Quality by Design and PAT. How to design effective manufacturing processes

18-07-2019

IMA ACTIVE
Solid Dose Solutions

QbD AND DESIGN SPACE

- QbD is the Scientific, Risk-Based approach to product design, manufacture and control use in the Pharmaceutical, Biopharmaceutical and Medical Device industries.
- Based on the pioneering industry guidance document “cGMPs for the 21st Century, A Scientific, Risk-Based Approach”.
- See globally as a move away from outdated practices that do not allow for innovation and the use of latest state of the art, Process Analytical Technologies (PAT) and Quality Management Systems.

http://www.fda.gov/downloads

QbD APPROACH

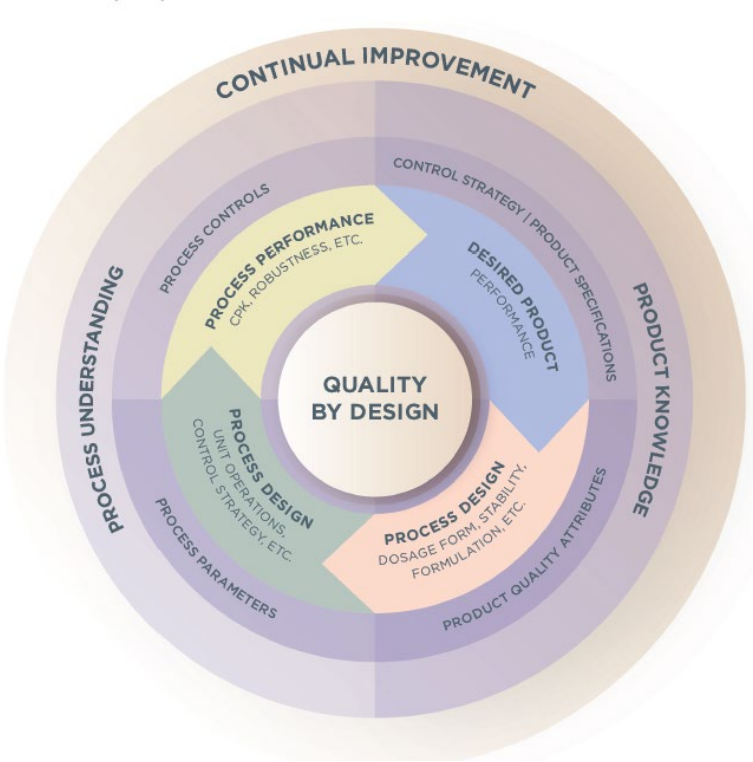
- QbD requires manufacturers to show regulatory bodies enhance product and process knowledge through detailed studies conducted during the entire product lifecycle.

- Initiated to reduce the regulatory burden of current practices.

- Processes designed to operate in a defined "Design Space". This space is the proven region where the products "Desired State" lies.

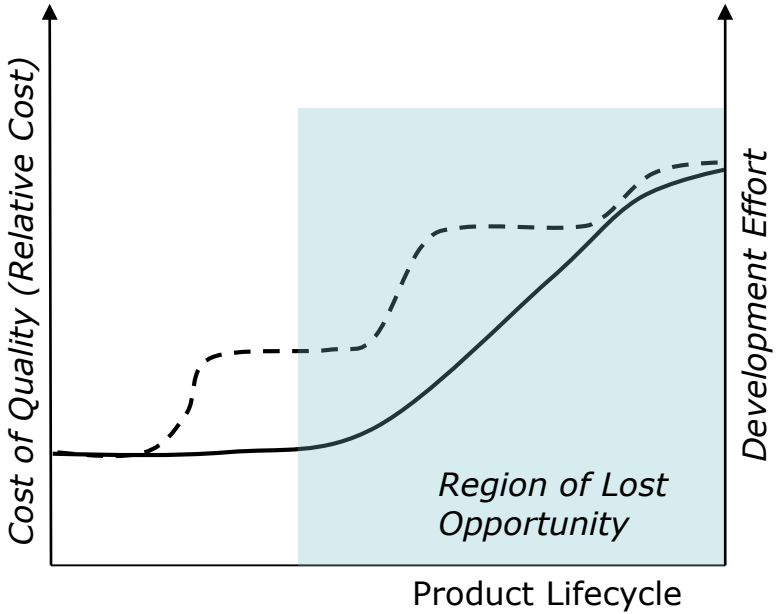
- Design Space can be defined using one, or any combination of the following tools,

