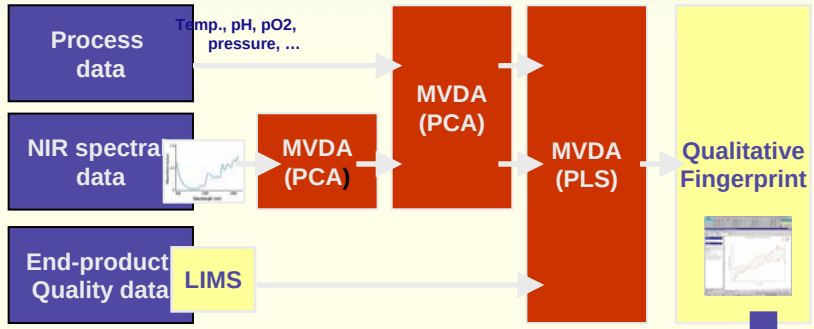
Operating limits ?

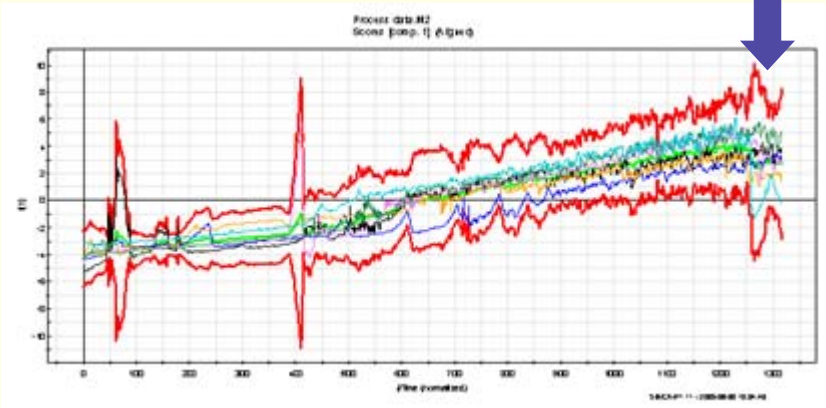
- Relationship between process parameters and end-product quality / performance ?

- Systematic approach to explore and document the design space:
- **Multi-factorial DoE**



Design space exploration

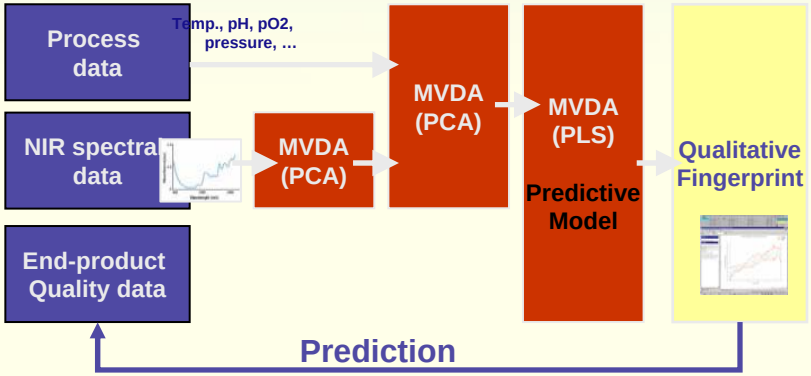




Golden batch trajectory
Design space limits = Control limits

PAT shifts monitoring and control from process data to product quality

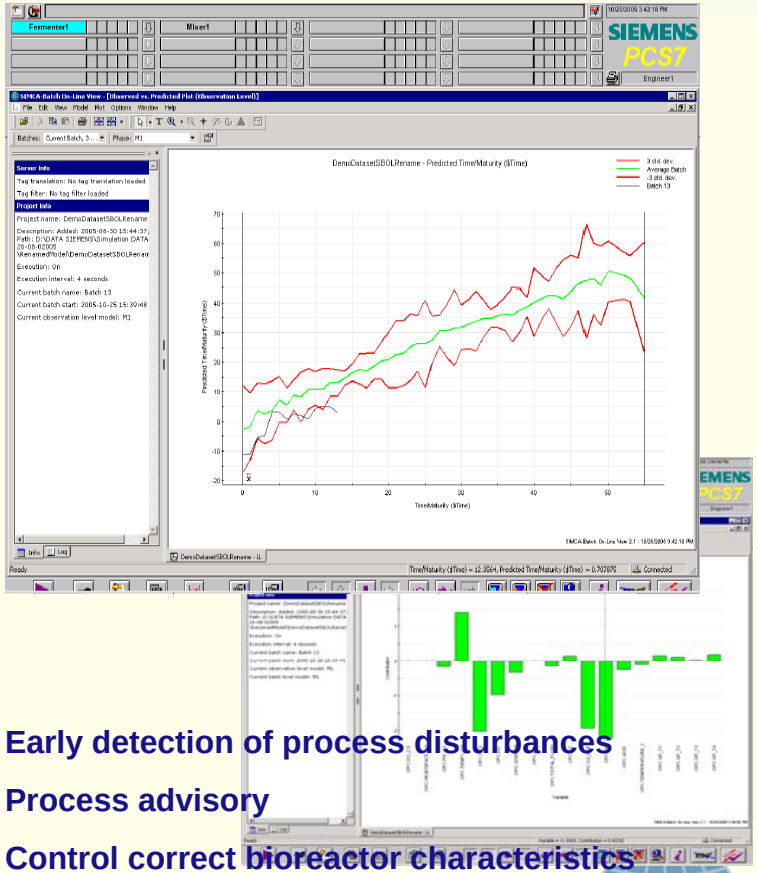
Predicting end-product quality



- **Based on real-time monitoring of NIR trajectories and process data, predict end product quality and performance**

- **CTQ parameter:**
  - Continuously measured **OR**
  - Aperiodically measured **OR**
  - Real time value Inferred from calibration model **OR**
  - End-point value inferred from calibration model **OR**
  - Scores of calibration model are CTQ parameters

PAT as part of the process control environment



- **Early detection of process disturbances**
- **Process advisory**
- **Control correct bioreactor characteristics**

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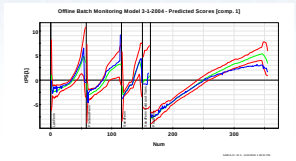
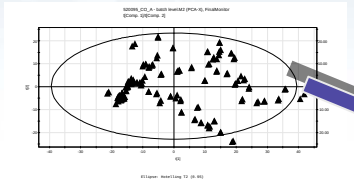
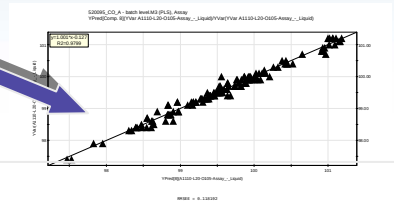
And from design space to process control

Batch process visualization across different unit operations

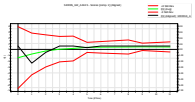


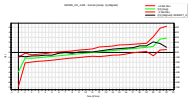


Release



PAT hi level system





Raw mats./ conditioning	Synthesis/ Downstream	Formulation	Finishing	Packaging

PAT	PAT	PAT	PAT	PAT

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The PAT/QbD system architecture

- Integrating PAT with process automation and control systems
- the wider perspective

PAT / QbD as part of the overall architecture

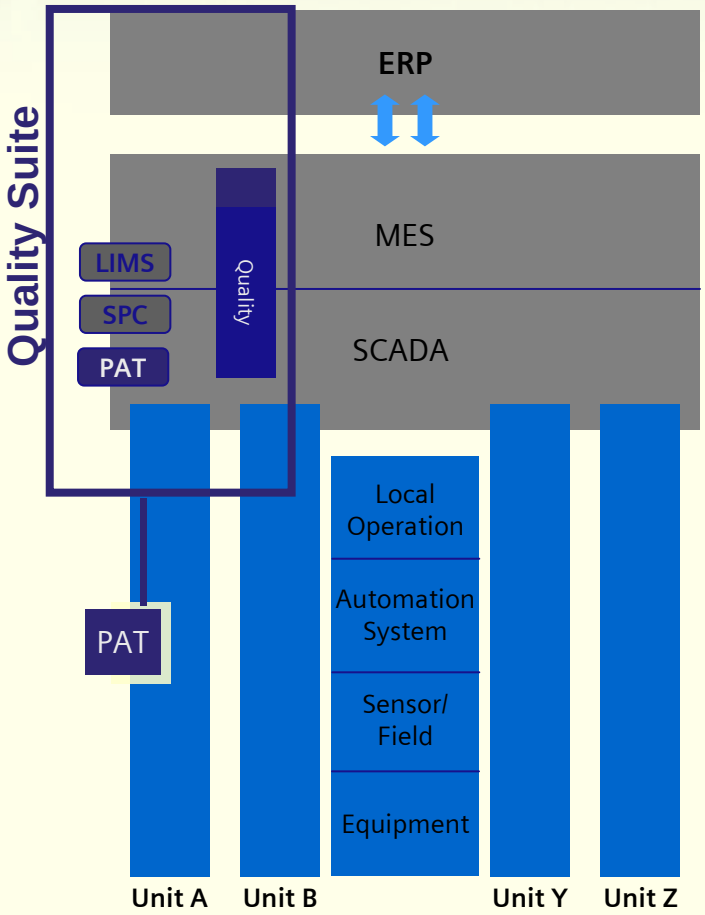
Just measuring the quality of the end product is not good enough anymore

An integrated Quality System, from shopfloor to boardroom to support:

- **6 sigma and continuous improvement**
- **Regulatory process & review (continuous quality verification)**
- **Management performance (time-to-market, progress in development process, optimisation of quality, manufacturing costs, manufacturing cycle times, etc.)**
- **Demand driven manufacturing and supply**
- **That reflects product & process understanding and knowledge**

Time-based information Management

Manufacturing Architecture



Quality Suite

An integrated Quality System, from shopfloor to boardroom to support:

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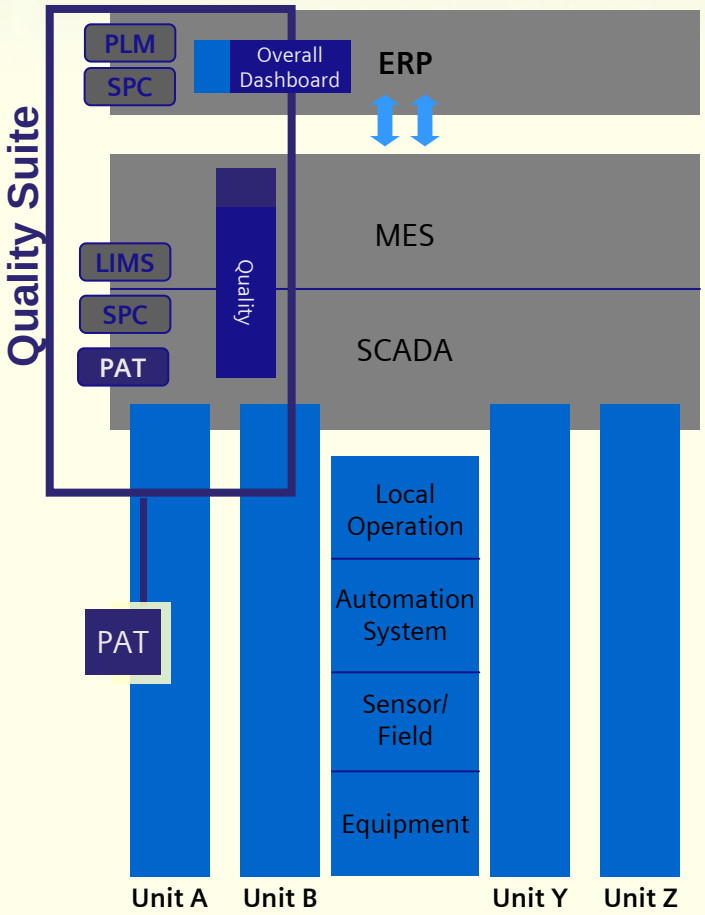
Quality Suite

Manufacturing Architecture



Quality Suite

- **Quality Suite**, contains:

- **On shopfloor (in manufacturing):**
  - PAT
  - LIMS
  - M-SPC/SQC
  - Business intelligence suite (Quality cockpit)

- **On boardroom level**
  - SPC
  - Dashboards
  - Central data warehouse + integration layer to R&D and manufacturing
  - PLM and Knowledge Management

All integrated from shopfloor to boardroom

Mid term future (in 5 to 10 years time)

What will be future challenges?

