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PHARMA & ENGINEERING

Process Analytical Technology - PAT

INNOVATIVE TECHNOLOGY

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PAT – Process Analytical Technology

PAT is defined as a system for designing, analysing, and controlling production through timely measurements (i.e., during processing), which consistently ensures quality in the final product.

Which allows

Critical process parameters (CPP) that affect critical quality attributes (CQA) to be determined and measured in real time, through in-process controls that take their measurements throughout the manufacturing process.

Making it possible to

Detect potential errors or deviations, allowing to act before the deviations occur or correct them while the product is still being produced, through SPC* (Statistical Process Control).

*SPC is based on analysis of data, that monitors and analyzes the process conditions using statistical techniques.

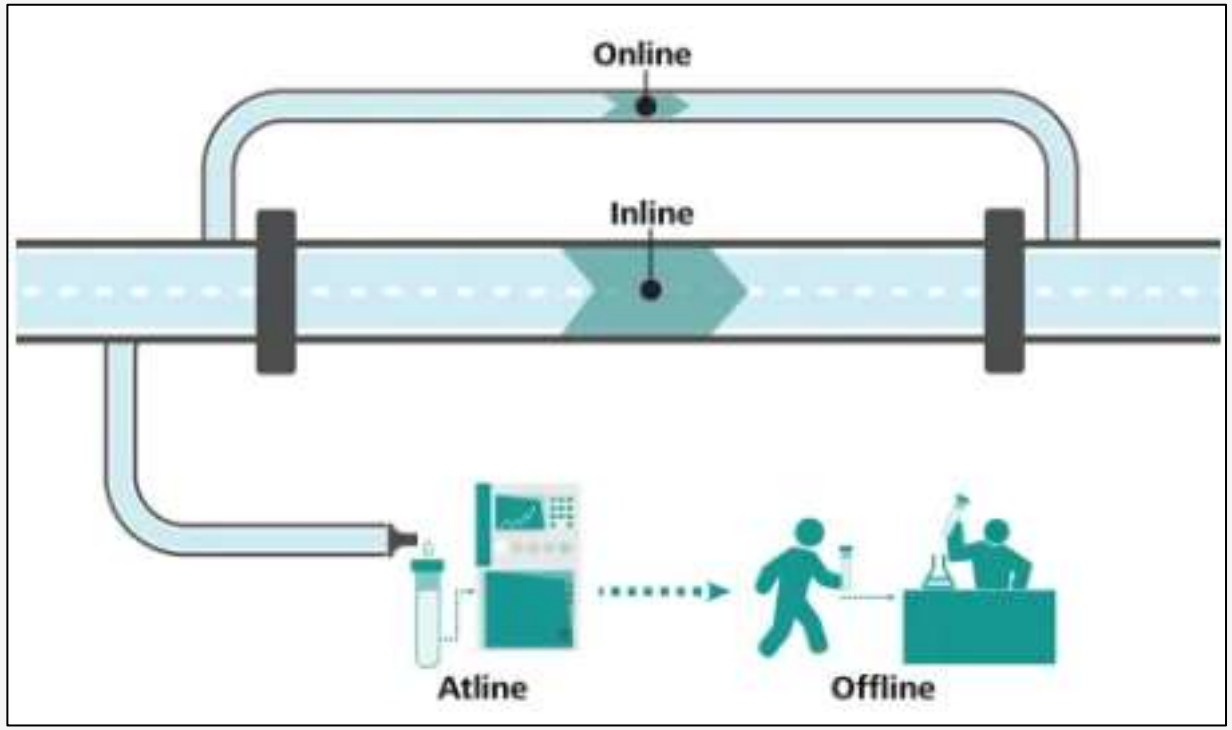
How can PAT improve your process?

- Better process understanding
- Prevention of rejects and reprocessing
- Reduction of production cycle times by using in-, on-, at- and/or off-line measurement and control
- Real-time batches release
- Increasing automation to improve operator safety and reduce human errors
- Improvement of energy and material utilization and increasing capacity
- Facilitates continuous processing to improve efficiency and manage variability

How can the process be controlled by PAT?

Measurements and controls in PAT can be:

- In-line: Measurement where the sample is not removed from the process stream
- On-line: Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.
- At-line: Measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream.
- Off-line: Measurement where the sample is removed, isolated from, and analyzed in another room.

