Review Article

# A COMPLETE REVIEW OF PROCESS ANALYTICAL TECHNOLOGY (PAT)

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**ABSTRACT**

Process analytical technology (PAT) has been defined as a mechanism to design, analyze, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (CPP) which affect Critical Quality Attributes (CQA). It will encourage the voluntary development and implementation of innovative pharmaceutical development, manufacturing, and quality assurance. Novel analytical techniques, such as Fourier Transform Infrared (FT-IR), Near Infrared (NIR), Raman and Focused Beam Reflectance (FBRM) are popular PAT tools used to understand and control pharmaceutical processes. Main goal of PAT is to provide successful tool such as Partial least square, Principle component analysis, Multivariate T-Squared and EWMA Control Charts, ARIMA Control Charts, Neural Network Classifier, Multivariate Capability Analysis, Design of Experiments. PAT covered four major areas like industrial pharmacy and pharmaceutical engineering, process analytical chemistry, Regulatory reform, manufacturing science.

**Keywords:** Process analytical technology, Quality by design, pharmaceutical manufacturing.

## INTRODUCTION

The term "**Process Analytical Technologies** (PAT)" has been used to describe "a system for designing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes for raw and in-process materials and also processes with the goal of ensuring final product quality". The PAT initiative focuses on building quality into the product and manufacturing processes, as well as continuous process improvement.

Process analytical technology (PAT) has been defined by the United States Food and Drug Administration (FDA) as a mechanism to design, analyze, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (CPP) which affect Critical Quality Attributes (CQA).

The concept actually aims at understanding the processes by defining their CPP's, and accordingly monitoring them in a timely manner (preferably in-line or on-line) and thus being more efficient in testing while at the same time reducing over-processing, enhancing consistency and minimizing rejects.

The FDA has outlined a regulatory framework for PAT implementation. With this framework – according to Hinz – the FDA tries to motivate the pharmaceutical industry to improve the production process. Because of the tight regulatory requirements and the long development time for a new drug, the production technology is "frozen" at the time of conducting phase-2 clinical trials.

Generally, the PAT initiative from FDA is only one topic within the broader initiative of "Pharmaceutical cGMPs for the 21st century – A risk based approach".

It will encourage the voluntary development and implementation of innovative pharmaceutical development, manufacturing, and quality assurance. Working with existing regulations, the Agency has developed an innovative approach for helping the pharmaceutical industry address anticipated technical and regulatory issues and questions.

## SCOPE[2,3]

The potential benefits to industry include the following:

- Better understanding of processes.
- Batch-to-batch reproducibility.
- Fewer batch failures.
- Regulatory relief.
- Increased operating efficiency.
- Cycle time reduction.
- Close coupling of batch steps to produce semi-continuous operations.
- The ability to use of larger scale processing equipment.
- Greater utilization of production equipment.
- Minimized storage space required for Work in Progress (WIP).
- Reduced risk of processing errors.
- Reduced risk of product contamination, by products and product modification.
- Minimized variability using on-line measurements.
- Reduce production cycling time.
- Prevent rejection of batches.
- Enable real time release.
- Increase automation.

- ❖ Improve energy and material use.
- ❖ Facilitate continuous processing.
- ❖ Process Knowledge/Control.
  - Reaction optimization.
  - Process characterization.
  - Mechanistic/kinetic studies.
- ❖ Applications that can not be done any other way
  - Information which can only be obtained real-time, in/on-line (e.g. monitoring Transient non-isolated intermediate).
  - Process Safety and Industrial Hygiene
    - ✓ Sampling
  - Potent compounds
  - Hot temperature, high pressure etc.
    - ✓ Process

• Grignard reaction initiation, borohydride reduction

• Test burden reduction

• Cycle time reduction

Novel analytical techniques, such as Fourier Transform Infrared (FT-IR), Near Infrared (NIR), Raman and Focused Beam Reflectance (FBRM) are popular PAT tools used to understand and control pharmaceutical processes. In this presentation, benefits of these technologies to development and manufacturing of Active Pharmaceutical Ingredient (API) processes will be demonstrated in several case studies.