- Design of Experiments (DoE)
- Multivariate Analysis (MVA)
- Statistical Process Control (SPC)
- Risk Analysis

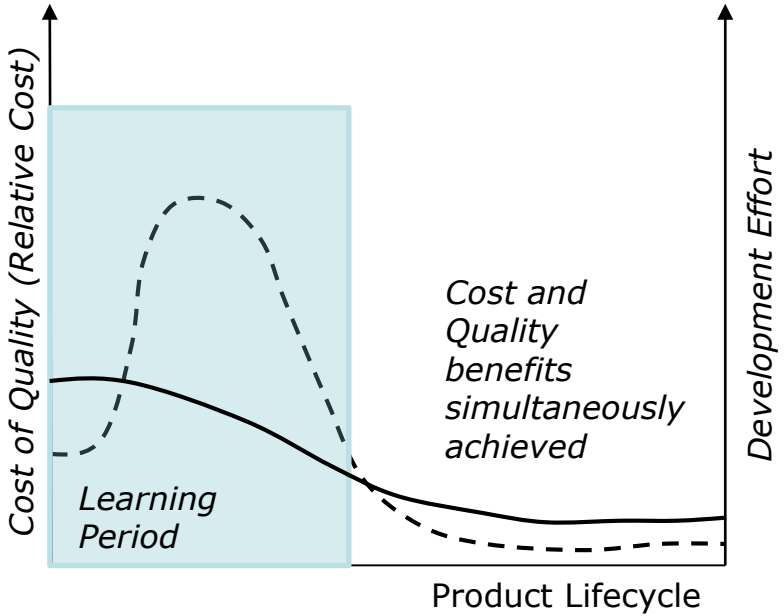


THE COST OF QUALITY

Traditional Process Development



QbD Process Development

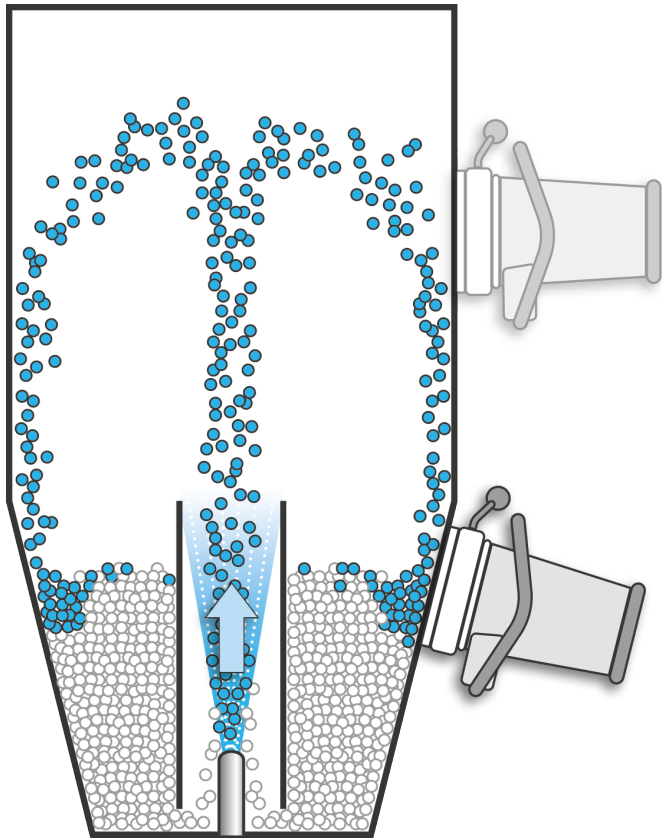


Cost of Quality — Development Effort

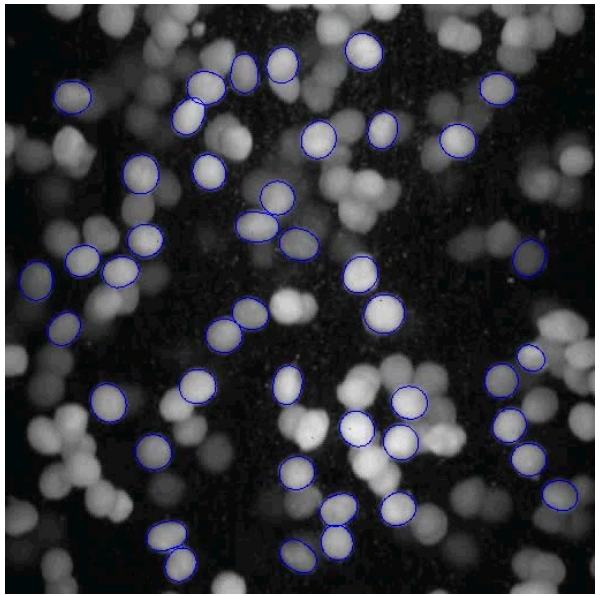
Swarbrick, Gadsby and Wempel: *QbD and PAT for Dummies*

