Process Analytical Technologies View Point of the Regulators

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Cannes, 3 May 2004

Process analytical Technologies

This presentation is made on behalf of the EU-PAT Team

Composition:

3 + 1 Assessors and 3 + 1 Inspectors

Observer: EDQM

EMEA Website for more details

Overview of the Presentation

- PAT: Setting the Scene
- Challenge/ Claimed Benefit for Industry
- Challenge for the Regulators
- Current PAT Activities within QWP/GMP-WP
- Potential contribution from the European Pharmacopoeia
- Conclusion

PAT: Setting the Scene

Process Analytical Technology:

Very narrow definition:

Analytical Technology used during process controls.

e.g. Weighing, Temperature, HPLC,

but also

NIRS, Raman, Acoustics, LIF, Imaging Technology, …….

PAT: Setting the Scene

FDA Process Analytical Technology:

"PAT is considered to be 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 processes with the goal of ensuring final product quality"

Elements of pharmaceutical development

EU-PAT Team very much in agreement with the framework of this document

PAT: Setting the Scene

The quality (specifications) of a medicinal product is essentially influenced by:

- The characteristics/properties of the starting materials
- The manufacturing process

It is recognized that:

« *Quality cannot be tested into products, Quality has to be built in by design* »

PAT: Setting the Scene

Therefore PAT **can be/is** a very performant tool to design quality into the product not only due to the possibility of real time testing but by improving process understanding.

This can of course equally apply for the drug substance and the drug product

PAT: Setting the Scene

PAT is one element of a broader process which has received some dynamic with FDA's GMP initiative for the 21st Century and continues within the ICH process:

- Q8: Pharmaceutical Development
- Q9: Risk Management

PAT: Setting the Scene

Q8 – Pharmaceutical Development

(current wording)

"The aim of the pharmaceutical development is to design a quality product and the manufacturing process to deliver the product in a reproducible manner. It is a basis for risk mitigation…."

PAT: Setting the Scene

Q9: Risk Management

(current wording)

"The focus should be to identify hazards that have the potential for patient impact i.e. hazards that have the potential to affect product quality safety and efficacy."

PAT: Setting the Scene

PAT or advanced technology cannot only be used during a manufacturing process but also to test the final product (ds/dp) itself.

e.g. NIRS for identification or assay.

Claimed Benefit for Industry

- Better understanding of the process
- Introduction of real time release
- Reduction of cycle times
- Less batch failure
- Better management of change controls
- Regulatory relief

Challenge for Industry

- Amount/level of information to be presented to the regulators (chemometrics/statistics)
- Correlation between measurements during the process and release testing specifications (basis for release of the batch)

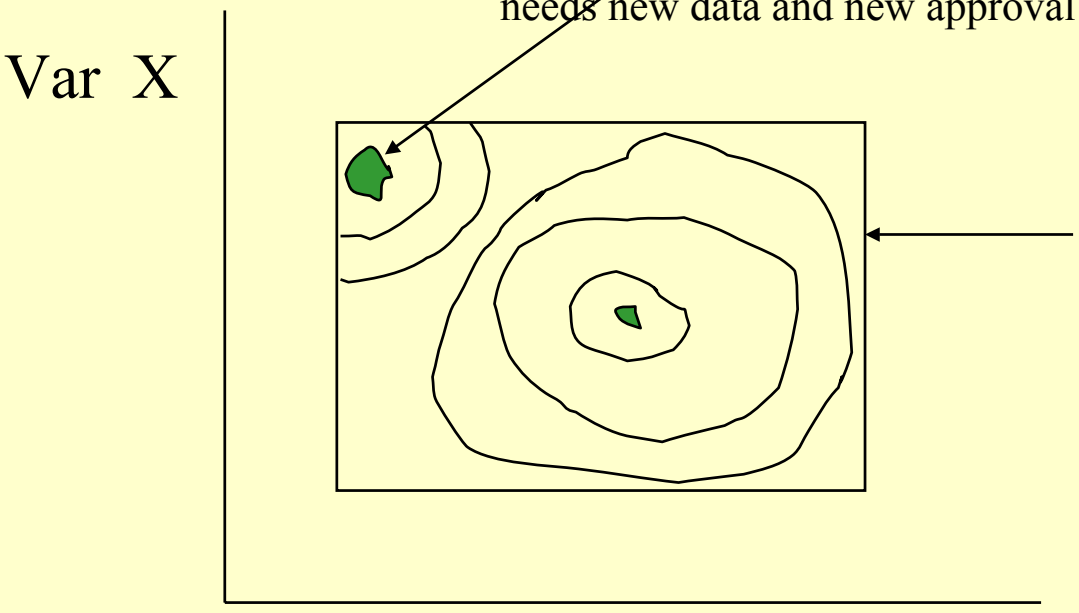
Challenge for Regulators

– EU: Great experience with the concept of pharmaceutical development, risk based approach
– CPMP/CVMP NfG on NIRS
– Will PAT become a standard requirement? **NO**
Q8: two approaches, but no differences in quality
- minimum: as currently requested in EU
- additional (optional): PAT concept

Company's strategic choice!!

ICH Q8:
Discussion on Regulatory Flexibility

Traditional process – limited knowledge – 3 batches, any change needs new data and new approval



New paradigm: influence of factors explored creating knowledge. Risk analysis of impact of change possible. Approval to move within defined area post-approval could give flexibility for continuous improvement without need for further approval

Challenge for Regulators

- Change in review process
- Enhanced collaboration between assessors and inspectors already at time of submission and during life cycle of the product
- Clarification of respective responsibility
- New definition for specifications needed? e.g. Uniformity of dosage units
- Batch release from 3rd countries
- Training aspects

GMP-QWP PAT-Team

Mandate:

– Definition of PAT
– Review legal/procedural implications
– Review and assessment of mock submissions
– Review of documents produced by other organisations
– Procedure for assessment of PAT related applications (Assessor / Inspector)
– Presentations from Companys

Potential Contribution from European Pharmacopoeia

Is there a need for a contribution?

– The PAT concept is a very fast moving field
– It is important to maintain flexibility
– The outcome of Q8 and Q9 should be awaited to better understand the future evolution
– Regulatory decisions will have to be taken by the Licensing Authorities

Current Contribution from European Pharmacopoeia

Compliance with the Pharmacopoeia:

« This does not imply that performance of all the tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopoeia before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopoeia quality from data derived, for example, from validation studies of the manufacturing process and from in-process controls. »

Elements of the PAT concept

Current Contribution from European Pharmacopoeia

– Concept of « Alternative Methods of Analysis »
– Parametric release see “Method of preparation of sterile products”. (chapt. 5.1.1.)

Elements of the PAT concept

– EDQM observer in the PAT Team

Conclusion (1)

Are regulators a barrier to PAT implementation?

NO

- Why can industry not introduce PAT into the manufacturing process on its own initiative?
- The system is in place to deal with it.

The main barrier is probably the uncertainty of regulatory consequences (relief, flexibility)

Conclusion (2)

- PAT is already possible today.
- However there are some challenges for both the Regulators and Industry:
  - How will it be assessed
  - Balance between information in the dossier and on site
  - What is the adequate level of information which will be or has to be submitted to the Licensing Authorities
- EU-PAT Team addresses these issues

Conclusion (3)

What ever system is chosen

PAT or not PAT

the patient should be our first priority