Currently NIR spectroscopy applications dominate the PAT projects. A possible next-generation solution is Energy Dispersive X-Ray Diffraction (EDXRD).

**The goal of process analytical technology[6-8]**

"To understand and control the manufacturing process, which is consistent with our current drug quality system: ***Quality cannot be tested into products; it should be built-in or should be by design."***

STATGRAPHICS Centurion provides the statistical tools needed to successfully implement PAT. This includes a number of important univariate and multivariate techniques, including:

**1. Partial Least Squares (PLS)** - Heavily used for chemometric calibration and construction of multivariate statistical models.

PLS is used to correlate data, such as finished product dissolution results, to raw material, process parameters, and in-line readings. Variables which affect the dissolution rate can be better understood and monitored. The effect of scale ups and post approval changes can be quantified. Critical parameters can be controlled, thereby creating high quality drug product, less level/stage 2 testing, and minimal product failure. When out of specification results do occur, drug products can be better investigated through the use of PLS to determine which underlying variables contributed to the failing drug product.

**2. Principal Components Analysis (PCA)** - Used to reduce dimensionality when many factors are involved.

PCA is a technique of creating data models of previously produced and tested batches to verify similarity to newly created batches. One advantage this technique has over the commonly used f2 metric is that batches are now compared to a substantial compilation of batches included in a validated model. Trends could potentially be identified earlier than with an f2 comparison. This could help improvement of process consistency after scale up and post approval changes. Another advantage of PCA is that it can handle the large amount of data produced by dissolution fiber optic (Dis-FO) techniques without the need to reduce data points.

**3. Multivariate T-Squared and EWMA Control Charts** - For controlling processes with correlated variables.

**4. ARIMA Control Charts** - For controlling dynamic manufacturing processes.

**5. Neural Network Classifier** - For use in classifying attribute data based on multiple quantitative measurements.

**6. Multivariate Capability Analysis** - For determining the capability of meeting specifications based on multiple variables.

**7. Design of Experiments** - Construction and analysis of experiments designed to aid in process optimization.

## RESOURCES FOR PROCESS ANALYTICAL TECHNIQUES[8,9]

1. Consortiums - University, government laboratories, and industrial partners
2. Conferences.
3. Websites
4. Books
5. Journals
6. National Agency and Laboratory Interactions

## IMPLIMENTATION AND PROCEDURES[10,11]

### A) Process Understanding

A process is generally considered well understood when (1) all critical sources of variability are identified and explained; (2) variability is managed by the process; and, (3) product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions. The ability to predict reflects a high degree of process understanding.

**B) Principles and Tools**

Pharmaceutical manufacturing processes often consist of a series of unit operations, each intended to modulate certain properties of the materials being processed. To ensure acceptable and reproducible modulation, consideration should be given to the quality attributes of incoming materials and their process-ability for each unit operation. During the last 3 decades, significant progress has been made in developing analytical methods for chemical attributes (e.g., identity and purity). However, certain physical and mechanical attributes of pharmaceutical ingredients are not necessarily well understood. Consequently, the inherent, undetected variability of raw materials may be manifested in the final product. Establishing effective processes for managing physical attributes of raw and in-process materials requires a fundamental understanding of attributes that are critical to product quality. Such attributes (e.g., particle size and shape variations within a sample) of raw and in-process materials may pose a significant challenge Contains Nonbinding Recommendations because of their complexities and difficulties related to collecting representative samples. For example, it is well known that powder sampling procedures can be erroneous.

Formulation design strategies exist that provide robust processes.