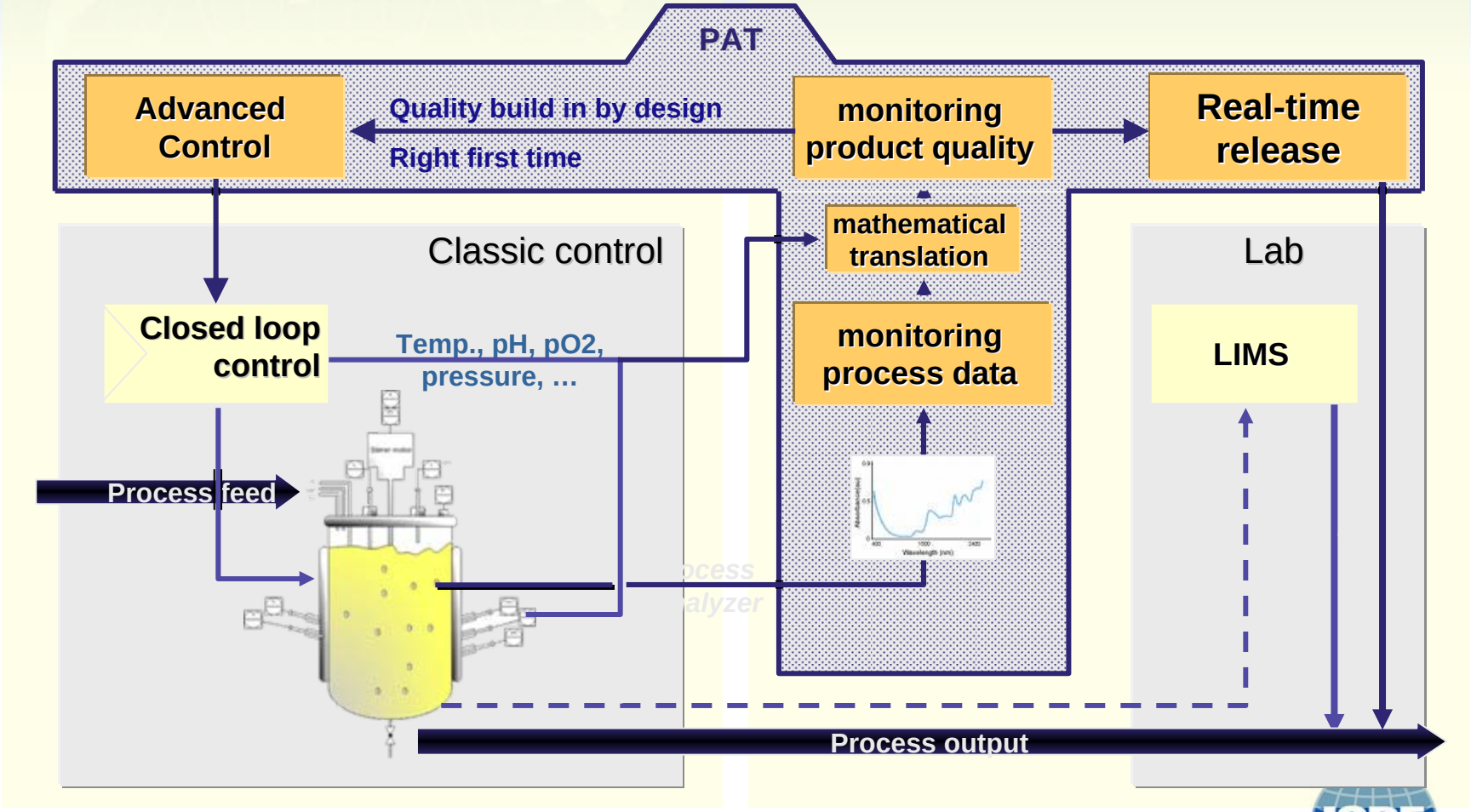
What will be the implications on the way we manufacture in future?

What is the strategic response?

- New manufacturing technologies: shift from batch to continuous manufacturing methods
- Real-time product release
- Just in time manufacturing
- Real-time enterprise

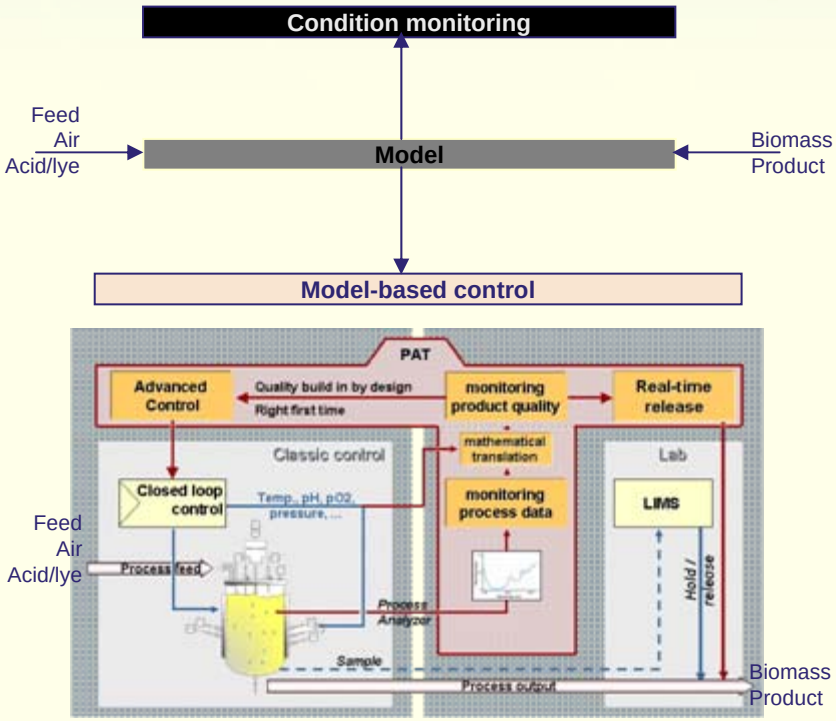
Scenario 2:
Continuous processing, RTPR, JIT production

PAT shifts monitoring and control from process data to product quality



Continuous manufacturing

PAT enabled continuous processing



- **Adjusting process conditions in real-time, based on PAT enabled end-product quality prediction**
- **Steady-state processing**

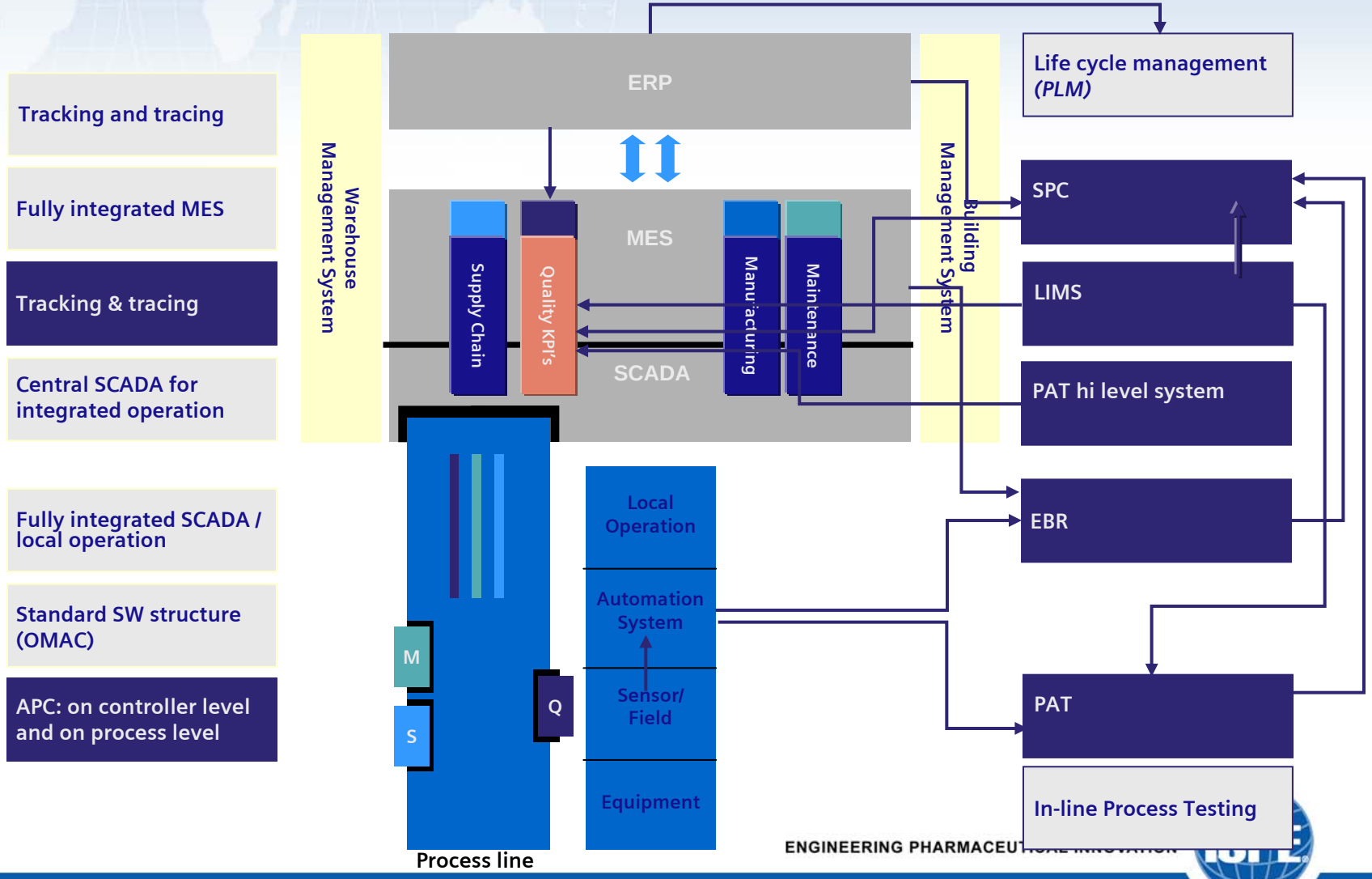
Continuous manufacturing

Multivariate condition monitoring and real- time optimizing to optimize raw material and utility usage in order to significantly reduce variable operating costs and, therefore, improve profitability of a manufacturing process.

Real time tools supporting continuous manufacturing:

- **PAT / QbD**
- **SPC**
- **APC**
- **Automation solutions for lab and manuf. (PLC – DCS)**
- **Tracking & tracing, genealogy**
- **Time-based information management (Historian)**
- **Reproducible & documented reconfiguration of continuous production**
- **Production tracking system**
- **Manufacturing performance and quality dashboards**
- **PLM: Automation designer, product & process specification management**
- **Micro-analytics (lab-on-a-chip, cell-on-a-chip, micro-spectroscopy) and Lab process technology**

Answer for data management in continuous manufacturing?