VISUAL INSPECTION SYSTEM FOR MONITORING OF PELLET COATING PROCESS

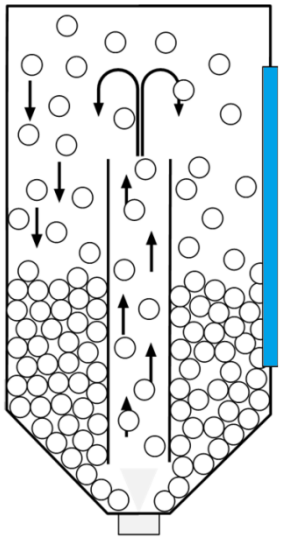
VISUAL INSPECTION SYSTEM FOR PROCESS MONITORING

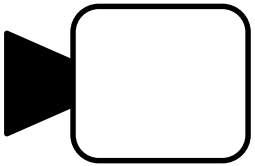


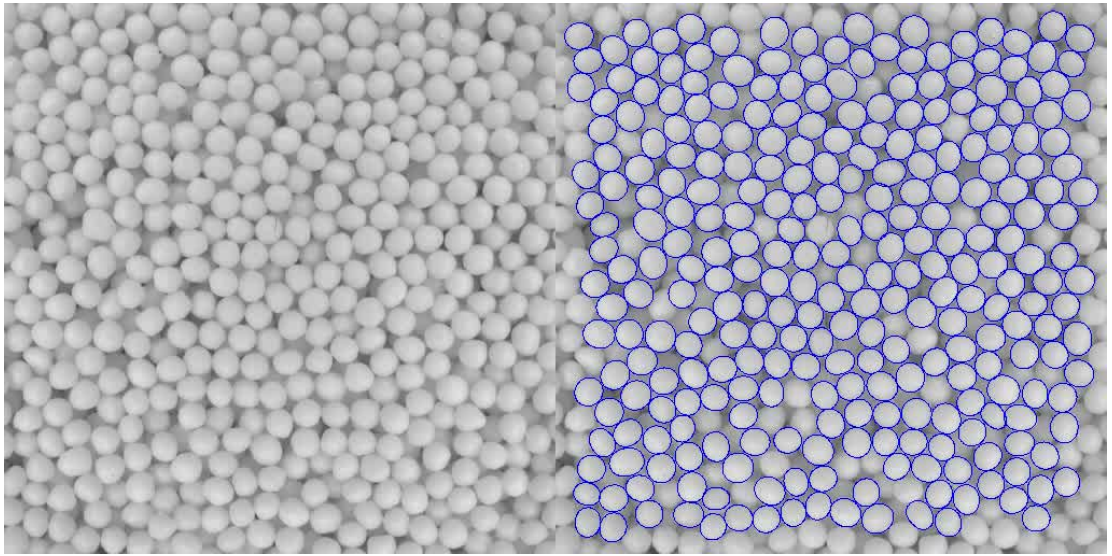
In-line and not-invasive monitoring of fluid bed pharmaceutical production processes.