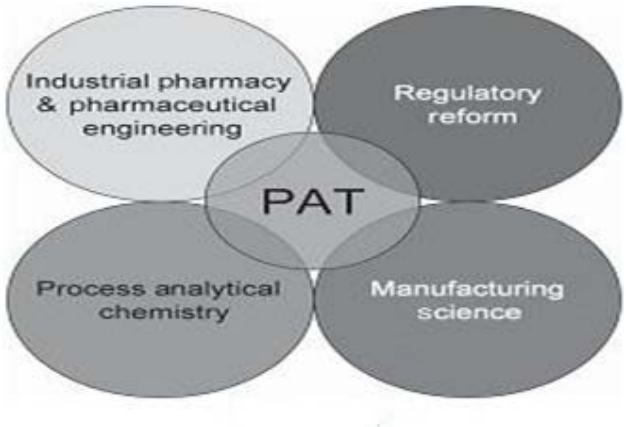



**Figure 1:** Major area covered by PAT

1) PAT Tools

Multivariate tools for design, data acquisition and analysis

• Process analyzers

• Process control tools

• Continuous improvement and knowledge management tools

2) Process Analyzers

**At-line:** Measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream.

**On-line:** Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.

**In-line:** Measurement where the sample is not removed from the process stream and can be invasive or non invasive.

3) Process Control Tools

4) Continuous Improvement and Knowledge Management

5) Risk-Based Approach

6) Integrated Systems Approach

7) Real Time Release

**Steps in conducting principal component analysis[13,14]**

Step 1: Initial Extraction of the Component

Step 2: Determining the Number of "Meaningful" Components to Retain

A. The eigenvalue-one criterion.

B. The scree test.

C. Proportion of variance accounted for.

D. The interpretability criteria.

Step 3: Rotation to a Final Solution

- Factor patterns and factor loadings
- Rotations

Step 4: Interpreting the Rotated Solution

Step 5: Creating Factor Scores or Factor-Based Scores

- Computing factor scores
- Computing factor-based scores

Recoding reversed items prior to analysis

Step 6: Summarizing the Results in a Table

Step 7: Preparing a Formal Description of the Results for a Paper

## IMPORTANCE[15]

**1. Immediate Adjustments to Production Parameters**

Real-time information is obtained, allowing in-line corrections if the measurements indicate that a parameter is out of range. Parameters such as oxygen levels, pH and stir-rates can be adjusted, or nutrients added. In-line monitoring is useful, not only for monitoring natural variations in a biological system, but for catching obvious human errors, before it's too late and the batch is ruined. Building in-line measurements and batch adjustments into the production line is an easy way.

**2. More Predictable Results**

In-line monitoring leads to less variability of end product quality. As a result, statistically speaking, the manufacturer can have more confidence in the quality of the product and the accuracy of end-point parameter measurements. This also results in less waste because

fewer batches are discarded at the end of the process for not meeting specifications. Of course, the obvious side effect of this is cost savings because less raw materials and batch time go to waste.

**3. Useful Data for Research and Development**

A valuable sideline to using PAT is that the data collected during process monitoring can be incorporated into research and development programs. A large amount of data is collected and, with proper organization and use of XML or other IT solutions, it can be immediately organized for analysis by researchers who may use the information to further improve product quality.

**4. Time Saved**

Time is saved in several ways: Reduced waste of QC time on non-value-added protocols, less time in production for repeating batches or cycles, and the opportunity for real-time release of product because the quality has already been established mid-stream.

## APPLICATIONS

**Chemometrics[16]**

Previously, manufacturing processes have been treated in a univariate manner, with single parameters tracked by control charts. However, the reality is that physio-chemical processes are multivariate with suitable interactions of variables. Chemometrics is the intersection of chemistry and the mathematics of large matrices of data. Chemometrics is complex and requires the use of computers and software to perform the necessary computations. These techniques reduce large amounts of data into a few recognizable components without any loss of data.

Two chemometric techniques that have been found to be useful are Principal Component Analysis (PCA) and Partial Least Squares Regression (PLS). These techniques are recognized for their ability to eliminate noise, identify latent variables, and extrapolate missing data.

