Process Analytical Technology (PAT) / Quality by Design (QbD):
Integrated Systems in the Future Pharma Business Landscape

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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
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

- **Social change**
  - Demographic
  - Life style
  - Patients

- **Regulations**

- **Technology change**
  - Industrial IT
  - Advanced control
  - Integrated solution

- **Economical pressure**
  - Low pipe line
  - Manufacturing
  - Supply Chain

- **Market change**
  - New therapies
  - Delivery form
  - Personalize

**Pharmaceutical Industry**

*driven by;*

- Cost
- Patient safety

ENGINEERING PHARMACEUTICAL INNOVATION
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 Mfg. 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 feedback 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 through 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

**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

**New regulations**

**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

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.”

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

FDA’s new draft guidance on process validation: General principles and practices
Nov 2008

New regulations

Guidance on Process Validation

Pharmaceutical CGMPs for the 21st Century — A Risk-Based Approach
Final Report

Guidance for Industry
PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

Guidance for Industry
Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations

Guidance for Industry
Process Validation: General Principles and Practices
Business Drivers for PAT/QbD

**Company Image**
- Reduced risk via technology platform, anti-counterfeiting
- Improved product tracking
- Reverse poor image
- Improved quality system through audits
- Reduced risk for recall, warning letter, consent decree

**Validation Optimization**
- Validation needs understanding
- Integral part of project
- Build validation into process

**Site to site transfer**
- Accelerate transfer
- Reduce validation effort
- Reduce project time
- Mitigate transfer risk
- Move manufacturing to most effective site

**New Product Development**
- Real Time Release (RTR)
- Fast time to market
- Fast scale-up
- Clinical batches
- Process optimization
- Reduced cost of quality

**End of Life-cycle**
- Transferability of process
- Scale down

**Improve Existing Process**
- Gain new process understanding
- Process optimization
- Reduced cost of quality
- Raw material specifications
- Know product availability + yield
- Real Time Release
PAT / QbD the skill set and architecture fit

PAT Toolbox / Skill set

Fit in development & manufacturing landscape

- Process Analytics
- Data Portals/Knowledge Mgt.
- MES
- Data Collection storage & retrieval
- Information management tools
- Product & process design
- (Advanced) Process Controls
- Data Analysis & mining
- DoE
- Process Analytics
- Process Controls
- Process Automation
- PLM
- Field equipment
- Process technology
- Data Portals/ Knowledge Mgt.

PAT regulations
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

Knowledge space

Design space (process understanding)

Operating space

Golden batch trajectory

Design space limits = Control limits

ENGINEERING PHARMACEUTICAL INNOVATION
Predicting end-product quality

PAT as part of the process control environment

- 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

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

And from design space to process control
Batch process visualization across different unit operations

Raw mats./conditioning  Synthesis/Downstream  Formulation  Finishing  Packaging

PAT hi level system

PAT

Offline Batch Monitoring Model 3-1-2004 - Predicted Scores [comp. 1]
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

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Quality Suite

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

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**Scenario 2:**
Continuous processing, RTPR, JIT production
PAT shifts monitoring and control from process data to product quality

- Advanced Control
- Classic control
- Closed loop control
- Process feed
- Temp., pH, pO2, pressure, ...
- Monitoring process data
- Mathematical translation
- Monitoring product quality
- Real-time release
- Quality build in by design
- Right first time

PAT shifts monitoring and control from process data to product quality, focusing on PAT (Process Analytical Technology) which integrates monitoring and control from process data to product quality. This approach ensures quality build in by design and right first time, leading to real-time release. The diagram illustrates the flow from process feed through advanced control, classic control, monitoring process data, mathematical translation, monitoring product quality, and finally real-time release. This integration is crucial for pharmaceutical and chemical industries to improve product quality and efficiency.
Continuous manufacturing

**PAT enabled continuous processing**

- **Condition monitoring**
- **Model-based control**

- **Advanced Control**
- **Closed loop control**
- **PAT / QbD**
- **Quality by design**
- **Right first time**

- **Monitoring**
- **Product quality**
- **Mathematical models**
- **Lab**
- **LIMS**

- **Real-time release**
- **Temporal, pH, pO2, pressure...**
- **Process data**
- **Sample**

- **Biomass**
- **Product**

- **Feed**
- **Air**
- **Acid/lye**

**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

- Adjusting process conditions in real-time, based on PAT enabled end-product quality prediction
- Steady-state processing
Answer for data management in continuous manufacturing?

