# Digital tools for optimised powder processing


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Research Scientist


# Content

**Introduction to CPI, and the complex particles facility**

**Overview of CPI research facilities for powder processing, highlighting the application of digital techniques:**

- **Oral solid dose manufacture**
- **Powder packing**

# Powder Processing at CPI

**We help companies to develop, prove, scale-up and commercialise new products and processes**

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Creating a **healthier** society, **cleaner** environment and a **vibrant** UK economy...

...by ensuring **every** great invention gets the **best** opportunity to become a successfully marketed product.

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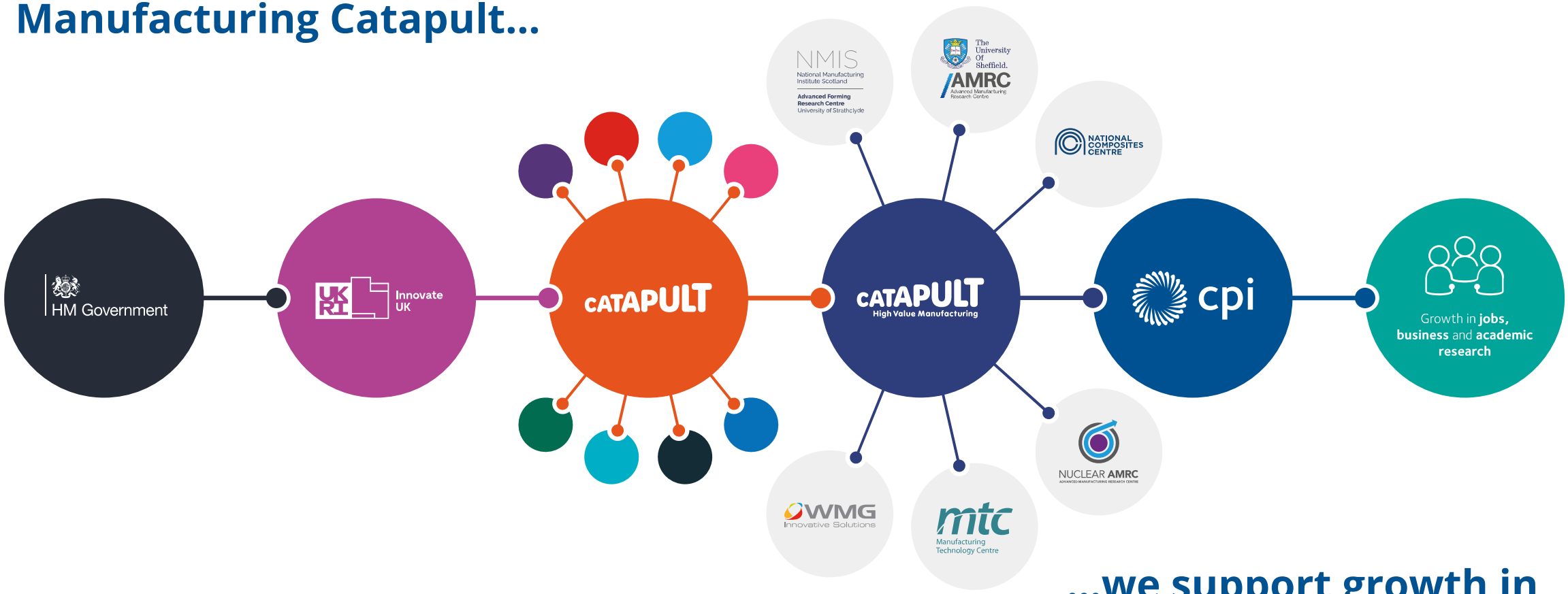
# As part of the UK's High Value Manufacturing Catapult...




# ...we support growth in advanced manufacturing

Biotechnology

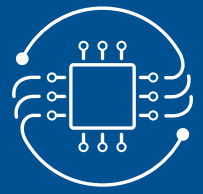
Biotherapeutics

Formulation and materials

Pharmaceutical processing

Photonics

Printed electronics



Flexible hybrid electronics

Digital

# ...with our expertise and core capabilities

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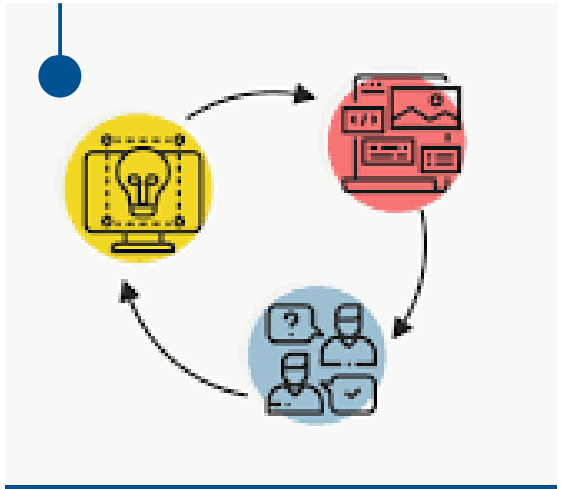
# Complex Particles



## Particle Prototyping

- Wet Granulation
- Dry Granulation & Tabletting
- Mixing
- Milling
- Coating

## Particle Characterisation

- Granulometry
- Dissolution
- Powder Flow
- Moisture Sorption
- Attrition


## Process Optimisation

- Contactless PAT (inline analysis)
- Chemometrics and complex data analysis
- Model based control
- Virtual Design e.g. DEM, CFD

## Process Scale-up

- Packing and Filling
- Wet Granulation
- Tabletting

*We innovate, design and optimise particulate components and the processes to make them*

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# Research facility for manufacture of oral solid dosage forms