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Long term vision:

R&D and Manufacturing integration
“Closing the gap”

Long term future (in 10 to 15 years time)

What will be future challenges?

What will be the implications on the way we develop and manufacture in future?

What is the strategic response?

- Integration of R&D and manufacturing
- Real-time enterprise
- Highly flexible plants
- Real-time planning & scheduling
- Continuous learning and continuous quality verification

Scenario 3 = Specialty Niche products:
Small scale pilot centers, Integration of R&D and production: Small batches 24/7 running

Scenario 4 = Gross / mass market:
Large-scale highly flexible plants, with high throughput

Move to personalized medicines

Clinical and patient feed-back loops

Continuous optimization and improvement

The Regulatory vision

Today

New initiatives to:

- improve manufacturing quality
- accelerate development
- Lower the regulatory burden

FDA new principles:

- Quality by design & design space
- Quality systems approach
- Reflecting product & process understanding and knowledge

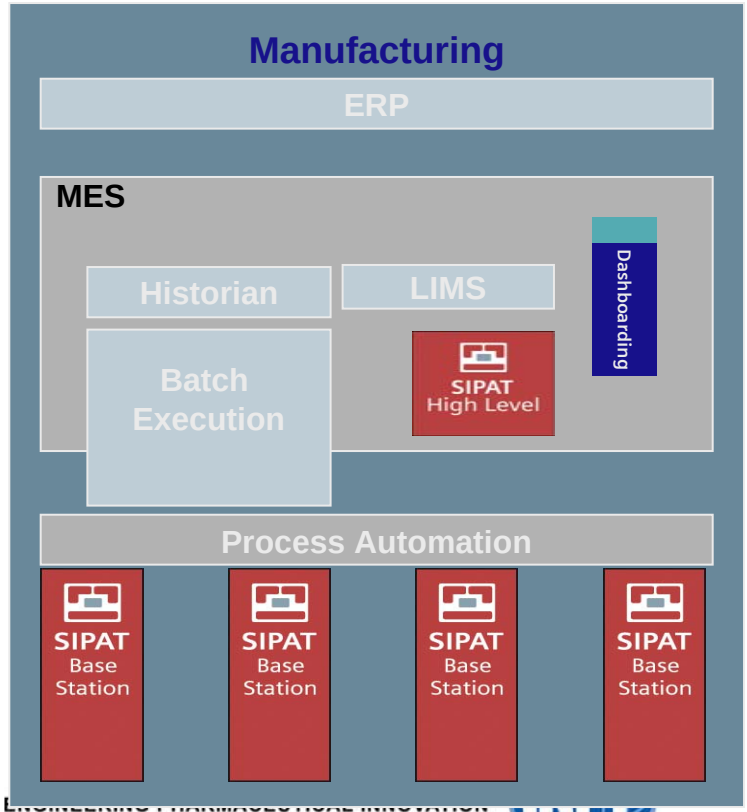
Vision

FDA's future focus:

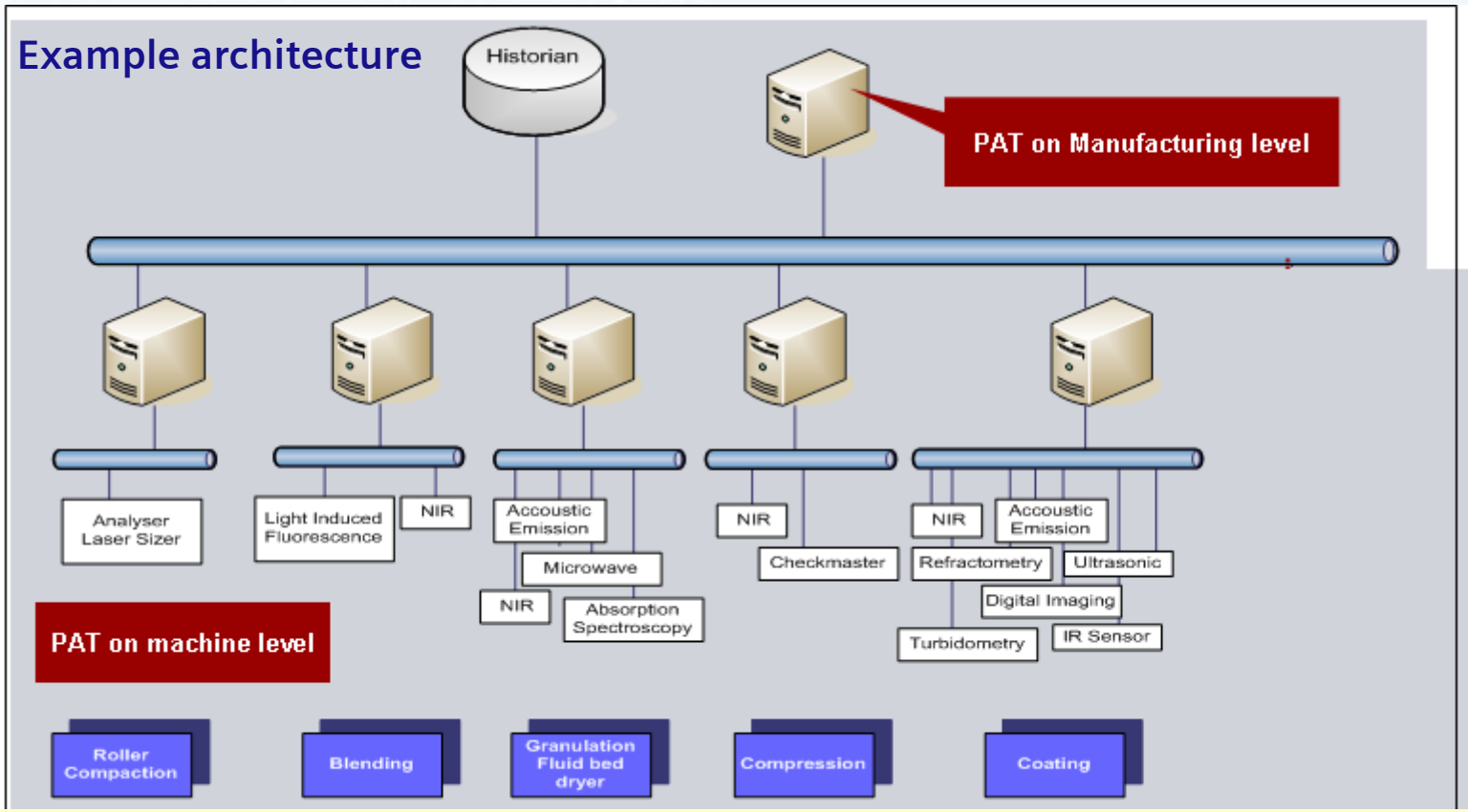
Keynote address at IFPAC February 2007, by FDA's Chief Medical Officer, Dr. Janet Woodcock, on

- Development & manufacturing should be integrated
- Development of quality surrogates for clinical performance (link critical product attributes to clinical outcomes)
- Rigorous, mechanistically based and statistically controlled processes

PAT/QbD in Manufacturing

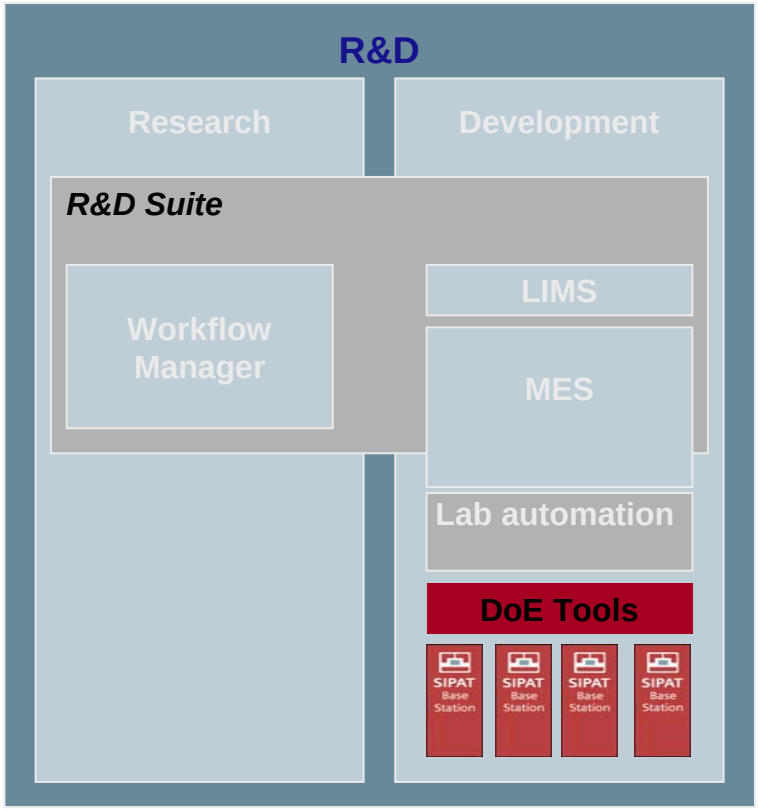


Case: PAT/QbD in Manufacturing



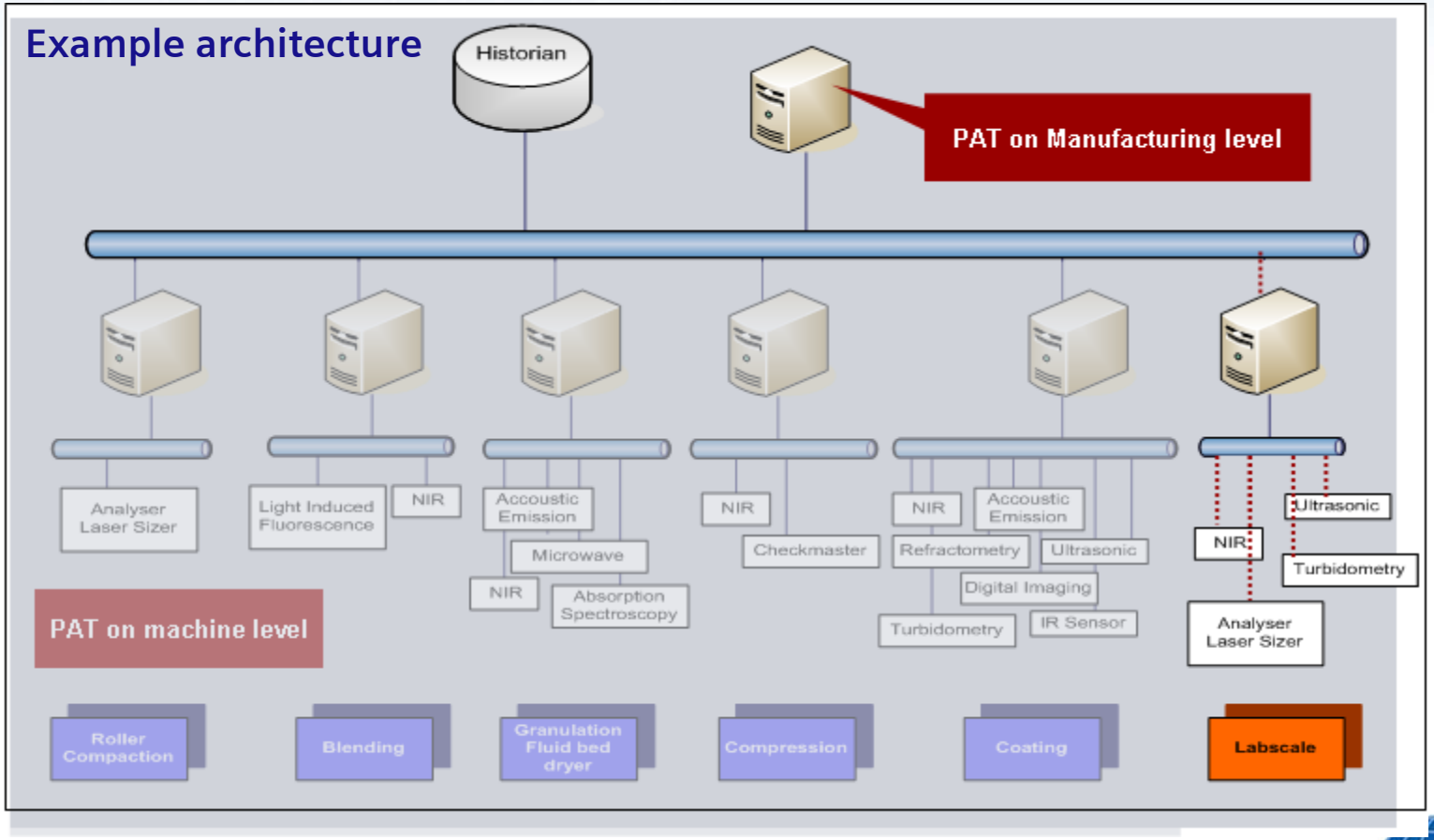
The overall Architecture is based on a distributed approach with a PAT/QbD software solution per process area