VISUAL INSPETCION SYSTEM FOR PROCESS MONITORING







Coating process

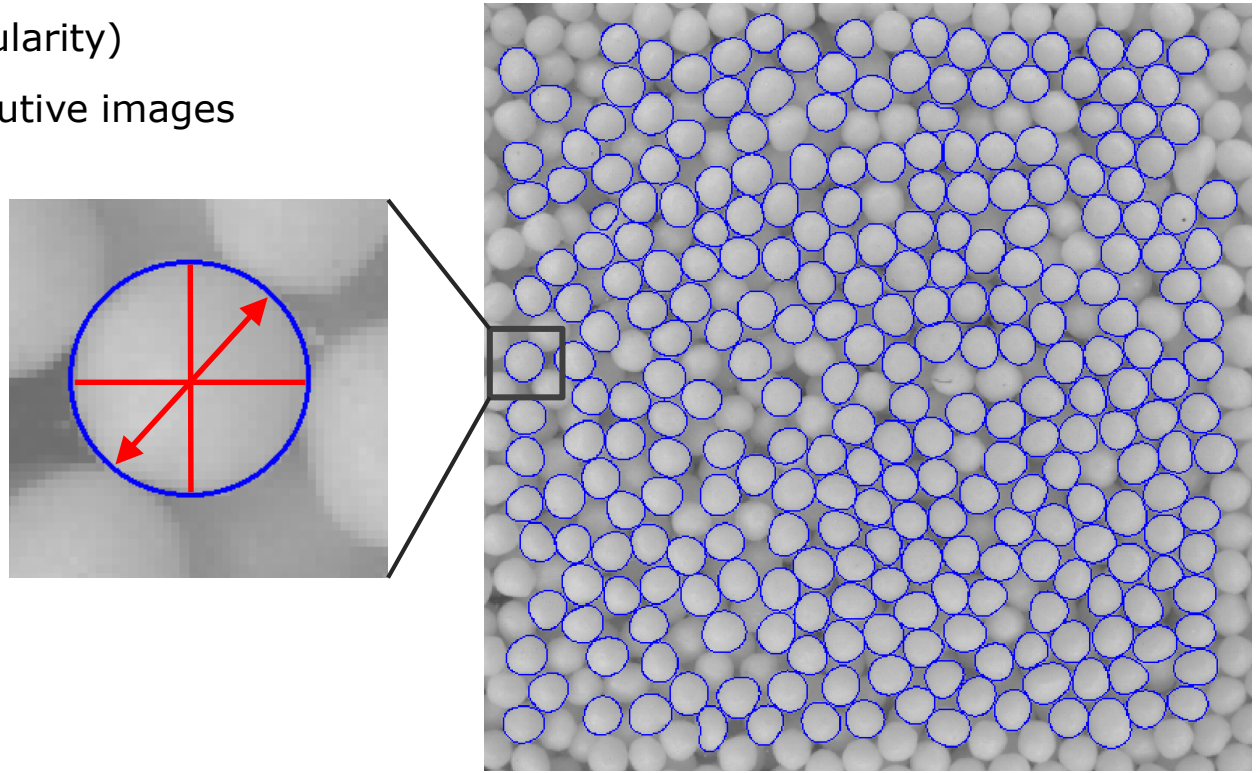
Imaging system

Images

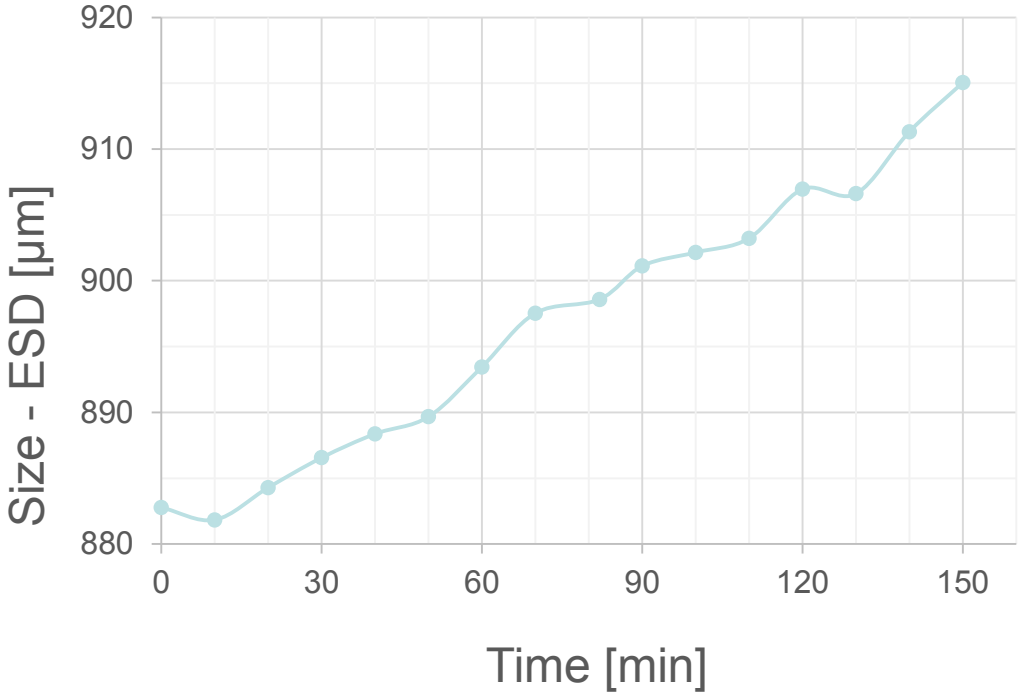
Analyzed images

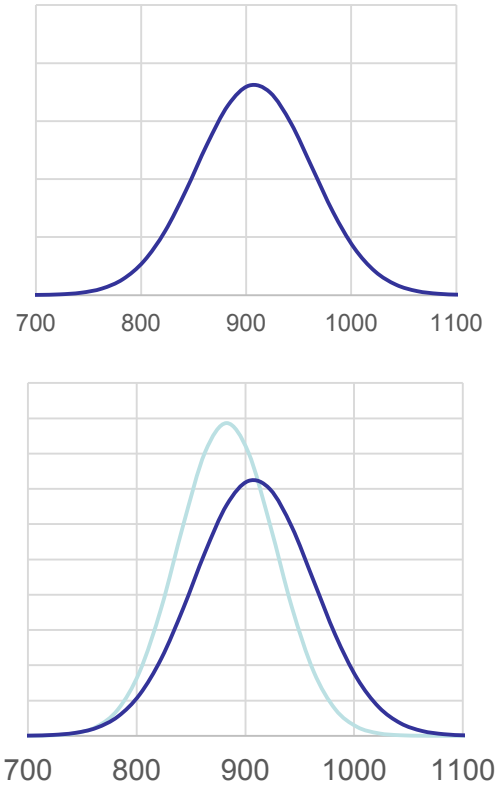
PELLET PARAMETERS MONITORING

- **Size** (ESD - equivalent spherical diameter)
- **Shape** (aspect ratio, circularity)
- **Velocity** by using consecutive images



PROCESS MONITORING





MICRO NIR IN OSD MANUFACTURING PROCESS

MICRONIR IN OSD MANUFACTURING PROCESS

RM ID and Conformity

- Purity and Identity for safety.
- Conformity to predict how to process material in a QbD environment.
- Campaign materials to products based on history and experience.

Granulation and Drying

- Engineer particles so that they blend uniformly.
- Monitor and control process using NIR to
- Generate high quality granules
- Dry granules to desired state.
- Ensure over-drying does not occur.

Blending