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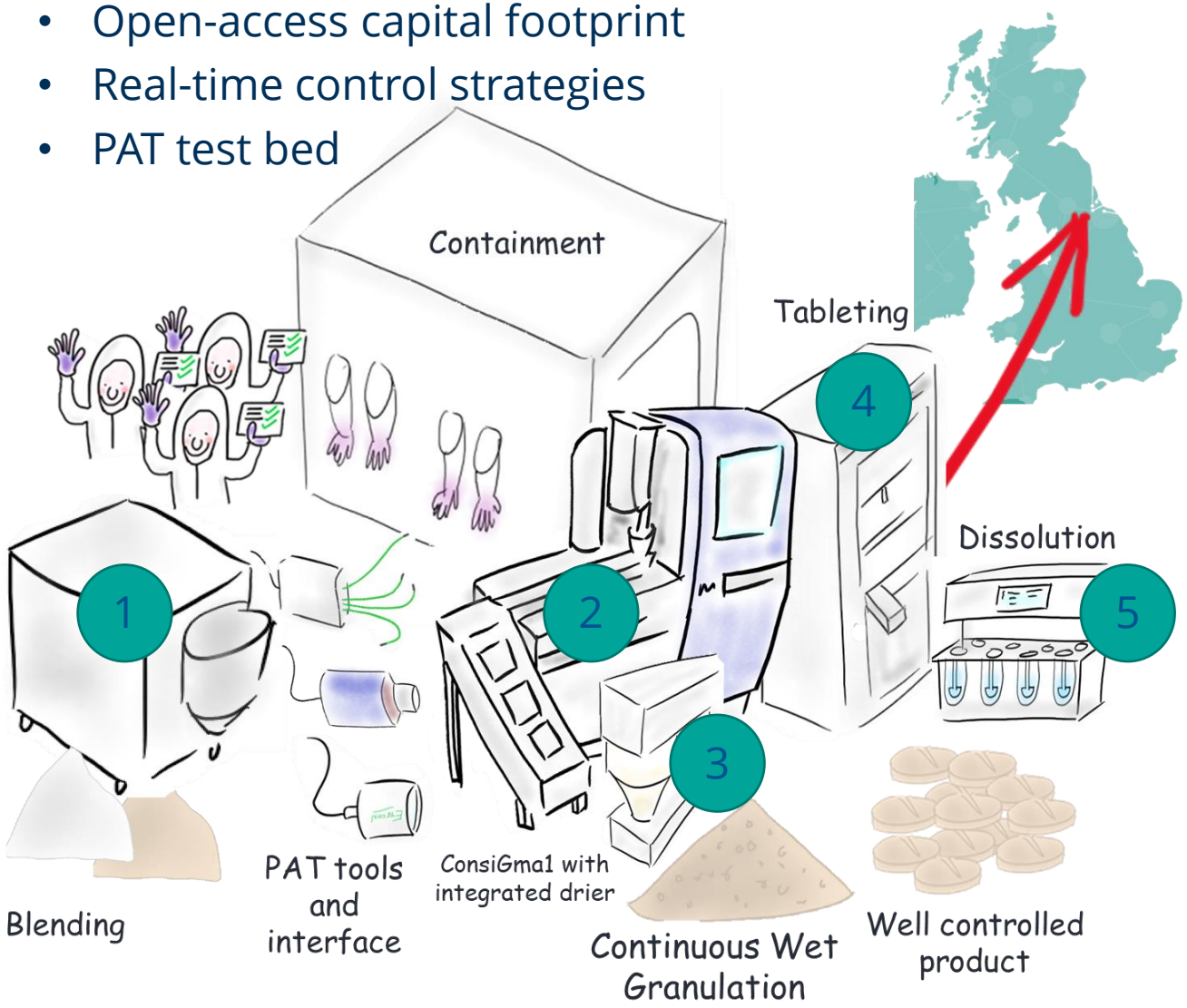
# Capability Overview

- Open-access capital footprint
- Real-time control strategies
- PAT test bed





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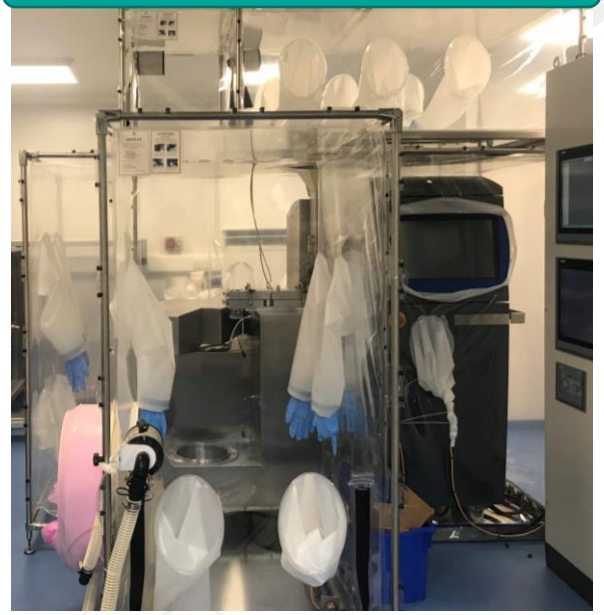
Tablet analysis