- Tracking and tracing
- Fully integrated MES
- Central SCADA for integrated operation
- Fully integrated SCADA / local operation
- Standard SW structure (OMAC)
- APC: on controller level and on process level
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

<table>
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<tr>
<th>Today</th>
<th>Vision</th>
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| *New initiatives to:* | FDA’s future focus:  
  *Keynote address at IFPAC*  
  *February 2007, by FDA’s Chief Medical Officer, Dr. Janet Woodcock, on* |
|  - improve manufacturing quality  
  - accelerate development  
  - Lower the regulatory burden |  - 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 |

**FDA new principles:**
- Quality by design & design space
- Quality systems approach
- Reflecting product & process understanding and knowledge

**Guidance for Industry**
- PAT — A framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance
- Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations
- Challenge and Opportunity on the Critical Path to New Medical Products
- Innovation Integration
PAT/QbD in Manufacturing

Manufacturing
- ERP

MES
- Historian
- LIMS
- Batch Execution

Process Automation
- SIPAT Base Station
- SIPAT Base Station
- SIPAT Base Station
- SIPAT Base Station
Case: PAT/QbD in Manufacturing

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

Knowledge loss occurs throughout the product lifecycle at each key stage.

Need for a Repository of Knowledge

Knowledge Generated

Knowledge Transfer

Knowledge is lost throughout the product lifecycle

R&D

Research, Development, Clinical and stability data etc

Research, Development, Clinical and stability data etc

Manufacturing

Process verification, Continuous Improvements, Data Trending, etc

Process verification, Continuous Improvements, Data Trending, etc

Knowledge Generated

Knowledge Generated

Knowledge is lost throughout the product lifecycle

R&D Suite

Workflow Manager

LIMS

MES

Lab automation

DoE Tools

Knowledge-Driven Discovery

Integrate information and enable knowledge-driven applications

Manufacturing

ERP

MES

Historian

LIMS

Batch Execution

Dashboarding

Knowledge Transfer

Knowledge loss occurs throughout the products life cycle at each key stage.
Closing the gap: R&D and Manufacturing integration

PLM
Product & Process Lifecycle Management

Knowledge Management System
Transform Knowledge Generator
Data Portal

R&D
Research
Development
R&D Suite
Workflow Manager
Lab automation
DoE Tools

Manufacturing
ERP
MES
Batch Execution
LIMS
Process Automation
SIPAT Base Station

Lab automation
DoE Tools
Knowledge-Driven Discovery
Integrate information and enable knowledge-driven applications
...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

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)

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

Offering a consistent and accurate dataflow.
Case: PAT / QbD as part of overall system architecture

PAT / QbD architecture for Process Development

- R&D
- Knowledge Mgt
- PLM

- SIPAT High Level
- Data Warehouse

- Analyser Laser Sizer
- Light Induced Fluorescence
- NIR
- Accoustic Emission
- Microwave
- NIR
- Absorption Spectroscopy
- Refractometry
- Ultrasonic
- NIR
- Digital Imaging
- Turbidometry
- IR Sensor
- Labscale

- Roller Compaction
- Blending
- Granulation Fluid bed dryer
- Compression
- Coating
Closing the gap: R&D 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

PAT

MES
(Advanced) Controls
Modeling
Process development
Chemometrics / MVDA
Process understanding
Process Analytics
Moving forward in manufacturing and R&D
Biotechnological Manufacturing

- 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.
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?
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**
- 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

Raw Material → Blender → Granulator → Dryer → Tablet press

Quality check → Buffer

PAT

Manufacture → Release → Test / Wait

ISPE
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 than 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

Business

BMS
ERP
Knowledge Management
PLM
LIMS
PAT
Lab Automation
Pilot
DCS / PLC
MES
Historian
Batch

PLM software
R&D suite
Integrated system approach
PAT system
Expensive sales
inefficient supply chain

Price

Engineering Pharmaceutical Innovation
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
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
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
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
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)
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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