PAT / QbD in R&D



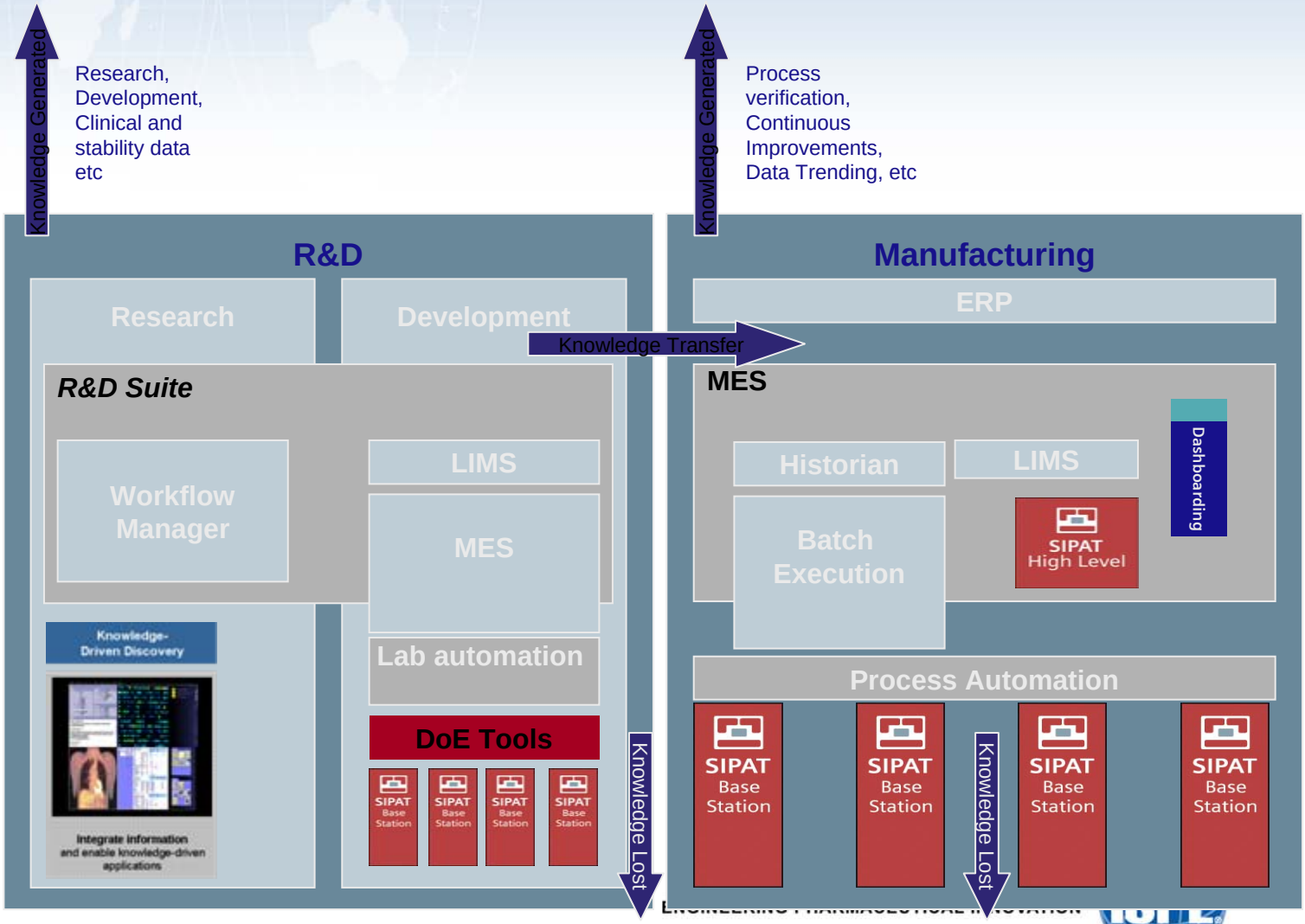
- To support process development / Explore the design space Collects process knowledge on:
  - equipment/product interaction
  - equipment behavior
  - impact on final product quality
- To support production of clinical batches
- Allows to fasten process up-scaling and transfer (to manufacturing)

Case: PAT/QbD in Development



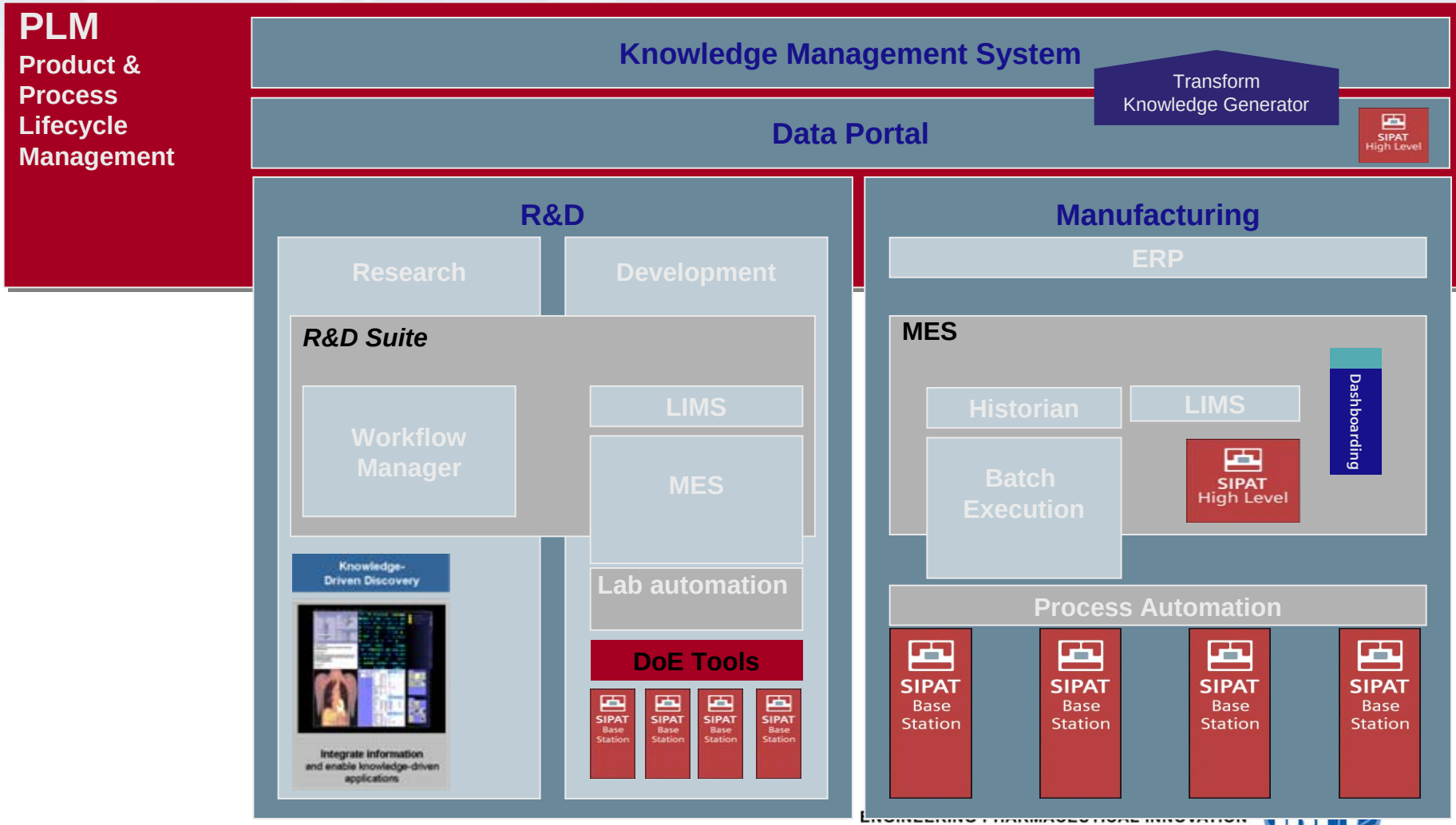
Knowledge is lost throughout the product lifecycle