**Bespoke API containment**



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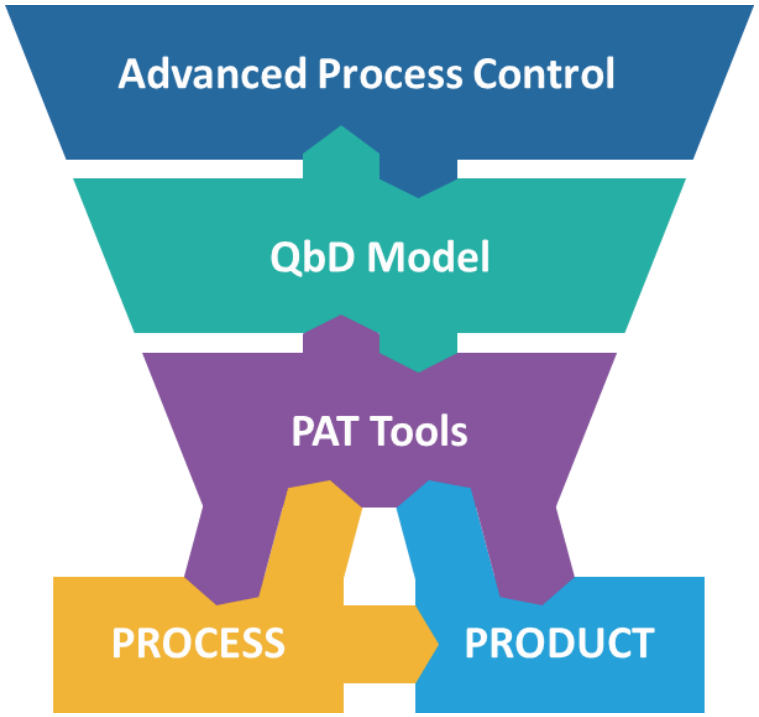
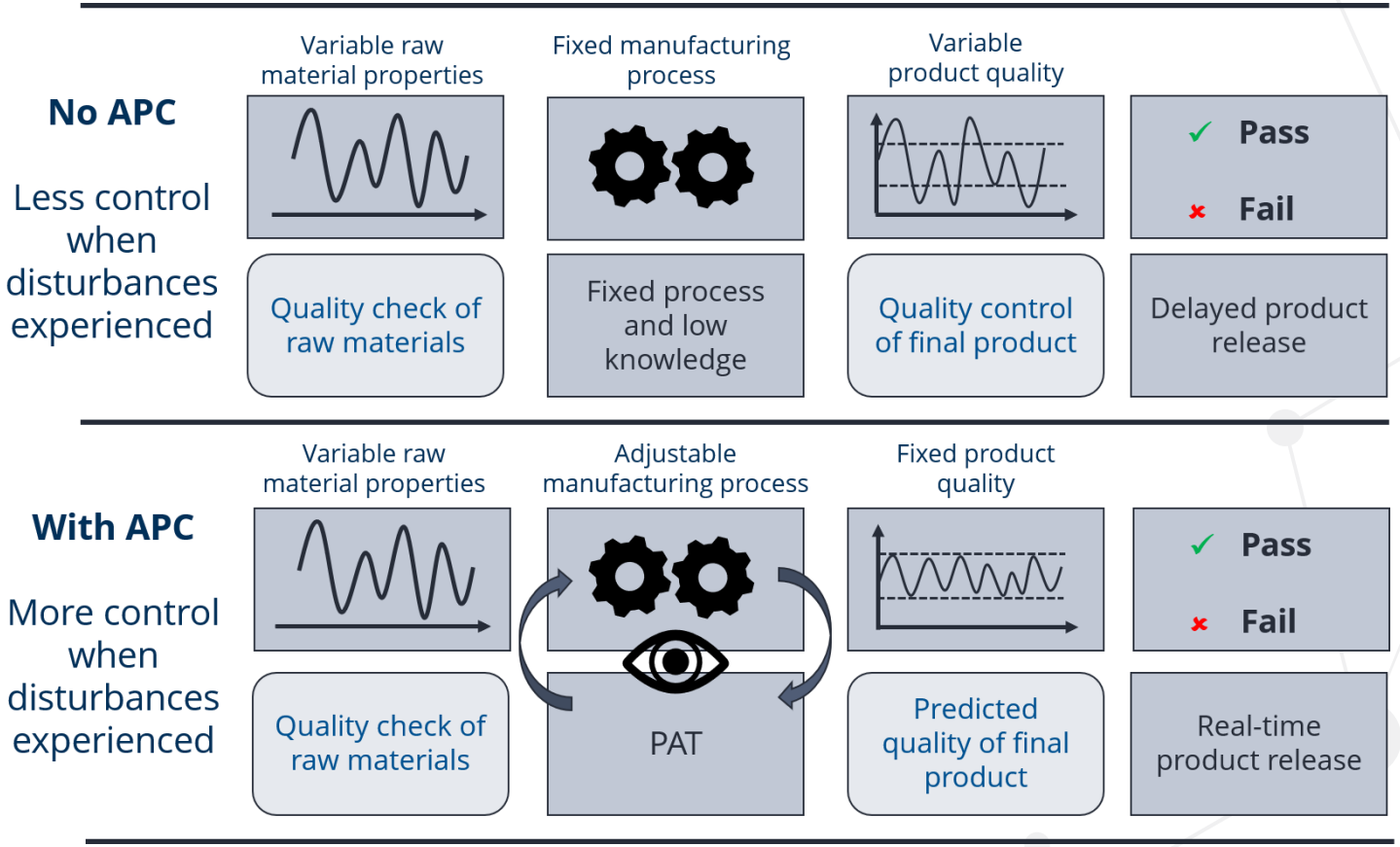
# Importance of PAT & Advanced Process Control




Real-time insight from PAT enables Quality by Design, and Advanced Process Control




Advanced Process Control protects product quality against raw material and process variability