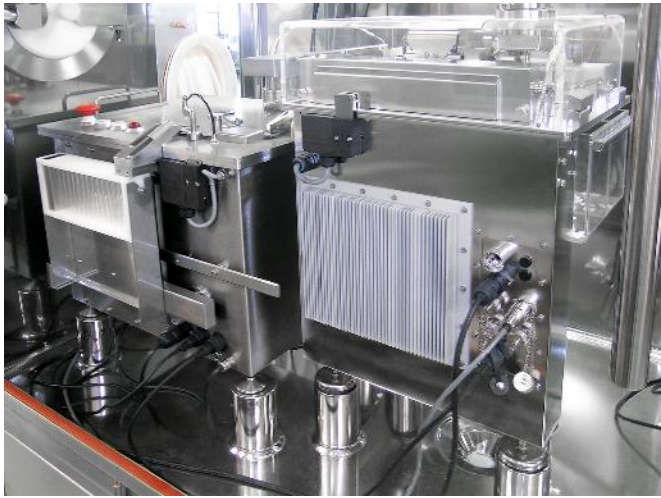
- Generate blends with the lowest 'Residual Heterogeneity'
- NIR ensures that powders are not under or over blended.
- Overblending generates 'fines' that can result in poor tablet compression.

Compression

- Ensure that powder flow is consistent for reliable tablet compression.
- Monitor feed-frame to ensure.
- Powder blend is not segregating during compression.
- Potency is consistent over entire process.

COMPRIMA APPLICATION OF NIR - 2007

Traditional application: sampled tablets by IPC with NIR



CASE STUDY: APPLICATION OF NIR ON A TABLET PRESS WITH RETROACTIVITY FUNCTION

WHY TABLETING?

Tablets are most used pharmaceutical forms all over the world.

Benefits for the manufacturer:
- preparation easier and cheaper
- stability
- convenience in packaging, stocking and transport

Benefits for the patient:
- accuracy in API dosage
- facility of administration

WHAT IS TABLETING?