Need for a Repository of Knowledge

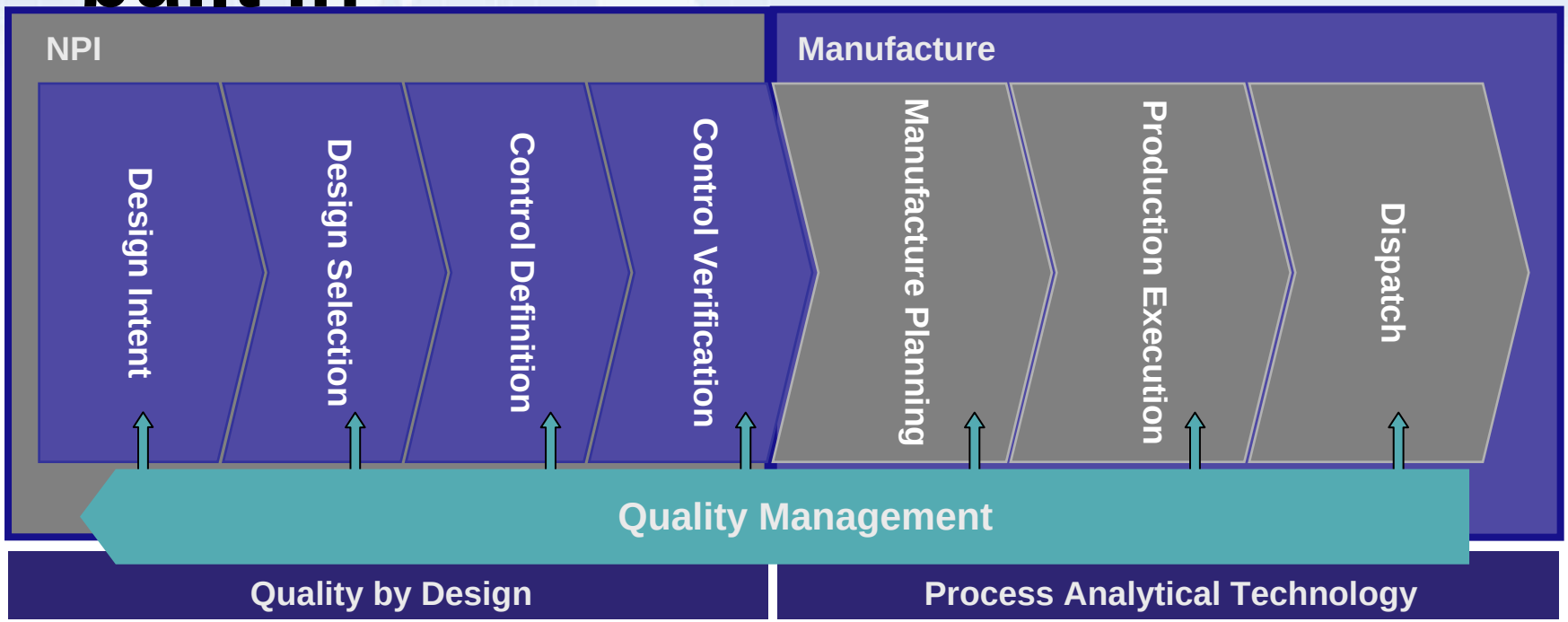


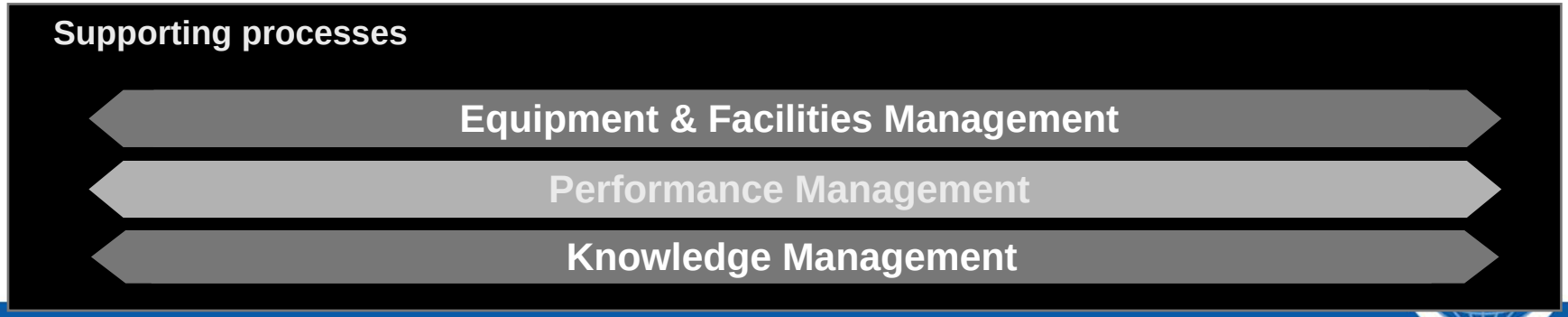
Knowledge loss occurs throughout the products life cycle at each key stage

Closing the gap: R&D and Manufacturing integration



…To a situation where quality is ‘built in’

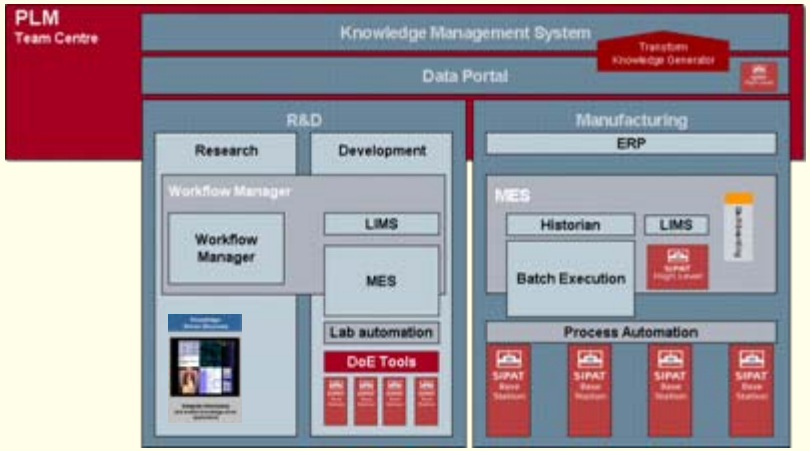




To-Be business model where we have a continuous learning environment

Closing the gap: development and manufacturing integration

Closing the gap



Answers FDA's future focus:

- **Development & manufacturing should be integrated**
- **Development of quality surrogates for clinical performance**
  (link critical product attributes to clinical outcomes and critical process parameters)
- **Rigorous, mechanistically based and statistically controlled processes**

Development and manufacturing integration

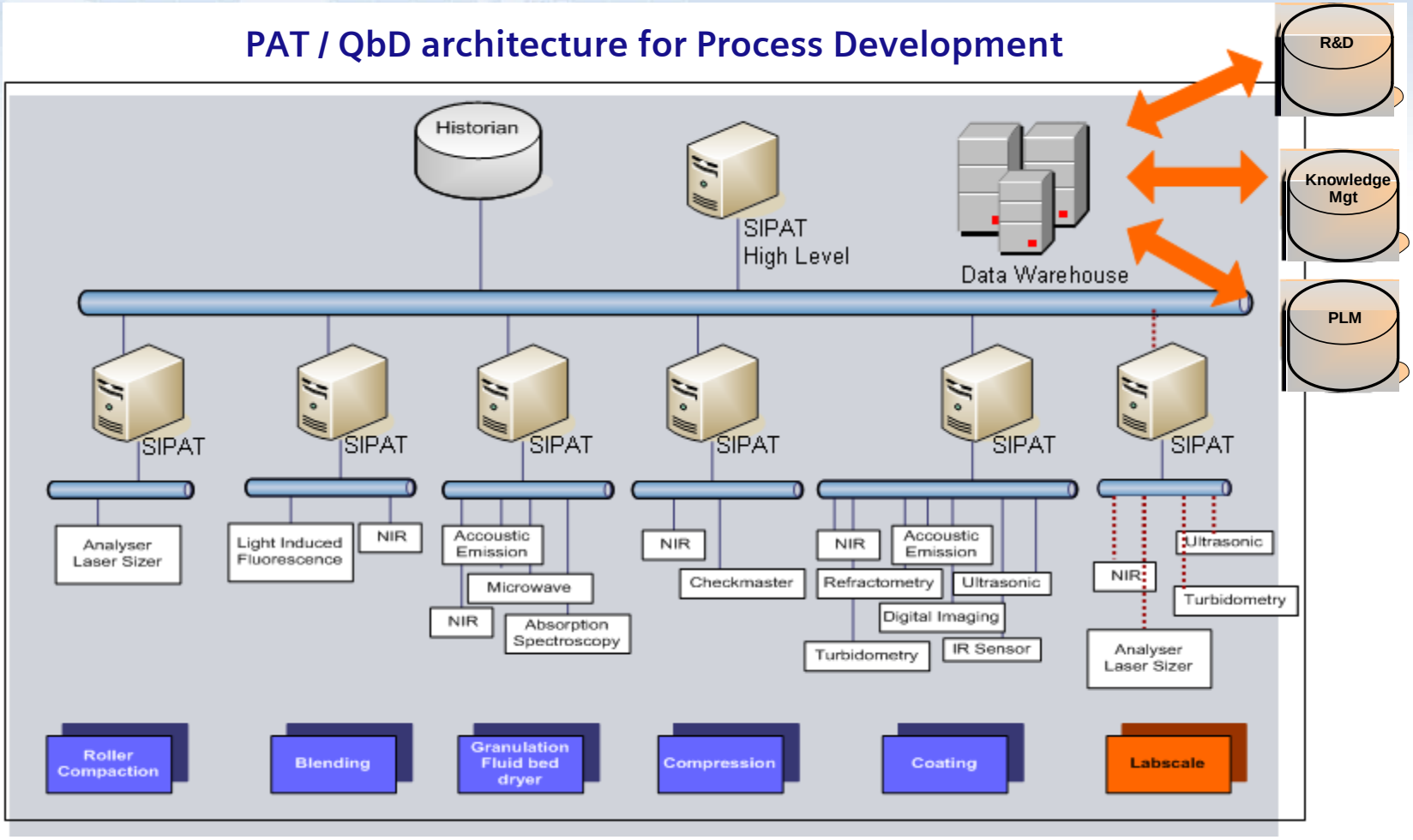
•Integration of R&D and manufacturing: Same products and solution for development and for manufacturing, facilitating tech transfer and time to market.

- **PAT / QbD: a continuous process understanding and improvement tool to collect knowledge on:**
  - product performance (therapeutic / clinical)
  - process / product interaction
  - part of the knowledge hierarchy
- **Data portals and data integration**
- **PLM (product and process)**

Offering a consistent and accurate dataflow.

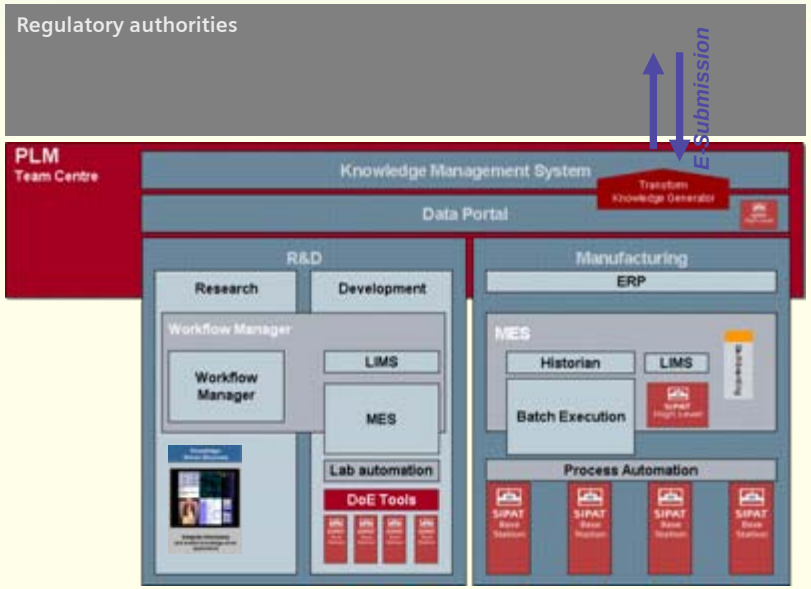
Real Time Release Process Understanding				S95
Knowledge Management				ISA 95 Level 4
PAT Data Management and Process Historian				ISA 95 Level 3
Chemometric Model Maintenance				
Sensor & Instrument Management & Control	Process Monitoring & Control			ISA 95 Level 2
Instruments & Simulators	Instrument Performance Monitoring	Instrument Standardisation		ISA 95 Level 1
Support	Training	Strategy	Standards	