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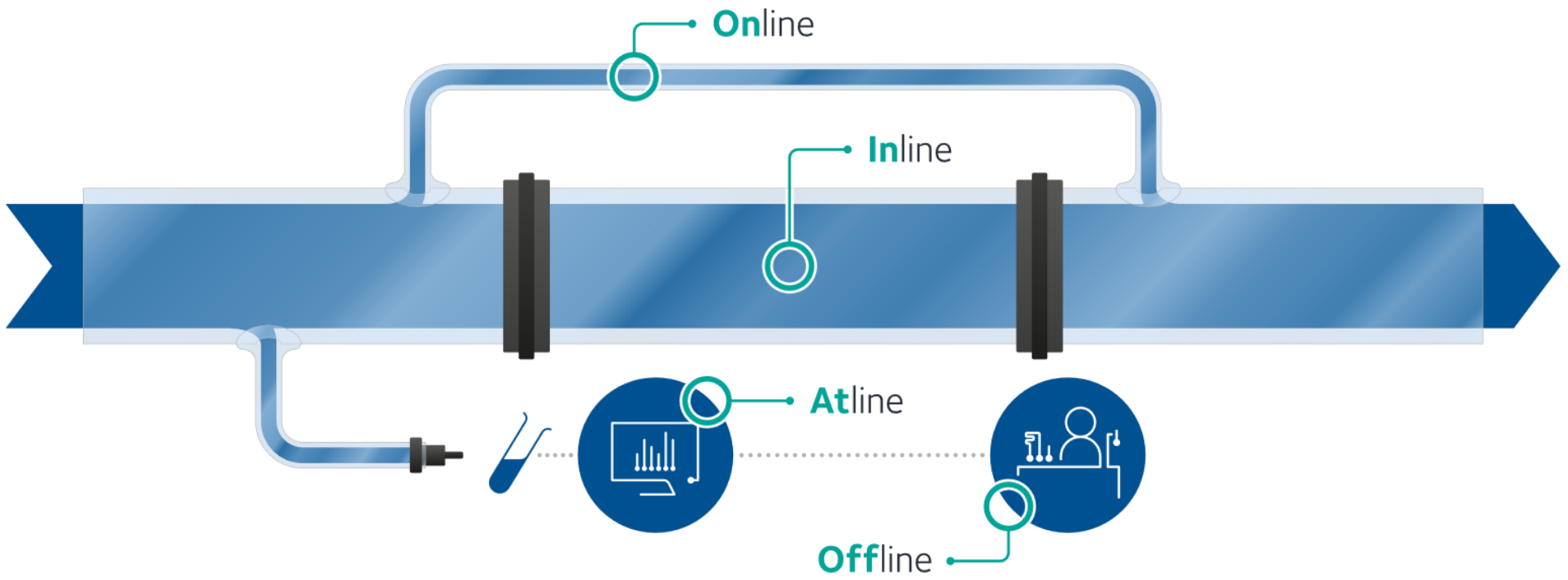
# Introduction to In-Process Measurement

## On-line, in-line, at-line, off-line – which definition to use?

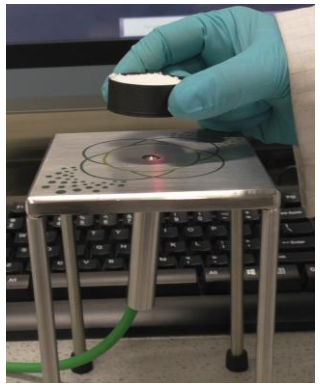


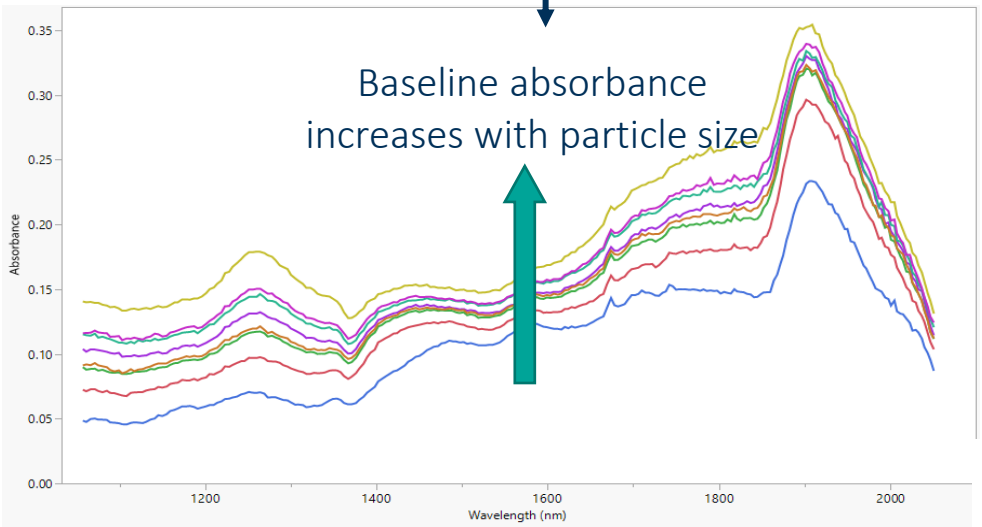

**FDA definition (**https://www.fda.gov/media/71012/download**):**
**At-line:** Measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream.
**On-line:** Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.
**In-line:** Measurement where the sample is not removed from the process stream and can be invasive or noninvasive