RAW MATERIALS

MIXING

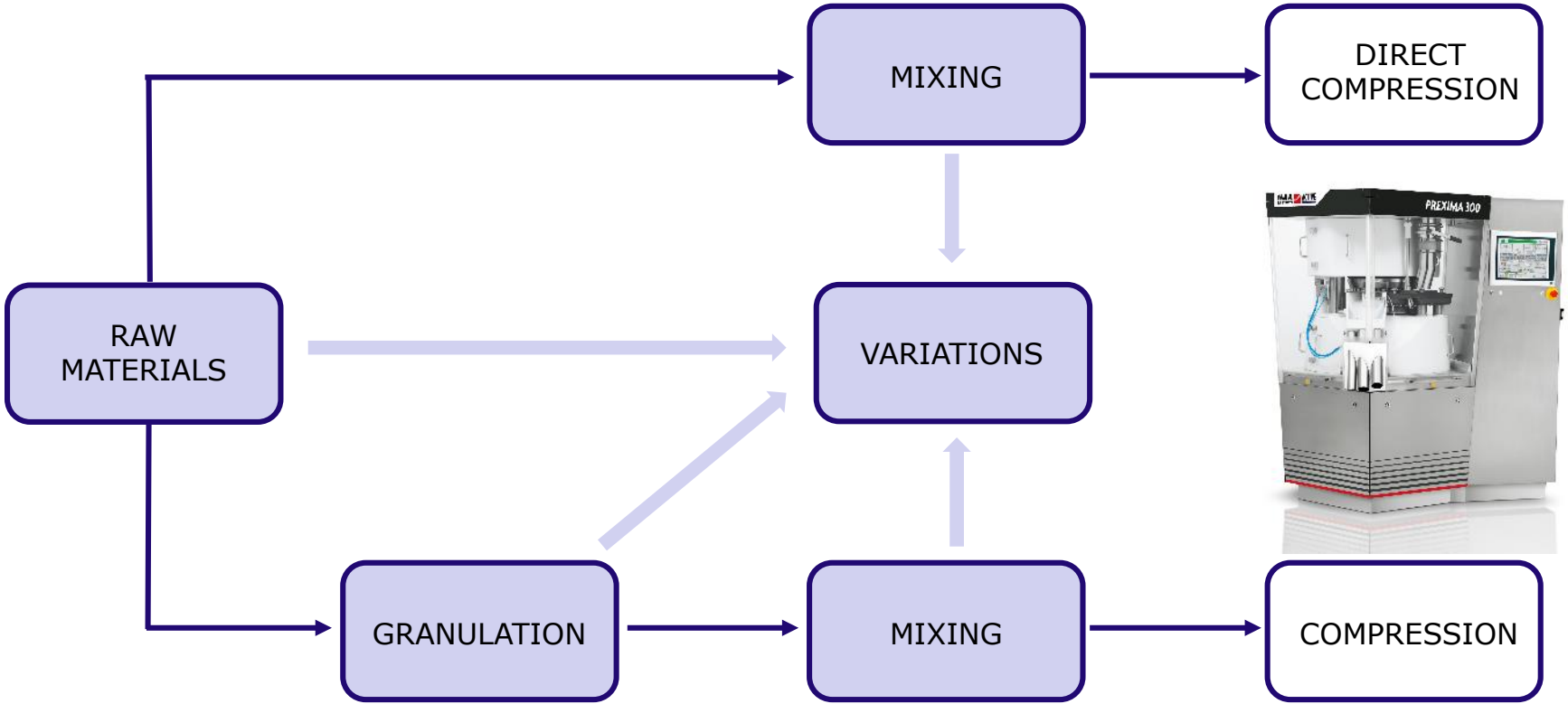
DIRECT COMPRESSION

GRANULATION

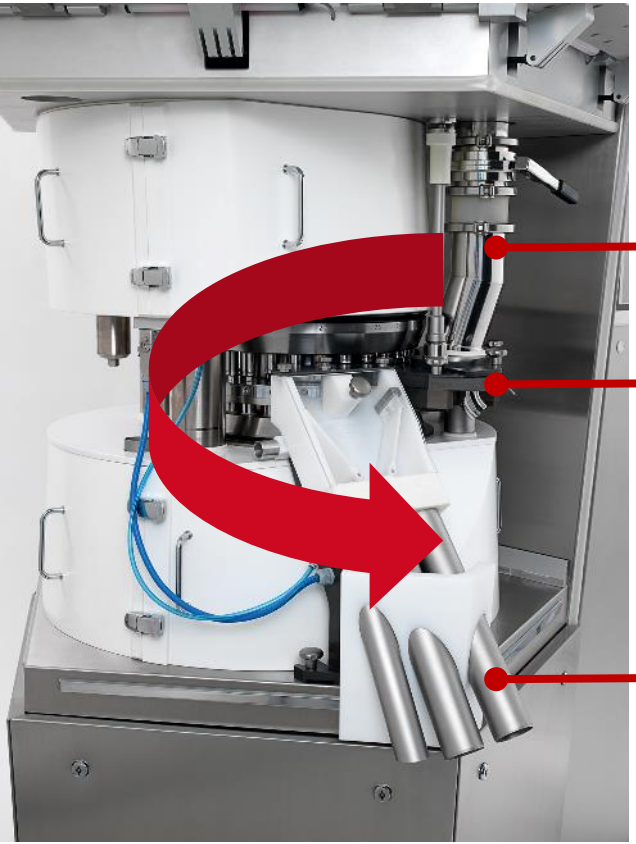
MIXING

COMPRESSION

TABLETING PROCESS FLOW



QbD APPROACH



Using specialized sensors as NIR, placed in accessible area of tablet-press can deliver real-time data about chemical and physical attributes of the raw materials, intermediate or final products.

AIM OF THE STUDY

Evaluate potential mixing trouble using three different formulations through NIR probes positioned on feed frame and on loading system pipe of PREXIMA 300.

MATERIALS & METHOD: FORMULATIONS