Case: PAT / QbD as part of overall system architecture



Closing the gap: R&D and manufacturing integration

Pharma landscape

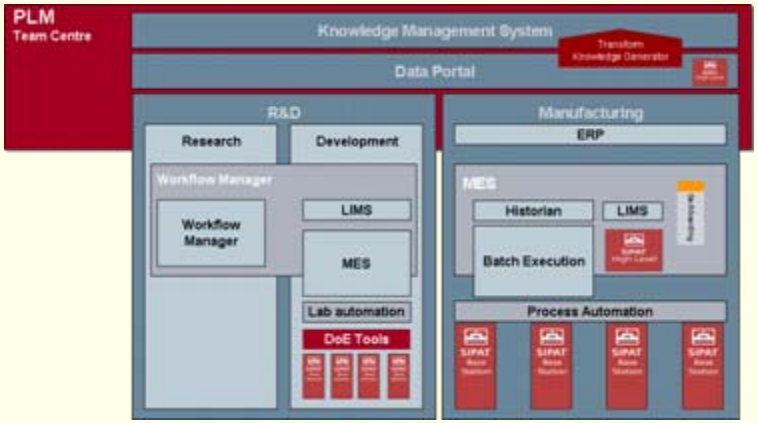


Development and manufacturing integration

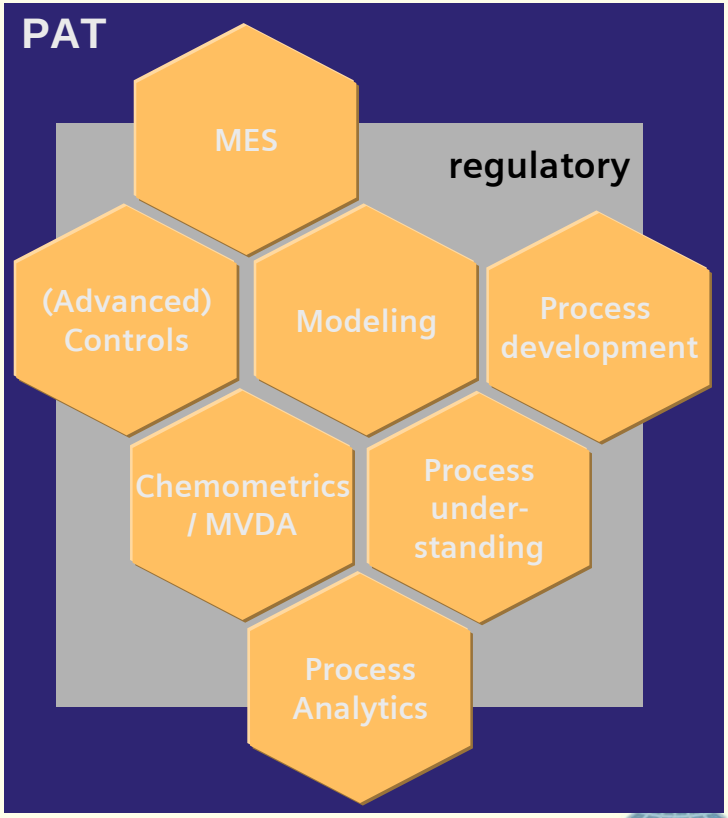
- Offering a consistent and accurate dataflow, increased flexibility and management oversight, reduced complexity.
- e-CTD (e-submission to regulators)
- Supporting live-licensing

Requires a multidisciplinary approach to ensure success

Required infrastructure



Required disciplines



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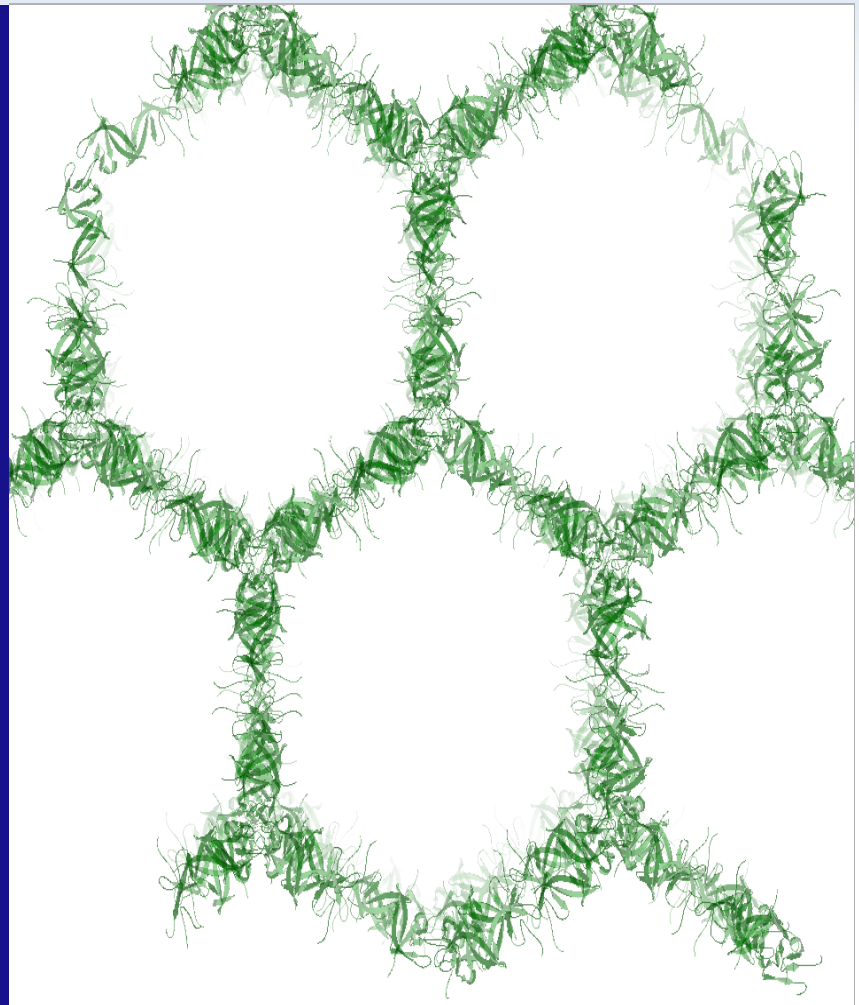
Moving forward in manufacturing and R&D

Biotechnological Manufacturing

General Trends

- high value, low yield
- scaling / up-scaling
- ‘scientific’ environment
- critical CIP/SIP
- Biowaste
- use of disposable processes
- new technologies
- [demand for] Process Understanding



Disposable Manufacturing

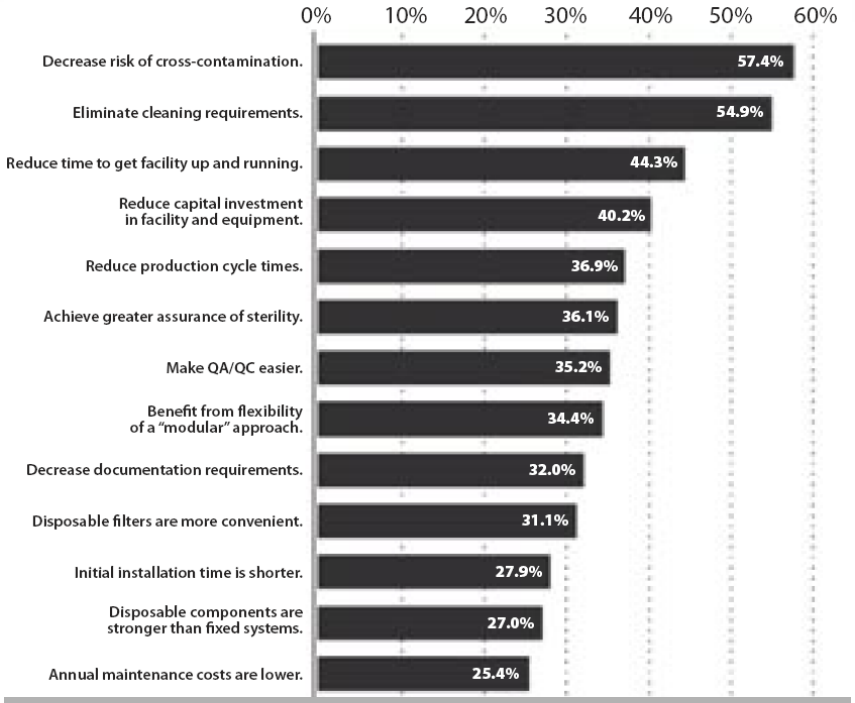
Trends

Development of production companies move from the use of stand-alone disposable devices to **fully-integrated multi-component assemblies**.

The proliferation of disposable technologies will be applied on both **upstream and downstream** operations.

Challenges

Advantages



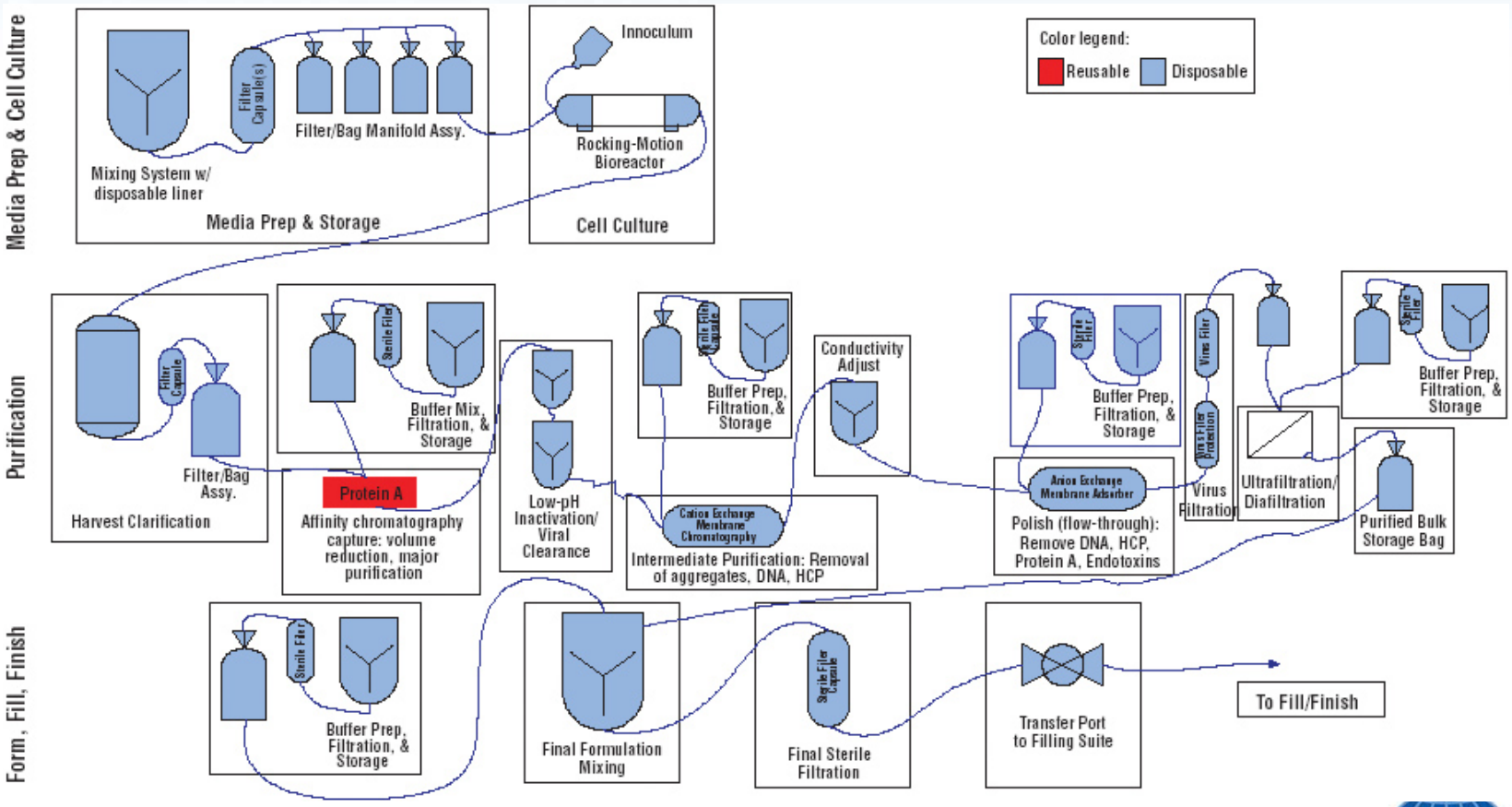
3rd Annual Report and Survey of Biopharmaceutical Manufacturing, Capacity, and Production (survey of 187 biopharmaceutical companies and CMO)

Challenges

Although there are many advantages there are however a couple of issues related to this technology:

- No basic process research or experience yet
- Waste production/ need of incineration of used disposable materials (cost!)
- Process monitoring: disposable sensors (in situ monitoring)?
- Applicable to the whole manufacturing process (upstream & downstream)
- Cost implications
- Applicable for chemical API production?
- Which steps should be done with disposables? -> Need for evaluation & strategy
- Ease of use?
- Continuous manufacturing operations with disposable technologies?