Picture taken from: https://metrohm.blog/on-in-at-offline/

# In-Line Measurement

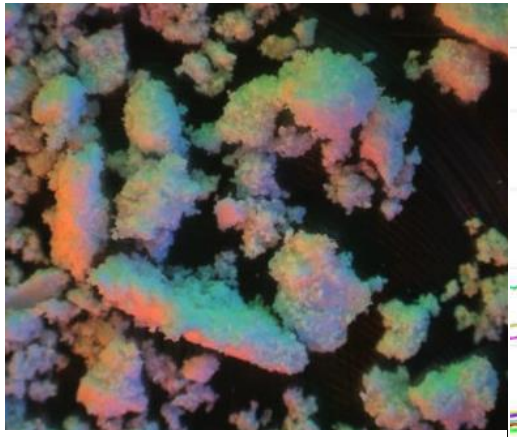
## Innopharma MultiEye2 NIR






**Moisture Content & PSD**

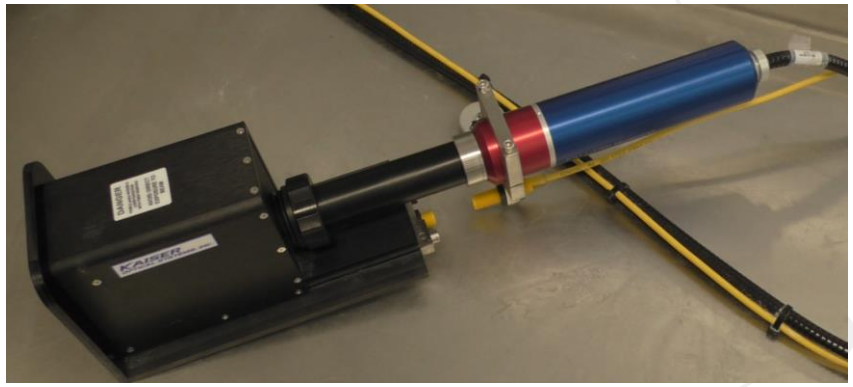
## Innopharma Eyecon2 Particle Analyser

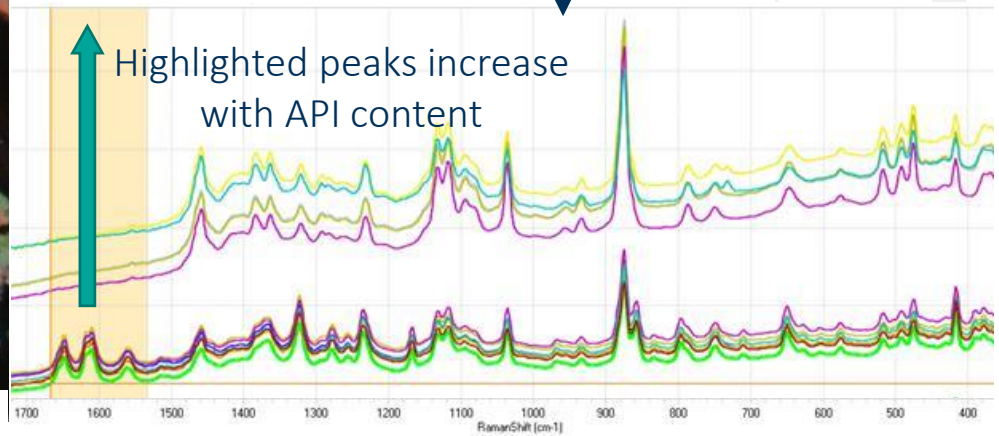



High speed camera captures microscope images

**Particle Shape & Size**

## Kaiser Raman PhAT Probe






**API Content**

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# Sampling Interface

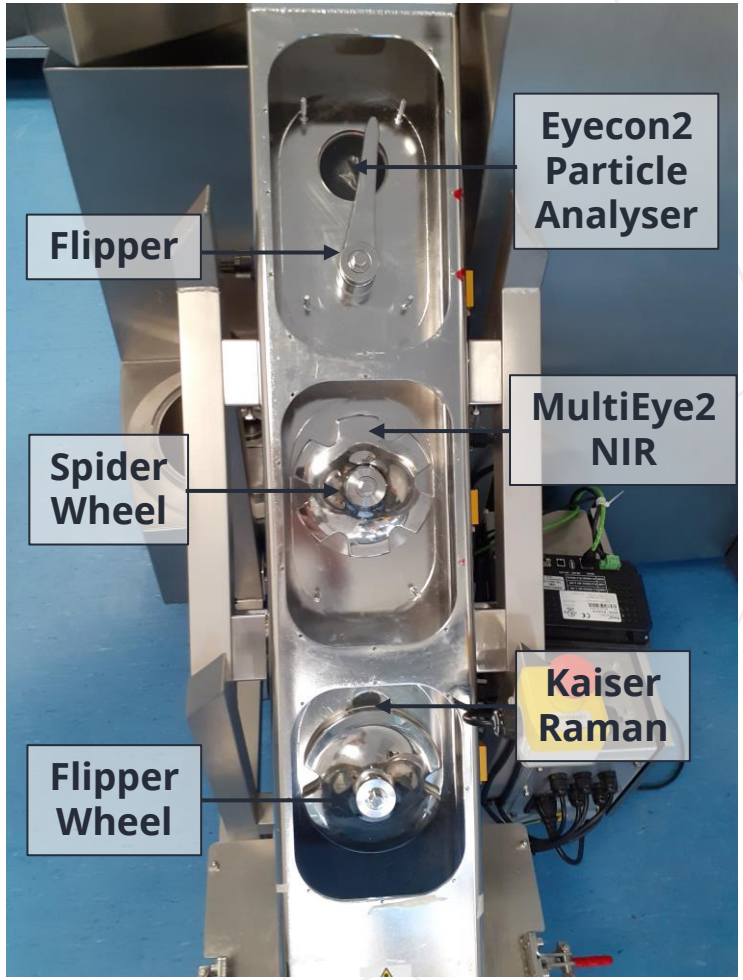
Bespoke sampling interface ensures **optimal sample presentation** for the three PAT tools.

Interface connects directly to the barrel exit, allowing **continuous monitoring** of the product.

Diverters guide the product through the interface, to **minimise segregation and dead zones**.

Each wiper **moves independently**, and is optimised for the beam size and integration time of its PAT tool.

The product can be collected from the bottom of the interface.

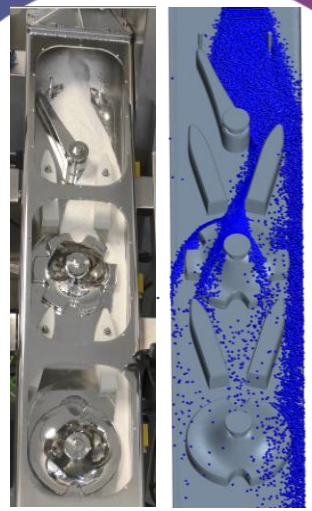
# Interface Optimisation Using Discrete Element Modelling

## 3D digital model of the interface

First, a **working model of the PAT interface was created based on the CAD design** as it was supplied. Several different mesh techniques were used to simulate the moving parts, allowing us to investigate optimal timings for best sample presentation to the probes.

## Particle Characterisation

Then, **granules were added, represented by spheres**, a typical simplification. Particle parameters were adjusted to **match key behaviours** such as angle of repose to account for differences in shape from real granules.



## Predict flow through PAT

Granule flow using particles of varying sizes were then injected into the model to characterise the flow. The model can be used **to investigate differences in residence time, which cannot be measured experimentally**.

## Powder Diverter Optimisation

Residence time differed between sizes, with segregation identified in the model. We are now investigating different diverter designs to **optimise flow and minimise segregation**.