**BioPAT [16,17]**

BioPAT as process analytical technologies applied throughout development, scale-up and commercial scale bioprocess-based production of drug substances (including manufacturing of intermediates, APIs and the final drug products. In this report, we will focus on what PAT means in practice for the biotechnological manufacture of pharmaceuticals.

The aim of this study is to:

- Get a technological insight of the status of the Process Analytical Technology (PAT) Initiative with regards to pharmaceutical bioprocesses
- Study the regulatory framework and future activities in Europe and the USA
- Survey the needs for monitoring bioprocesses for pharmaceutical production
- Survey the monitoring methods and technologies available
- Find key players for collaboration in Finland and globally (both research and industrial)
- Find key ongoing projects.

Moreover, the aim of this study is to analyze the situation in BioPAT and propose actions, build up a consortium for future actions and also to find funding possibilities.

**Crystallization[18]**

Crystallization at production scale is typically a poorly understood unit operation, with little implementation of the first principles aspect of crystallization in its design, optimization, and control. Problems with production crystallizers include the following: (1) inconsistencies of batch-to-batch in terms of the size and number of crystals produced and (2) the purity profile (residual impurities in crystals, or wrong polymorph or chiral purity). This can have a significant impact both on product quality and downstream process unit operations including filtration, drying, milling, and product formulation. This contribution reviews typical problems encountered in production crystallization, with case studies, advice, and strategies to understand and avoid these problems through the use of in situ crystallization characterization tools.

**Case study and application of process analytical technology (PAT) towards bioprocessing: Use of ultra-performance liquid chromatography (UPLC) for making real-time pooling decisions for process chromatography.**

The biopharmaceutical community is interested in using Process Analytical Technology (PAT) for continuous real-time quality assurance. PAT has the potential to improve operational control and compliance. The operational definition of PAT is as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality."

A desired goal of the PAT framework is to design and develop well-understood processes that will consistently ensure a predefined quality at the end of the manufacturing process. A process is generally considered well understood when (1) All critical sources of variability are identified and explained; (2) variability is managed by the process and (3) product quality attributes can be accurately and reliably predicted over the ranges of acceptance criteria established for materials used, process parameters, manufacturing, environmental, and other conditions.

**Protein refolding[18,19]**

Protein refolding typically runs with a time-based recipe. The time is set based on the rate of refolding (as determined by process development studies) and operational constraints (manufacturing shifts). There are

two consequences of performing refolds by fixed time. The refold step produces varying product quality as measured by percent purity or percent impurities (e.g., reduced and oxidized forms of product, misfolds, etc). The refold rate will vary from lot to lot due to variability in feed materials, and so refold time is often set conservatively. This makes production operating costs higher than optimum.

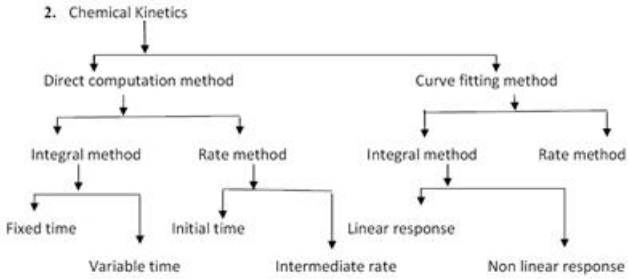
1. Enriching Phosphoproteins & Phosphopeptides
2. Stable Isotope Labeling by Amino Acids in Cell Culture [SILAC]
3. Mass Spectrometry
4. Chemical Modification
5. Mass Spectrometry
6. Stable Isotope Labeling by Amino Acids in Cell Culture [SILAC]
7. Phosphoprotein Profiling by Pa-GeLC-MS/MS

**Analytical method used for followings[19]**

1. Biological samples
2. Environmental samples
3. Determination of chloromethane in biological samples like exhaled air, blood, urine, human milk, adipose tissue