Workflow


Media Prep & Cell Culture
Purification
Form., Fill, Finish
Color legend:
Reusable
Disposable
Filter Capsule(s)
Filter/Bag Manifold Assy.
Mixing System w/ disposable liner
Media Prep & Storage
Innoculum
Rocking-Motion Bioreactor
Cell Culture
Filter Capsule
Filter/Bag Assy.
Harvest Clarification
Sterile Filter
Buffer Mix, Filtration, & Storage
Protein A
Affinity chromatography capture: volume reduction, major purification
Low-pH Inactivation/ Viral Clearance
Sterile Filter Capsule
Buffer Prep, Filtration, & Storage
Cation Exchange Membrane Chromatography
Intermediate Purification: Removal of aggregates, DNA, HCP
Conductivity Adjust
Sterile Filter
Buffer Prep, Filtration, & Storage
Anion Exchange Membrane Adsorber
Polish (flow-through): Remove DNA, HCP, Protein A, Endotoxins
Virus Filter
Virus Filtration
Ultrafiltration/ Diafiltration
Sterile Filter
Buffer Prep, Filtration, & Storage
Purified Bulk Storage Bag
Sterile Filter
Buffer Prep, Filtration, & Storage
Final Formulation Mixing
Sterile Filter Capsule
Final Sterile Filtration
Transfer Port to Filling Suite
To Fill/Finish

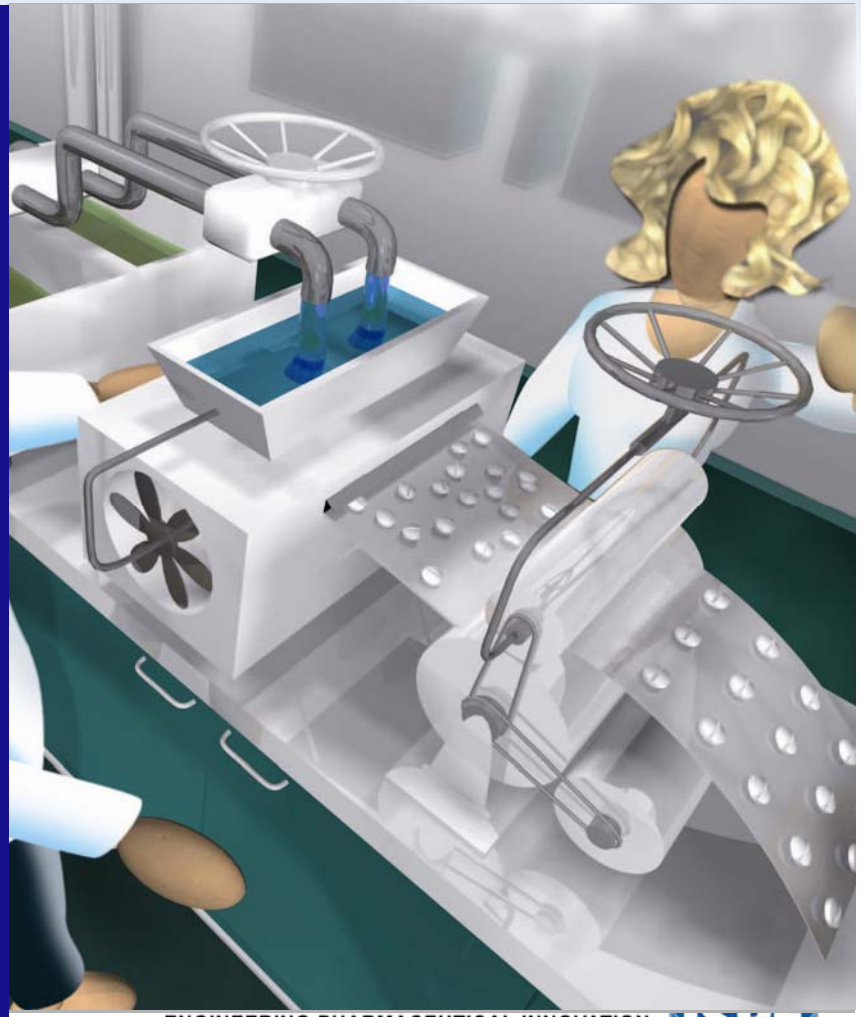
Continuous Manufacturing

Drivers & Challenges

- pressure on manufacturing costs
- product non-conformities
- scrap, rework & waste
- Quality, QbD & PAT (‘enabler’)
- OEE
- regulatory compliance
- time / time / time

“by 2013 the majority of GSK’s OSD plants will be continuous” °)

°) Dr. Frank Roche, GSK, June 2008



Batch processing vs. Continuous processing

Batch Processing

produced according to a single manufacturing order during the same cycle of manufacturing

Transition

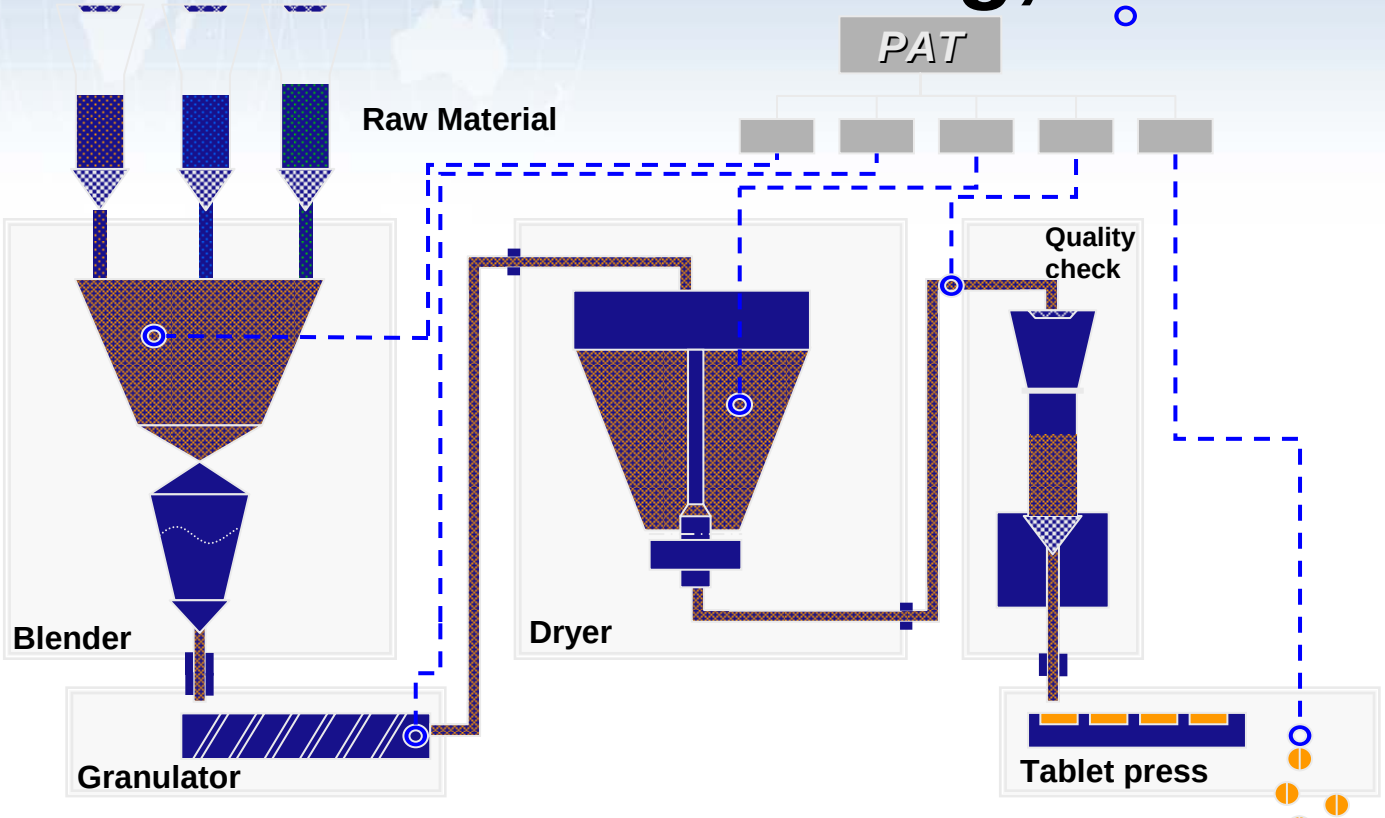
- Gradually
- As "on pot" manufacturing
- As a hybrid implementation (batch and continuous parallel)

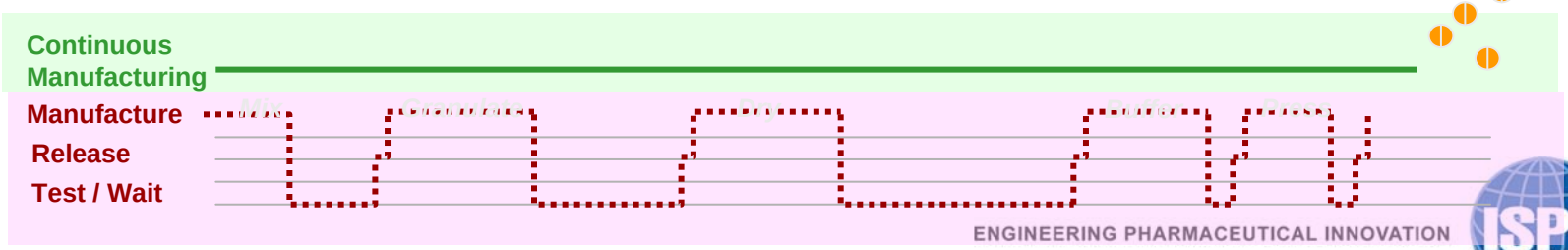
Continuous Processing

New materials are added and products removed continuously at a rate that maintains the volume at specific level = "one in – one out"

- Fully Continuous: a nomically steady state flowrate from the inlet to the outlet
- Quasi Continuous: flowrate within the process may vary significantly