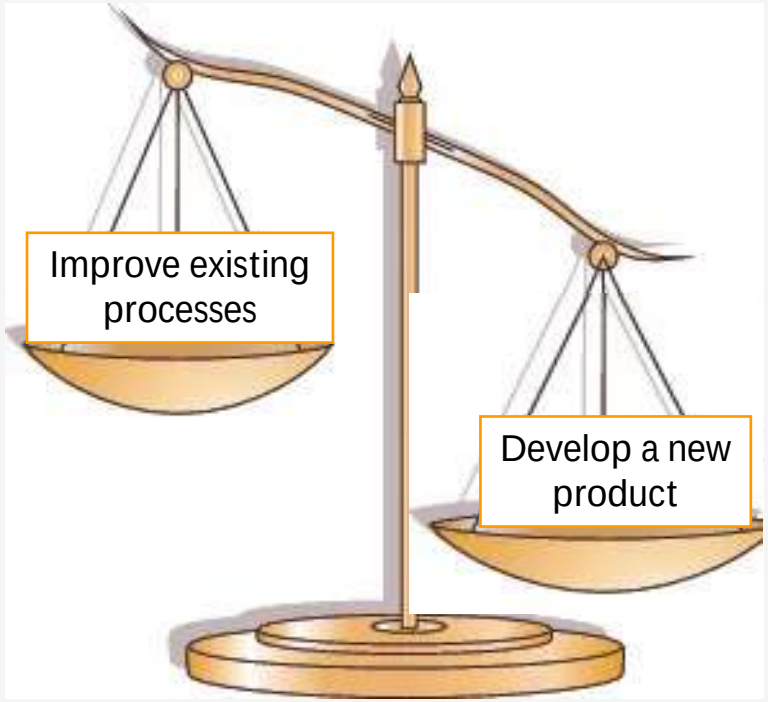


- On-line and In-line analyses allow a continuous control of the process;
- At-line and Off-line analyses, are performed by manual sampling.

PAT in Pharmaceutical Industry

PAT has been used and implemented in several industries (e.g., chemical, automotive, and food).

Why has the Pharmaceutical Industry adopted PAT at a slower pace?



Traditionally the approach was focused on new product development.

However, driven by the need to optimize its processes, the pharmaceutical industry is introducing new strategies to assure:

- The production of high quality drugs;
- The consistent production of viable products in a ever increasing regulatory environment;
- The optimization of production cycles and development of new drugs.

Pharmaceutical Industry and PAT initiative

One of the points of innovation and improvement, is focused on process analysis and control.

The pharmaceutical industry traditionally approves the quality of the final product by performing a laboratory analysis (off-line measurement) when the process has already ended. This is not only costly and time consuming whereas at the same time prevents the detection before the process ends

- In order to:

Improve and modernize pharmaceutical manufacturing to achieve significant health and economic benefits

- Without:

Jeopardizing product validation and product delays

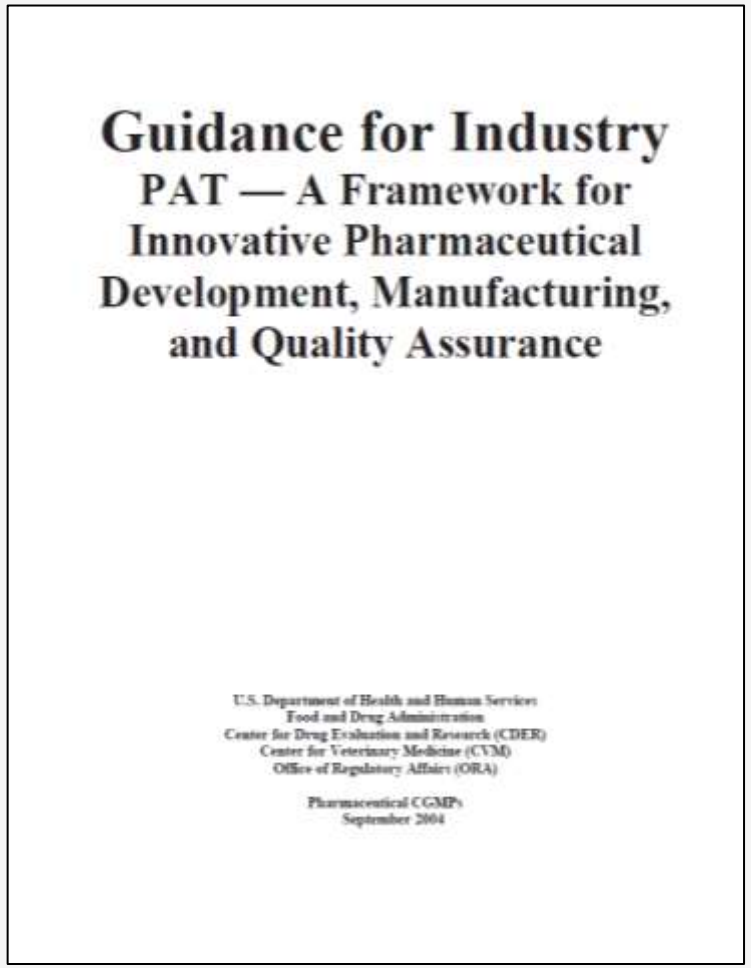
- The Food and Drug Administration (FDA), announced in August 2002 the initiative:

“Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century - A Risk Based Approach"

This initiative facilitated the adoption of Process Analytical Technology (PAT).

Guidance for Industry PAT

In September 2004, the final version of the PAT Guidance was released with the help of the Center for Veterinary Medicine (CVM) and the Office of Regulatory Affairs (ORA).


Guidance for Industry

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

Pharmaceutical CGMPs
September 2004

Who else supported PAT initiative?

- European Medicines Agency (EMA), in January 2004 the EMEA PAT team was created
- Japanese Ministry of Health, Labor, and Welfare (MHLW)
- International Conference on Harmonization (ICH) guidelines, where PAT has been introduced in ICH process, namely:

  -ICH Q8 - Pharmaceutical Development

  -ICH Q9 - Quality Risk Management

PAT Framework

- The goal of PAT, enhance understanding and control the manufacturing process, is consistent with our current drug quality system:

Quality cannot be tested into products,
it should be built into products.

- PAT is also aligned with the "Quality by Design" (QbD) approach, in creation of a robust control strategy for the process, in which SPC tools are used, for ongoing process monitoring.

PAT in Pharmaceutical Industry

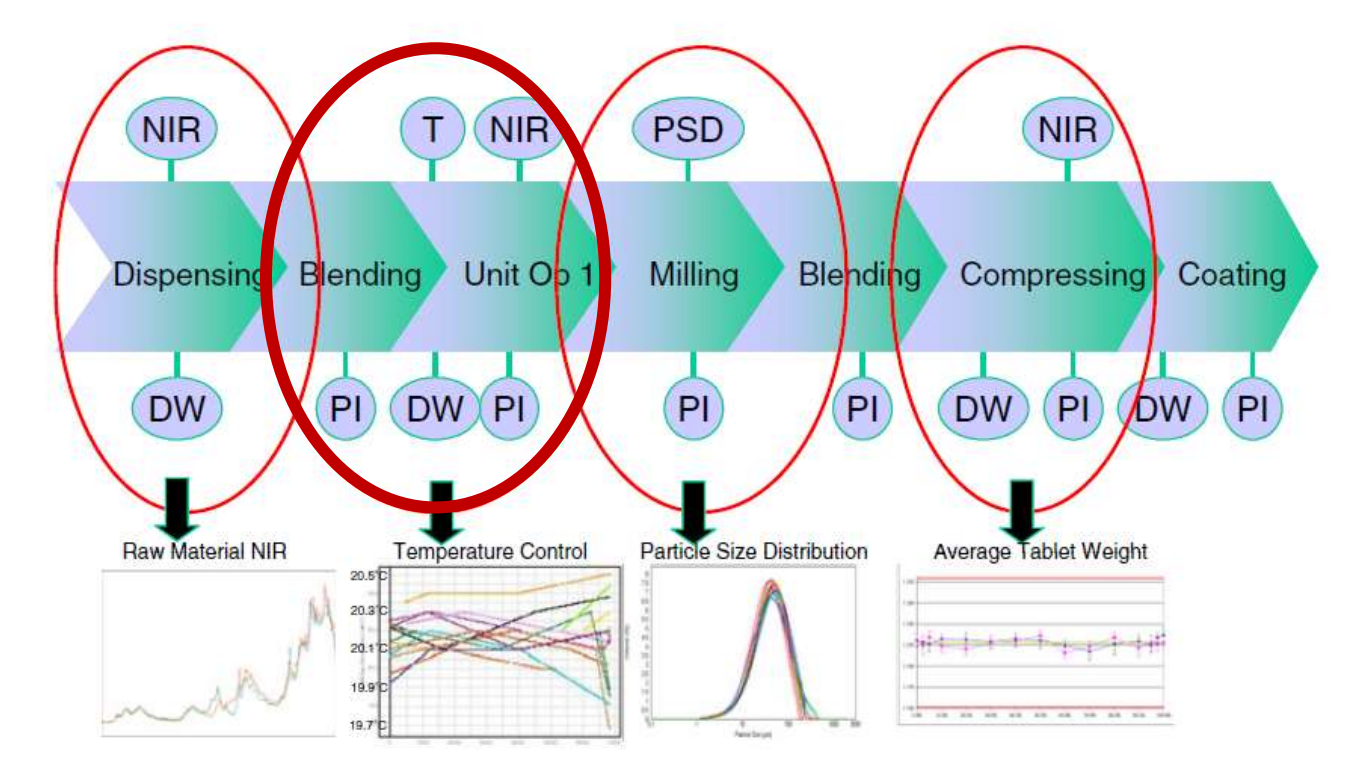
- A variety of analytical techniques have been used in the pharmaceutical industry, including Near Infra Red (NIR); Process Raman Spectroscopy; Fourier transform infra-red spectroscopy (FTIR); UV Spectrocospy, Gas Chromatography, High Performance Liquid Chromatography and Process MS.