**Kinetic method[19,20]**

1. Kinetic Methods Versus Equilibrium Methods
2. Chemical Kinetics




Quantitative application

1. Enzyme catalysed reaction
2. Non enzyme catalysed reaction
3. Non analytical application

Characterization application

1. Determining *V*max and *K*m for Enzyme-Catalyzed reactions
2. Elucidating Mechanisms for the Inhibition of Enzyme Catalysis

**Radiochemistry[21]**

Quantitative application

1. Direct Analysis of Radioactive Analytes
2. Neutron Activation Analysis
3. Isotope Dilution
4. Characterization Applications : Sample age
5. Evaluation: Analysis of trace analytes in macro and meso samples.

**Flow injection analysis[22]**

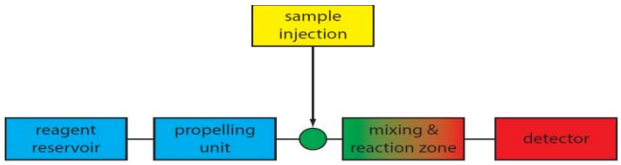



**Figure 2:** Flow Injection Analysis

Quantitative application

1. Used for environmental sample analysis
2. Analysis of clinical sample (blood, plasma, seram)
3. Determination of phosphate
4. Concentration of chloride in seawater
5. Analysis of $Cu^{+2}$ is based on its ability to catalyze the oxidation of di-2-pyridyl ketone hydrazone (DPKH).
6. For acid–base titrations using a carrier stream
7. By amperometric biosensor to determine the concentration of glucose in blood
8. Detecting cocaine in samples using an amperometric detector
9. Determining the concentration of $H_2SO_4$ in nonaqueous solvents

**Other Applications[23-30]**

- Determined using a two-point fixed-time integral method in which the concentration of A for the pseudo-first-order reaction is measured at times *t*1 and *t*2.
- The concentration of phenylacetate can be determined from the kinetics of its pseudo-first order hydrolysis reaction in an ethylamine buffer.
- Analysis of a set of standard solutions of $H_2O_2$
- Concentration of chromic acid can be determined by reducing it with an alcohol under conditions that are pseudo-first order in analyte.
- Malmstadt and Pardue developed a variable time method for the determination of glucose based on its oxidation by the enzyme glucose oxidase.
- Deming and Pardue studied the kinetics for the hydrolysis of *p*-nitrophenyl phosphate by the enzyme alkaline phosphatise.
- Enzymatic decomposition study
- Decomposition of acetylcholine to choline and acetic acid in presence of enzyme acetylcholine esterase.