Continuous manufacturing, solids





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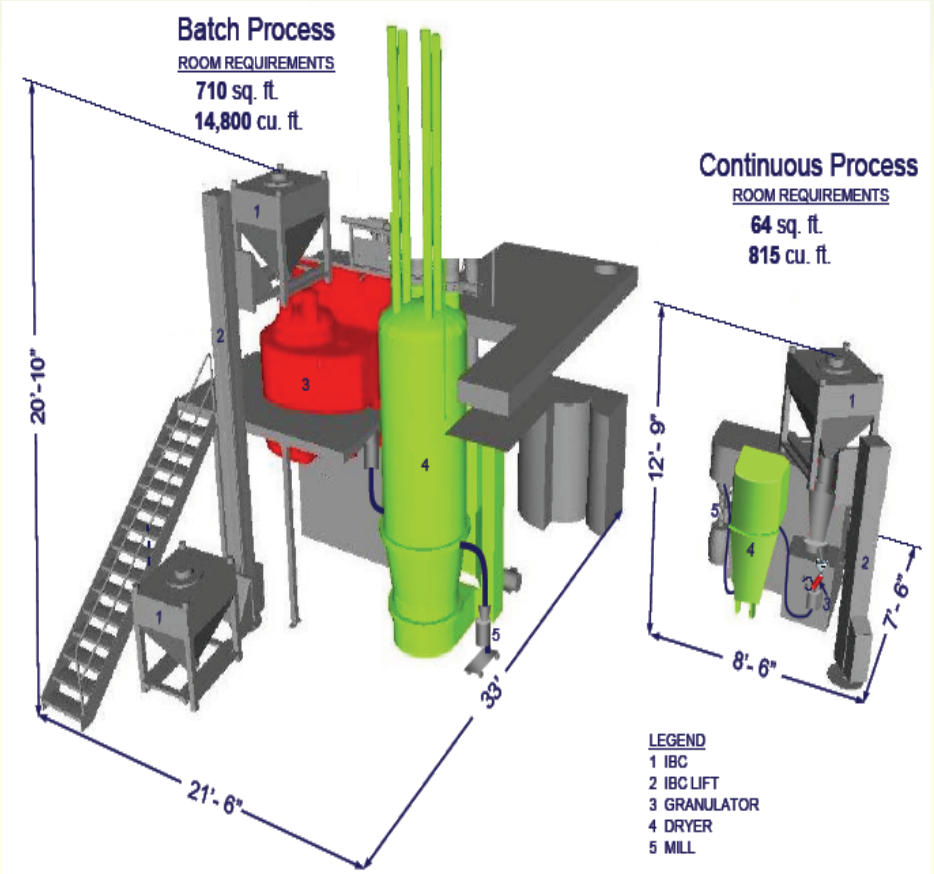
The manufacturing architecture implications

Benefits

- **New facility models which are:**
  - smaller
  - more energy efficient
  - less wasteful
  - more productive
  - significantly less costly to build and operate (more then 55% less costly), no WIP
- **Improves quality consistency (less variations, better homogeneity)**
- **Decrease scale up issues and cycle time**
- **Faster go-to-market of new products**
- **Potential reduction of OEE**



Picture courtesy of GSK

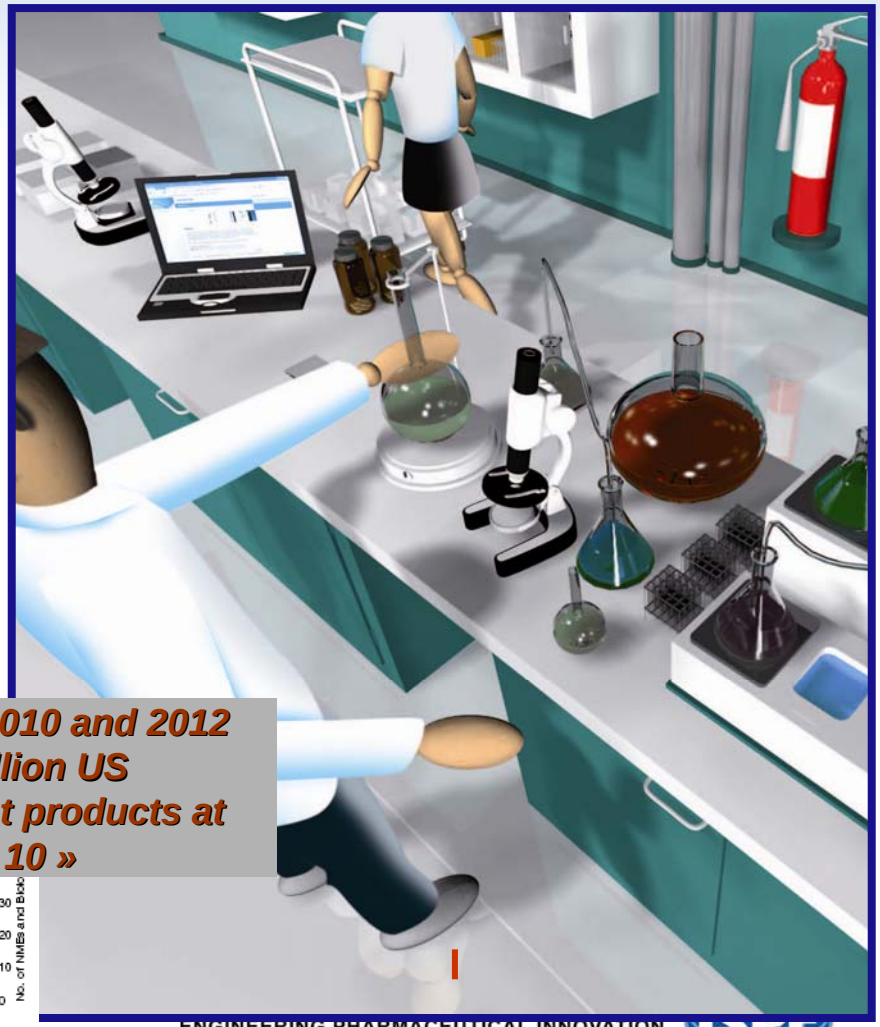
Research & Development

Drivers & Challenges

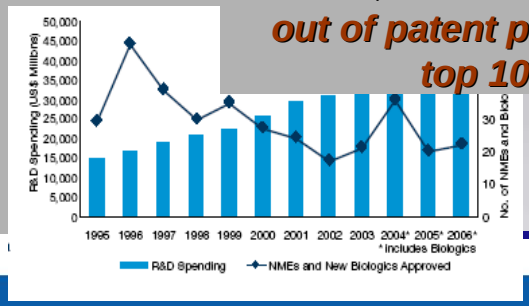
- Reduce Time to Market
- Reduce R&D costs
- Strengthen pipeline
- Improve efficiency R&D and clinical trials
- Retain talented researchers (move to U.S. and Asia)

Needs:

- Technology innovation
- Biomarker development (imaging, diagnostics)
- Dashboards for R&D progress, based on WFM systems
- Product LifeCycle Management (PLM)
- Data integration
- …



« Between 2010 and 2012 $90 billion US out of patent products at top 10 »



Changes in R&D (drug development)

Drug development

- More iteration/feedback loops & parallel work
- In-life testing and live licensing
- More transparency on clinical trial result
- More exchange of data

Reduction of patient population

- Smaller batches
- Shortening time to market
- Bio markers
- Bioinformatics

Closing the gap between R&D and manufacturing

Price

Business

BMS

ERP

Knowledge Management

PLM

LIMS

MES

Historian

PAT

Batch

Lab Automation

Pilot

DCS / PLC

PLM software

R&D suite

Integrated system approach

PAT system

Sensors

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ISPE

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NVI
nederlands
vaccin
instituut

Pharmaceutical Technology July 2009 Online Exclusive Integration of PAT in Biopharmaceutical Research (A Case Study)

Netherlands Vaccine Institute (NVI)

Description of Customer

- Produces vaccines for all government vaccination programs in The Netherlands
- Has R&D and Manufacturing activities
- Cooperates with other vaccine producers

Netherlands Vaccine Institute (NVI)

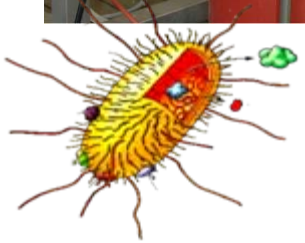
Description of Customer

- Application of PAT / QbD on an existing product
- Implementation of PAT for the development of a new production process for a whole cell vaccine against Pertussis or whooping cough disease
- In process development
  - -Improved process understanding
  - -Faster process development and upscaling
- In manufacturing:
  - -Cycle time reduction
  - -Waste reduction

Netherlands Vaccine Institute (NVI)

Description of the Solution

- Design and execution of a PAT strategy for process development PAT strategy / implementation procedure (roadmap):
- Step 1 – Appoint multidisciplinary team to apply and integrate the different disciplines needed for PAT method design and implementation
- Step 2 – Quality characterization
- Step 3 – Process assessment of Critical to Quality production steps
- Step 4 – Design of Experiment (DoE) and Multivariate data analysis of DoE results. Identification of “golden batch trajectory” and design envelop.
- Step 5 – Development of Control Strategy
- Step 6 – Development of a future release philosophy with quality built into the control system
- Step 7 – Optimization of the complete process



Netherlands Vaccine Institute (NVI)

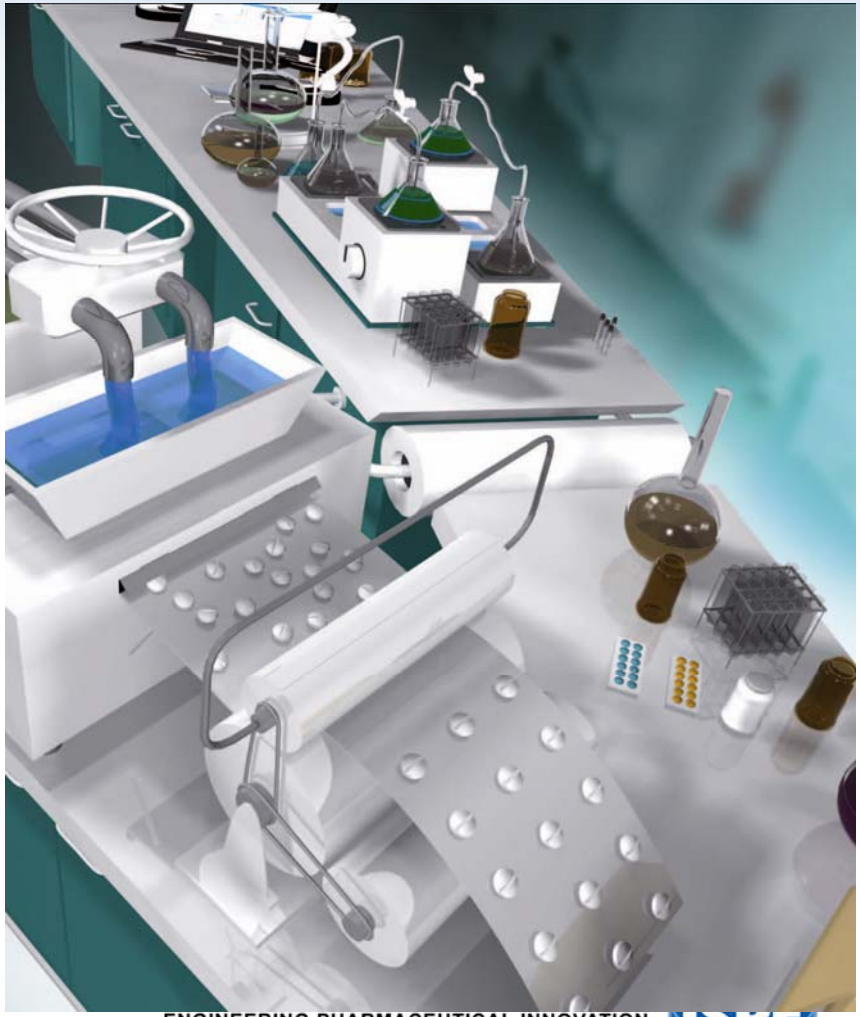
Key Benefits

- better process understanding
- improvement of quality
- reduction from 20% to 5 % waste
- increase production yield by a factor 3
- potentially eliminate animal testing
- full integration of information flows during processing and online comparison with historical data

Conclusion

Key Learning Points

- Develop the future vision for manufacturing and development
- Select the PAT tools that are supporting the vision
- Develop the PAT / QbD architecture that supports the vision
- Develop the PAT / QbD implementation strategy (roadmap)



Conclusion

- **Today, the pharma market is more then ever looking for solutions to bring development and manufacturing closer to each other (closing the gap), accelerate time-to-market and real-time decision making.**

- **New technologies transform development and manufacturing and merges these activities. Knowledge management tools will play a prominent role.**

- **The future is not a million miles away; much of it is here today!**

Questions?

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