Application Examples of analytical techniques:

Application	Process Analyzer	Statistical Tool	Measurements and Controls (examples)	Observation
Evaluation of content uniformity for low-dose tablets	Near Infra Red (NIR)	Principle-components analysis (PCA)	In-line On-line At-line	NIR/PCA was used to predict content uniformity of low-dose tablets manufactured by a direct compression process
Analysis of liquid formulations containing sodium chloride	Laser-induced breakdown spectroscopy (LIBS)	Partial least-squares (PLS) analysis	In-line On-line	Method does not need any sample preparation and is less time-consuming
Quantification of the active ingredient in pharmaceutical injectable formulations	NIR and UV–visible spectroscopy	-	In-line On-line	More economical and less time-consuming method for quantification of the lysine clonixinate

PAT Example: Tablet Manufacturing Process

The following figure illustrates a typical tablet manufacturing process in a pharmaceutical facility.



Source: "*Process analytical technology (PAT) for biopharmaceutical products*"
DOI: 10.1007/s00216-010-3781-x

Where:
PSD: Particle size distribution; T: Temperature;
DW: Dry weight; PI: Product impurity

Blending step: using a PAT such as NIR spectroscopy, with in-line measurement and control

Will allow that Critical Process Parameters (CPP), including:

- ✓ Blending Time
- ✓ Blending Speed

That affect Critical Quality Attributes (CQA), like:

- ✓ Blend Homogeneity

Be determined and measured in real time.