- Enzyme fumarase catalyzes the stereospecific addition of water to fumarate to form l-malate
- Urease catalyzes the hydrolysis of urea.
- Concentration of Ni a new alloy is determined by a neutron activation analysis.
- Determination of vitamin $B_{12}$ content of a multivitamin tablet.
- Determine the age of the rock by Potassium–argon dating based on the nuclear decay.
- Determining Parent Compounds and Metabolites in Biological Materials.
- Determining Biomarkers of Exposure and Effect
- Determining Parent Compounds and Degradation Products in Environmental Media.
- Use of the analytical hierarchical process (AHP) to predict advanced manufacturing technology (AMT) implementation.
- Use of near IR in raw material identification and conformity analysis. Ex. analytical technology to master the process of busulfan paediatric capsules in a university hospital
- PAT is used in biopharmaceutical analysis of Multivariate batch process modeling, monitoring and control approaches in real-time are elaborated by providing industrial examples from the commercial manufacturing processes. Examples opportunities in cell culture (e.g., bioreactor applications) and purification (e.g., large-scale chromatography) by using Dielectric technique.
- Content uniformity and tablet hardness testing of intact pharmaceutical tablets by near infrared spectroscopy which is a contribution to process analytical technologies.
- Enhancing crystalline properties of a cardiovascular active pharmaceutical ingredient using a process analytical technology based crystallization feedback control strategy.
- PAT is used On-line monitoring of residual solvent during the pharmaceutical drying
- Process using non-contact infrared sensor.
- Process analytical technology applied for end-point detection of pharmaceutical blending by combining two calibration-free methods: Simultaneously monitoring specific near-infrared peak intensity and moving block standard deviation.
- NIR spectroscopy as a process analytical technology (PAT) tool for on-line and
- Real-time monitoring of an extraction process as well as for tablet evaluation of content uniformity, blend uniformity, coating, thickness.
- Pharmaceutical powder technology — from art to science: the challenge of the FDA's Process Analytical Technology initiative.
- Digital imaging as a process analytical technology tool for fluid-bed pellet coating process.
- PAT is used in food analysis also.
- NIR is used in qualification of ginkago biloba extract.
- Representative sampling for process analytical characterization of heterogeneous bioslurry systems—a reference study of sampling issues in PAT.
- PAT is used in for in-line monitoring of film thickness and mass of coating materials during a pan coating operation.
- Investigation of the Application of Process Analytical Technology for a Laser Welding Process in Medical Device Manufacturing.
- Monitoring batch-to-batch reproducibility of liquid–liquid extraction process using in-line near-infrared spectroscopy combined with multivariate analysis.
- Near infrared and Raman spectroscopy used for the in-process monitoring of pharmaceutical production processes, silicon based drug delivery.
- Quality-by-Design (QbD): An integrated process analytical technology (PAT) approach for a dynamic pharmaceutical co-precipitation process characterization and process design space development.
- "Push–pull" sampling device with fast reaction quenching coupled to high-performance liquid chromatography for pharmaceutical process analytical technologies.
- High-resolution ultrasonic resonator technology and Raman spectroscopy as novel process analytical tools for drug quantification in self-emulsifying drug delivery systems.
- PAT is used to maintain batch to batch reproducibility and robustness.
- Effects of instrumental and compositional variables on terahertz spectral data quality to characterize pharmaceutical materials and tablets.

## ISSUES FOR PAT

• Verification on site of information in the submission (design space, specifications, data verification etc.)

• Handling of OOS results and deviations in the manufacturing process

• Computerized systems

• Suppliers of active substances and excipients

• Training of employees

• Sampling (at-line)/cleaning of sampling devices

Submission of a Site Master File with PAT related information prior to the inspection is appreciated, How to improve regulatory compliance to drive success into your PAT processes?

Planning using appropriate tools:

• PAT instruments (NIR, Raman etc.)

• Design of experiments

• Multivariate analysis

• Risk assessment, ICH Q9

• ICH Q8 and ICH Q10

❖ **Other issues**

• Quality and storage of development data

• The other earlier-mentioned inspection focus points

• Regulatory flexibility (design space, protocols)

• Variation to approved product versus new application

• Approach regulatory authorities in the early phases and later

**QbD: Benefit for industry**

• Better understanding of the process

• Less batch failure

• More efficient and effective control of change

• Return on investment/cost savings

**QbD: Additional opportunities for industry**

An enhanced, QbD approach to pharmaceutical development provides opportunities for more flexible regulatory approaches, for example:

✓ Risk-based regulatory decisions (assessment and inspections)

✓ Manufacturing process changes within the approved Design Space without further regulatory review

✓ Reduction of post-approval submissions

✓ Real-time quality control, leading to a reduction of end-product release testing (Real Time Release)

**Design Space**

Design Space: The multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality (ICH Q8).

DS defines a multidimensional space; once a DS has been authorised, movements within the DS are not considered a change from a regulatory point of view (no variation to be submitted).