Three formulations, lactose based, have been tested variating talc content.

Ingredient	m.u.	Formulation 1	Formulation 2	Formulation 3
Lactose	%	98	96	94
Talc		**1**	**3**	**5**
Magnesium stearate		1	1	1

Selected as desired formulation

Deviation from correct blending process

MATERIALS & METHOD: EQUIPMENT

PREXIMA 300:

- 27 stations Eu-D turret
- Round biconvex Ø 9 mm
- Standard feeding system with flat profile with NIR probes

METHODS

Spectra acquired every second while powder flows continuously through the feeding system.

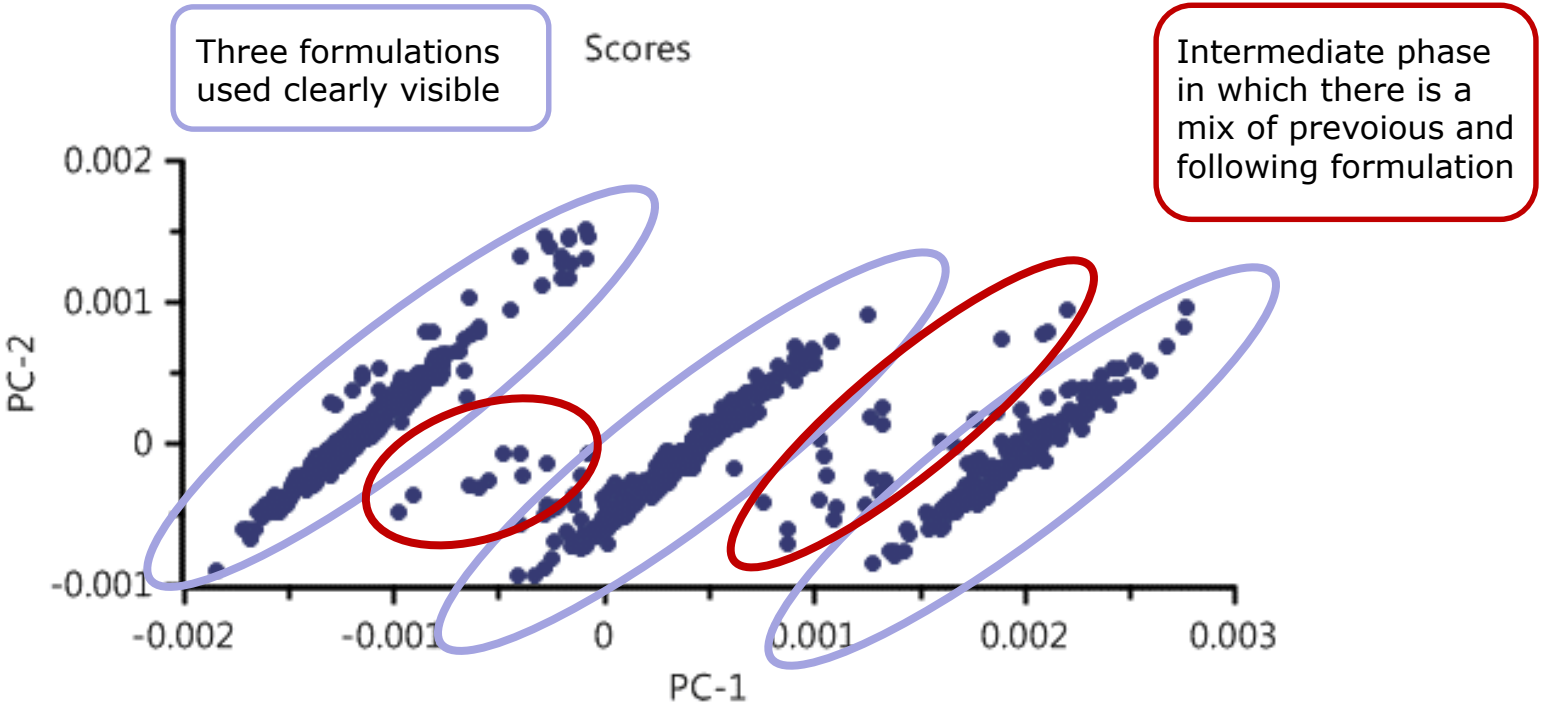
Blends, loaded continuously, can be monitored with two different approaches:

1. **Qualitative approach:** evaluate over the time the quality of the process and prevent eventual out of specifications situations (PAT approach);

2. **Quantitative approach:** follow over the time API or excipient concentration. This model needs calibration and a correct choice of modelling that allows Customer to control the content uniformity over the time.

RESULTS

Principle Component Analysis: looking at variability.



RESULTS

Spectra acquired during the batch production contains the information of the product flowing from the powder container to the die feeder of the tablet press.

To provide maximum chemical and physical information, NIR software helps in **prediction out of specification situations**, such as mixing trouble, segregation, pre-tableting process issues (raw material characteristics, storage, handling or granulation).

Why is it useful?

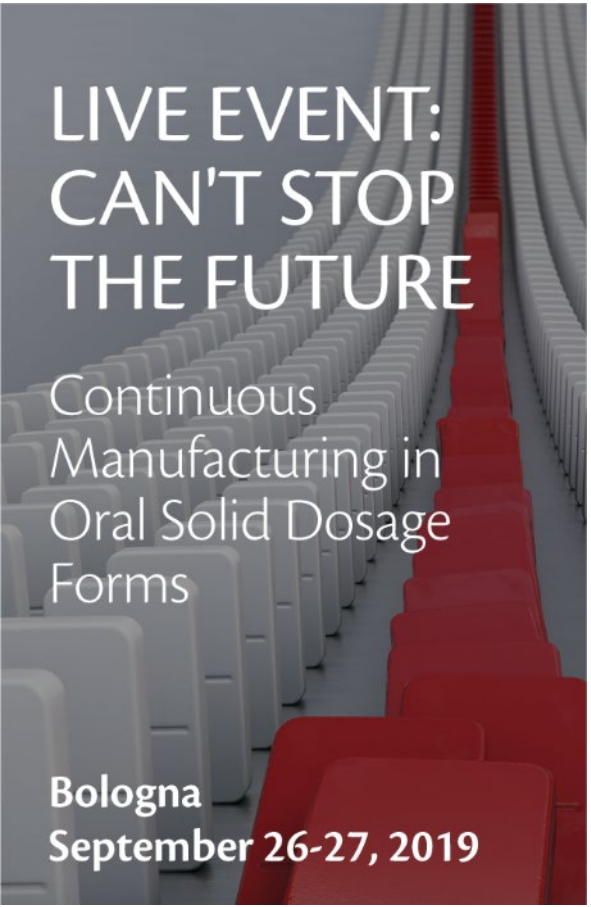
- Possibility to follow in real-time powder characteristics.
- Possibility to stop machine after deviations or out-of-specification situations when a calculated number of values are out of limit.
- Save good tablets without wasting time checking all technological characteristics.

CONCLUSIONS

CONCLUSIONS

- Applicability of NIR probes even on feed frame than on loading system pipe.
- Possibility to follow in real-time powder characteristics monitoring granulation, blending or handling problem e.g. pneumatic system.
- Define impact of probe location on data acquisition for through the window application.
- Possibility to stop machine after deviations or out-of-specifications situations when a calculated number of values are out of limit.
- Save good tablets without wasting time checking all technological characteristics.
- Improve knowledge about process and products studying fingerprints of blends.

FUTURE APPLICATION



Digitalization brings added value to drugs manufacturing in terms of agility, flexibility, productivity and costs thanks to end-to-end integrated system.

Real-time monitoring employs a combination of process parameter trends, measurements by PAT tools and sources of process analytical data that can facilitate decision making and follow-up action.