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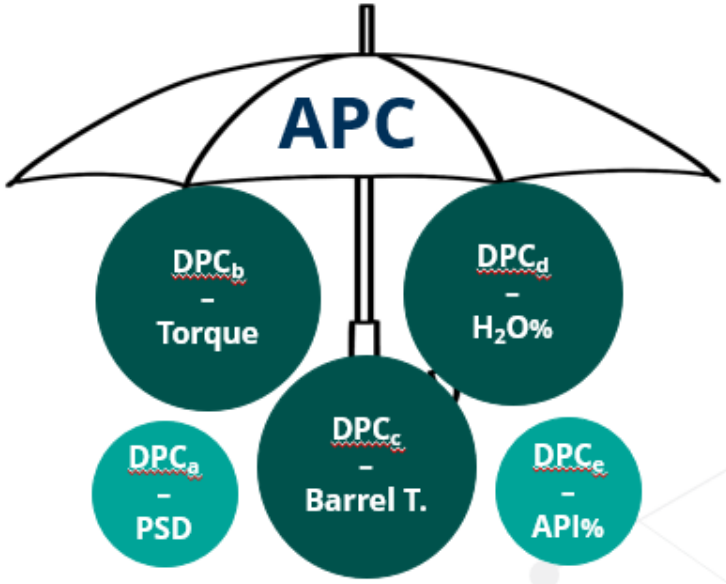
# Primary Control Mechanism - Granulator APC System

**Controlling granule properties indirectly controls tablet properties**

APC system preserves tablet properties when granule production is disturbed

Tablet properties are optimised to the target specification when made from granules produced using APC




**Control models:**
Torque
Temperature
Moisture content

**Monitoring models:**
PSD
API content

Torque and moisture content controlled to set point
Temperature controlled within constraints

pharmaMV v7.2

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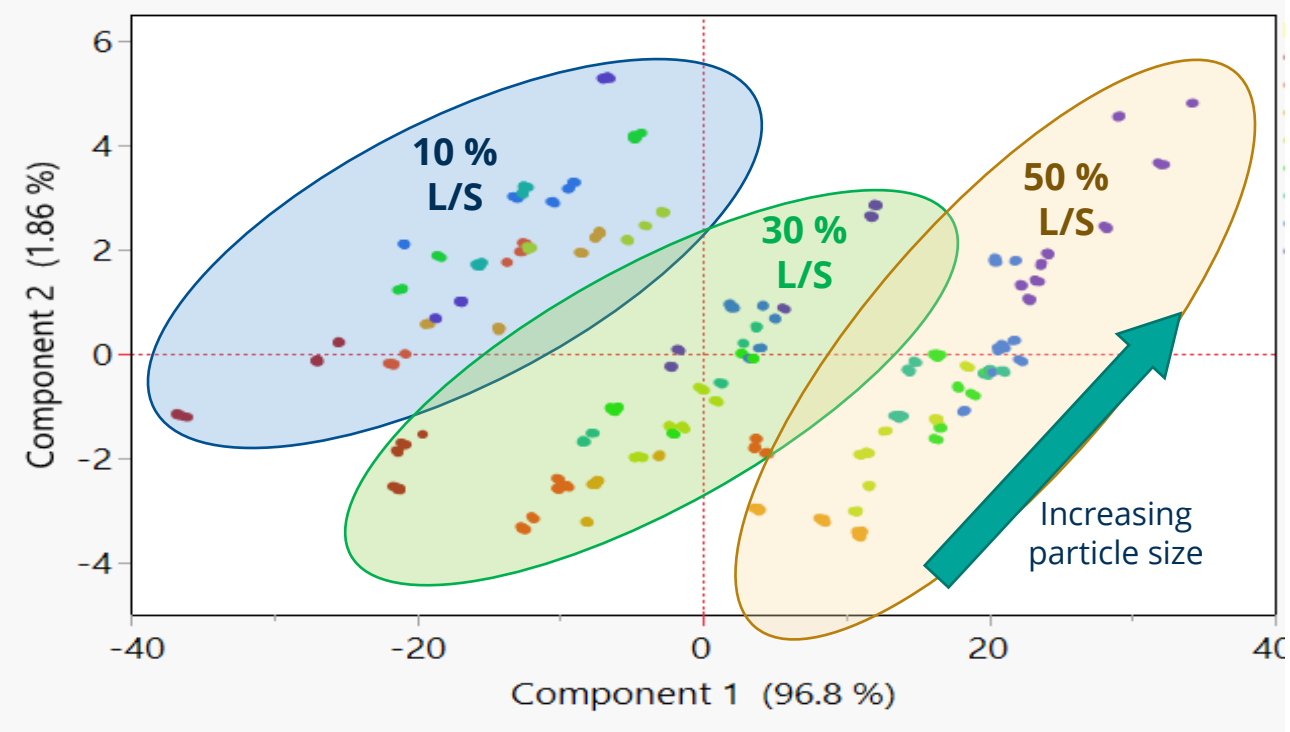
# Chemometric Modelling - PSD Soft Sensor

Maximising the benefits of one PAT probe by using the output in two separate models

Initial PCA showed strong correlation between **NIR spectra, PSD, and processing conditions**




All of these factors were used in the soft sensor – a **hybrid model** using spectral and process data

Data divided into 60 % training and 40 % validation

Model predicts the % by mass of the sample that will be contained in a series of sieve fractions