This is accepted in the EU and it has been recognised in the recently adopted revised Variations Regulations

## EMEA AND THE REGULATORY SYSTEM IN THE EU

- EMEA is not the European FDA
- EMEA co-exists with over 40 National Competent authorities in the EU/EEA, forming an integrated network
- The centralised procedure (EMEA) for Marketing Authorisation co-exists with MA procedures at national level (national procedures, de-centralised procedures, mutual recognition procedures)
- EMEA co-ordinates the existing scientific resources in Member States and provides an interface between all parties
- EMEA works towards harmonisation of regulatory and technical requirements within the EU

**EU PAT Team**

***Mandate (general objective)***

A forum for dialogue and understanding between Quality and Biologics Working Parties and GMDP Inspectors Working Group to prepare a harmonised approach in Europe on assessment of applications and inspections of products/systems/facilities for Process Analytical Technology, including Quality by Design principles and manufacturing science in the context of PAT.

***Composition***

✓ Chairman; 5 quality assessors (chemicals and biologicals); 4 GMP inspectors; chairs of the QWP, BWP and GMDP, IWG; observer from EDQM; EMEA staff (4).

✓ 1 delegate only (either quality assessor or GMP inspector) per involved country.

✓ Representation to cover both human and veterinary products expertise.

***EU PAT Team Activities***

- 4 meetings/year
- Liaison with a number of companies, equipment manufacturers and PAT topic groups, including biological Liaison with FDA (Teleconferences) Participation to workshops e.g. Design Space Workshop (May 2006), Workshop on PAT for Biologicals (March 2007), Seminar on Quality by Design/PAT (April 2008)
- Site visits to manufacturers using PAT techniques
- Training of assessors and inspectors

***EU PAT Team: Progress to Date***

• Published documents:

✓ PAT Q/As: clarifying regulatory requirements for changes to the manufacturing process when PAT use is implemented

- ✓ Reflection Paper on PAT related information in the MA dossier
- A mock (CTD P.2) submission (examplain) for a QbD/PAT finished product application has been discussed with industry and published by EFPIA
- Input to QbD/PAT applications in the Centralised Procedure and in the context of the Work Sharing Project
- Input to future PAT applications by discussion with applicants
- Training for assessors and inspectors (Sep 2004/Jan 2006)

***EU PAT Team: Ongoing Activities***

Continue and build the existing dialogue with companies on both general and product-related issues further develop existing expertise. Work with industry on a mock submission for a QbD/PAT biotech active substance application.

Develop guidance for assessors, inspectors and applicants on:

- ✓ Impact of PAT on batch release
- ✓ Impact of PAT on assessment of quality
- ✓ Impact of PAT on inspection practice

***Other Ongoing Related Activities***

- Revision of the NIR Guideline
- Revision of the Parametric Release Guideline (to take into account RTR concepts)

***Work Sharing Project***

- The Work Sharing Procedure for PAT Variations to Nationally Authorised Products was published in June 2006.
- Describes an approach for work sharing between NCAs in the EU.
- Has been developed for QbD/PAT related variations to nationally authorised products.
- Before the procedure was published, companies were coming to EMEA identifying difficulties in dealing with purely national variations.
- Dealing with QbD/PAT variations at national level was perceived by companies as a major barrier to introduction of QbD and/or PAT techniques.
- The procedure is co-ordinated by EMEA and aims at pooling and using the best available expertise in the EU on QbD/PAT.
- The procedure is not legally binding, however, it has been agreed by the Head of Medicines Agencies and EMEA.

**WS Project: Results**

3 applications were assessed within the project, involving the EU PAT Team. All the applications were successfully finalized. RTR was authorised for one product within the project, based on combination of extended knowledge of the process, use of information obtained using PAT techniques and use of conventional information

## CONCLUSION

QbD approach is supported by the regulatory community in the EU.

Appropriate regulatory tools, developed in the ICH context, for the implementation of QbD are available; others are under development QbD implementation in the EU is ongoing; however, applications including QbD and PAT elements have been already authorized both in the centralised procedure and within the work-sharing project (variations to nationally authorized products.

The Design Space concept is now included in the EU legislation.

The PAT Team is the key for implementation of QbD in the EU.

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