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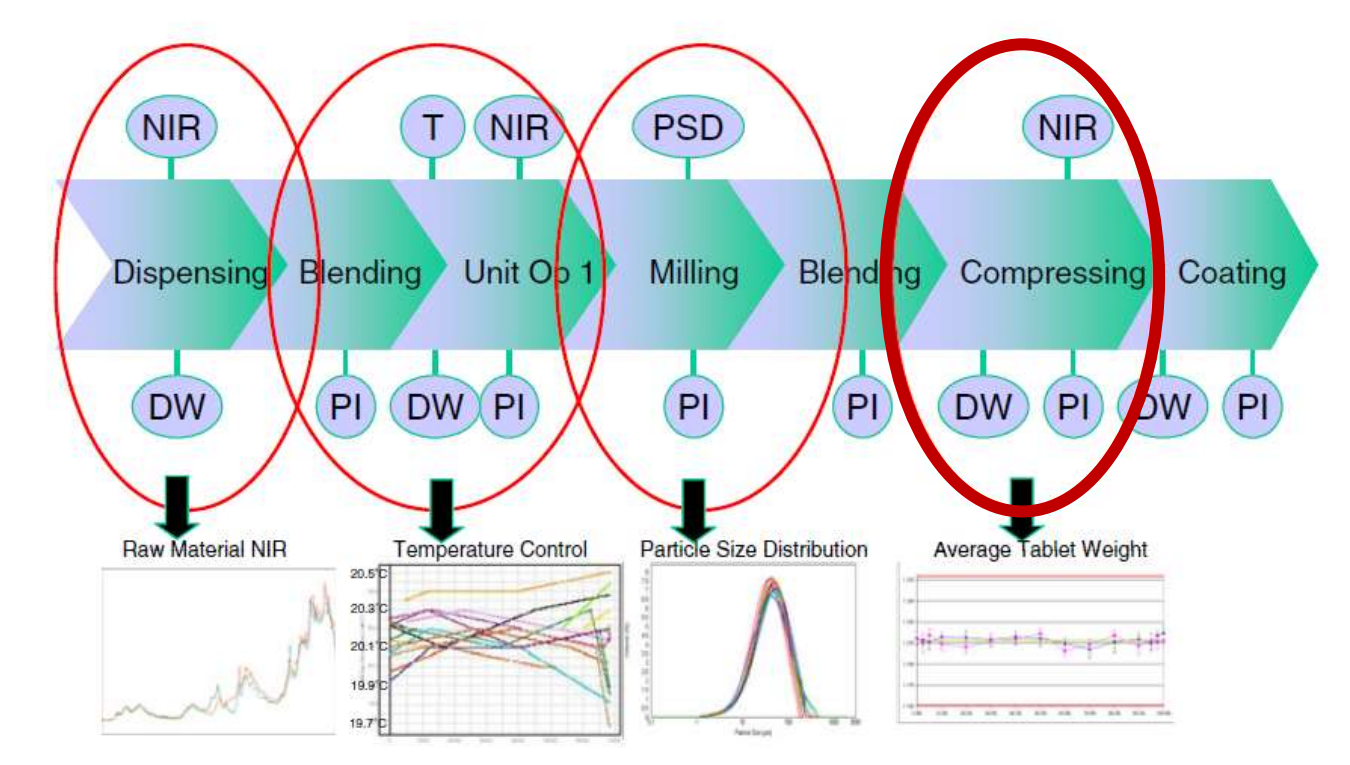

Source: "*Process analytical technology (PAT) for biopharmaceutical products*"
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Where:
PSD: Particle size distribution; T: Temperature;
DW: Dry weight; PI: Product impurity

Compression step: using a PAT such as NIR spectroscopy, with off-line measurement and control

Will allow that Critical Process Parameters (CPP), including:

- ✓ Compression Force
- ✓ Press Speed
- ✓ Dwell Time

That affect Critical Quality Attributes (CQA), like:

- ✓ Tablet Disintegration Time
- ✓ Dissolution
- ✓ Hardness

Be determined and measured in real time.

After all what are the benefits of implementing PAT?

- Provide timely analysis of critical quality parameters
- Improvement of final product quality
- Decreases sample preparation time
- Decreases the probability of sample preparation error
- Facilitates real-time release of the batches
- Reduces operating costs
- Correct use of PAT allows better batch-to-batch consistency and better product quality

The product is “engineered for Quality”, as opposed to “tested to Quality”

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About Stepwise

ENGINEERING SERVICES TAILORED FOR PHARMA INDUSTRIES

Stepwise Pharma & Engineering differentiates from other engineering companies by tailoring its services specifically for the highly GMP-regulated pharmaceutical and life sciences industries.

The entire pharmaceutical and life science industries manufacturing lifecycle is supported by us helping to set direction, assessing benefits of strategic investments and optimizing manufacturing and business processes. We assist our customers from Research and Development (R&D) to Commercial manufacturing.

Our highly qualified team combines a solid experience in the Pharmaceutical and Veterinary, Medicinal Cannabis, Cosmetics, Food Supplements and Medical Devices industries will support your business as it was ours.

Our goal is to help our customers to achieve and maintain GMP manufacturing excellence and assist them in the route to market.

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- Graduate in Biochemistry, at University of Évora.
- Masters' degree in Pharmaceutical Engineering, at Instituto Superior Técnico. With the thesis Theme “In silico Design of novel peptides for treating cancer through inhibition RANK-TRAF6 Interaction”.
- Had some experiences in clinical analysis laboratory and in a wine production winery.