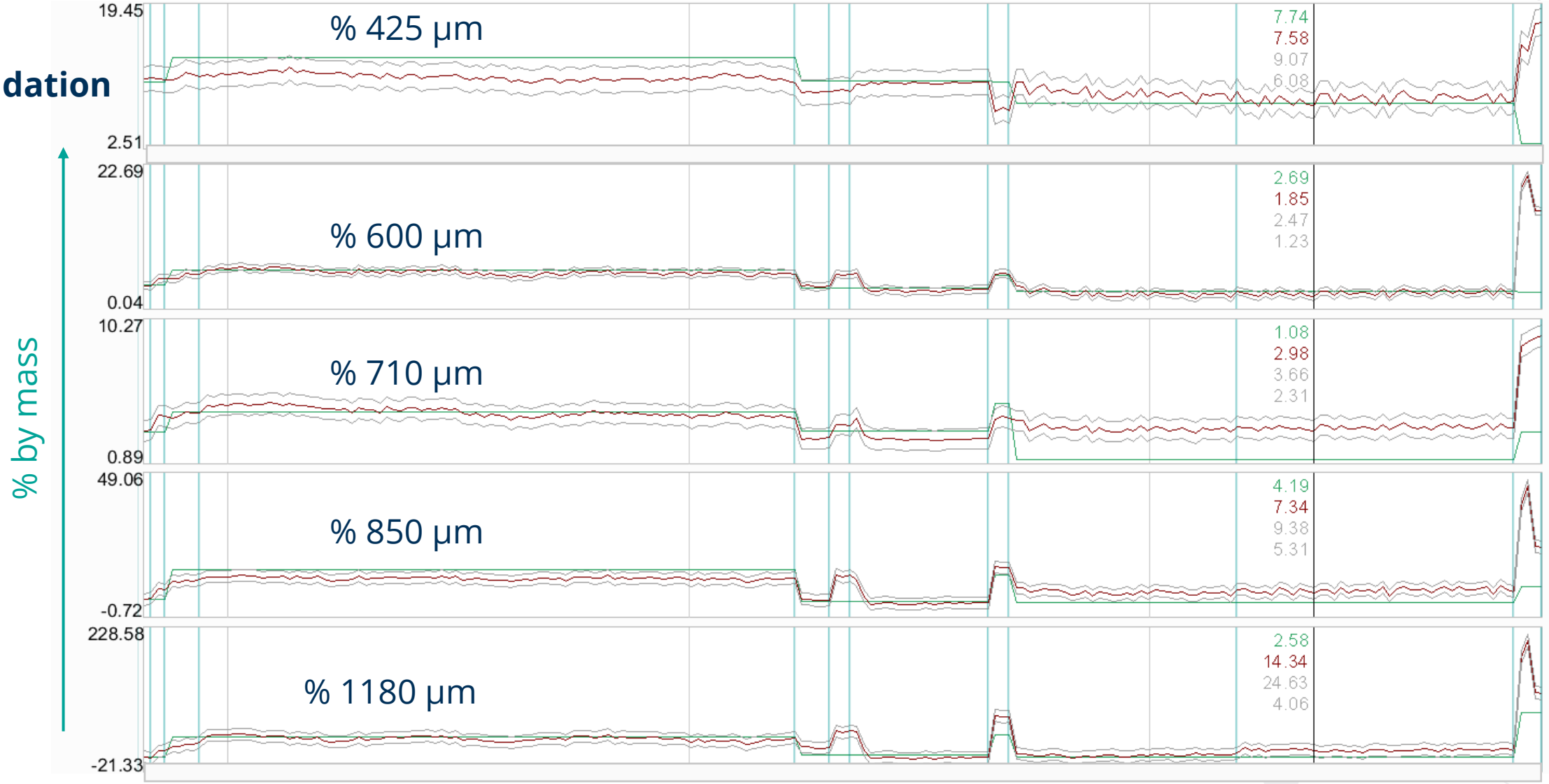
| Response Variable | Root mean square error of estimation (RMSEE) / % |
|---|---|
| % 0 µm | 3.75 |
| % 150 µm | 2.31 |
| % 250 µm | 1.51 |
| % 425 µm | 0.74 |
| % 600 µm | 0.31 |
| % 710 µm | 0.33 |
| % 850 µm | 1.00 |
| % 1180 µm | 5.07 |

Error between actual and predicted data **<5 %** for both training and validation sets

# Chemometric Modelling - PSD Soft Sensor

Actual
Predicted
Confidence Limits

Validation

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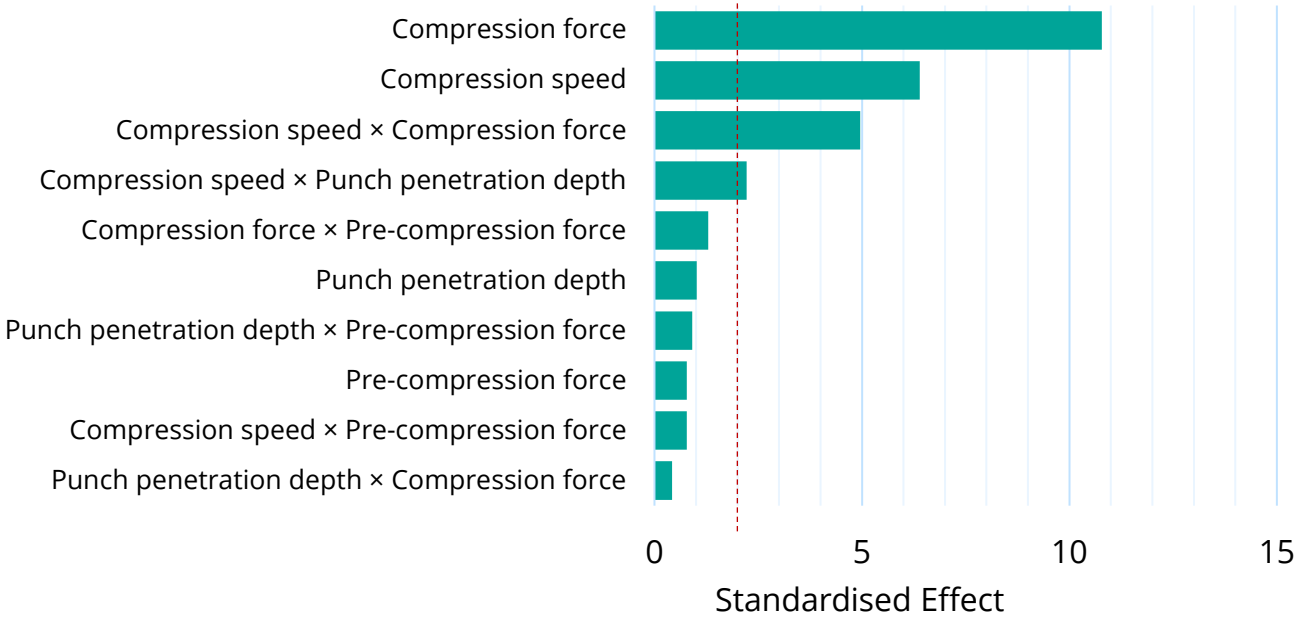
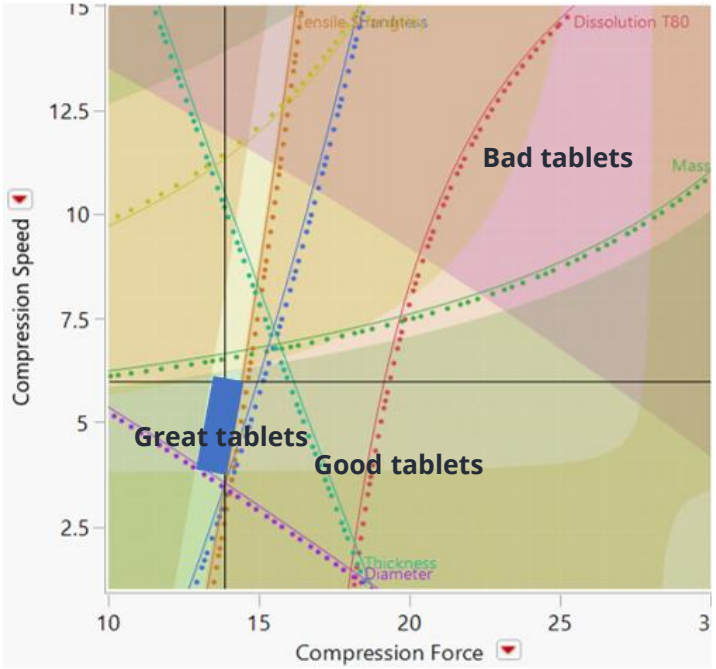
# Tabletting

A method to define the optimum tabletting conditions for a given granule, to achieve a target specification in tablet properties

1. Initial DoE identified the process parameters that had the strongest effect on tablet properties → **compression force** and **compression speed**.




2. A screening DoE was used to determine the ideal **operating space** (in compression speed and force) to meet the target specification.

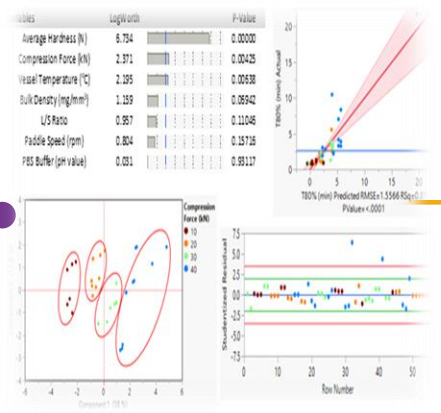


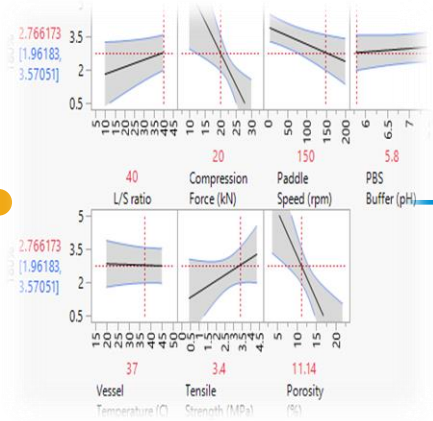

| Quality Attribute | Target | Batch Average |
|---|---|---|
| Mass (mg) | 500 | 520.7 |
| Diameter (mm) | 11.28 | 11.28 |
| Tensile strength (MPa) | 2 | 2.25 |

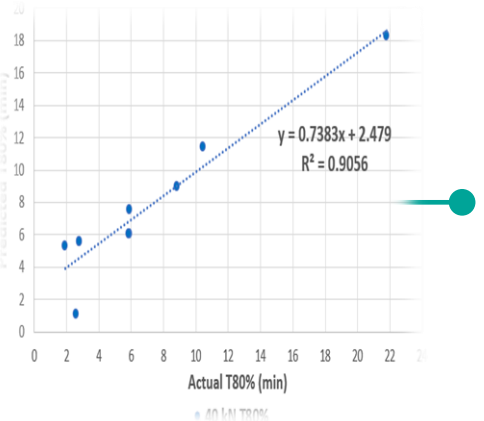
3. 10 tablets were produced using the ideal operating parameters. **All tablets met the target** specification.

# Dissolution

A method to predict the dissolution profile of a tablet from its manufacturing process parameters, and to define the operating space for provision of tablets with specific dissolution behaviour






## Identification

Identified the **manufacturing process parameters** that have the strongest impact on dissolution profile

- **Hardness**
- **Compression force**
- **Bulk density**
- **Granule L/S ratio**

## Analysis

Used multivariate analysis methods to investigate the **correlation** between the key process parameters and dissolution behaviour

## Modelling

Used ordinary least squares regression to build a model that **predicts dissolution profile** from process parameters

## Validation

30 % of the data set retained for **internal validation**

**($R^2$ > 0.8 for both models)**

## Future Application

This method can be applied to the prediction of **non-pharmaceutical** tablets, granules, and capsules.

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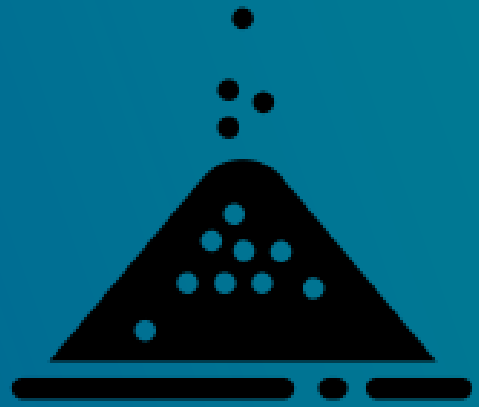
# Research facility for powder filling



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# Process Optimisation in Powder Packing

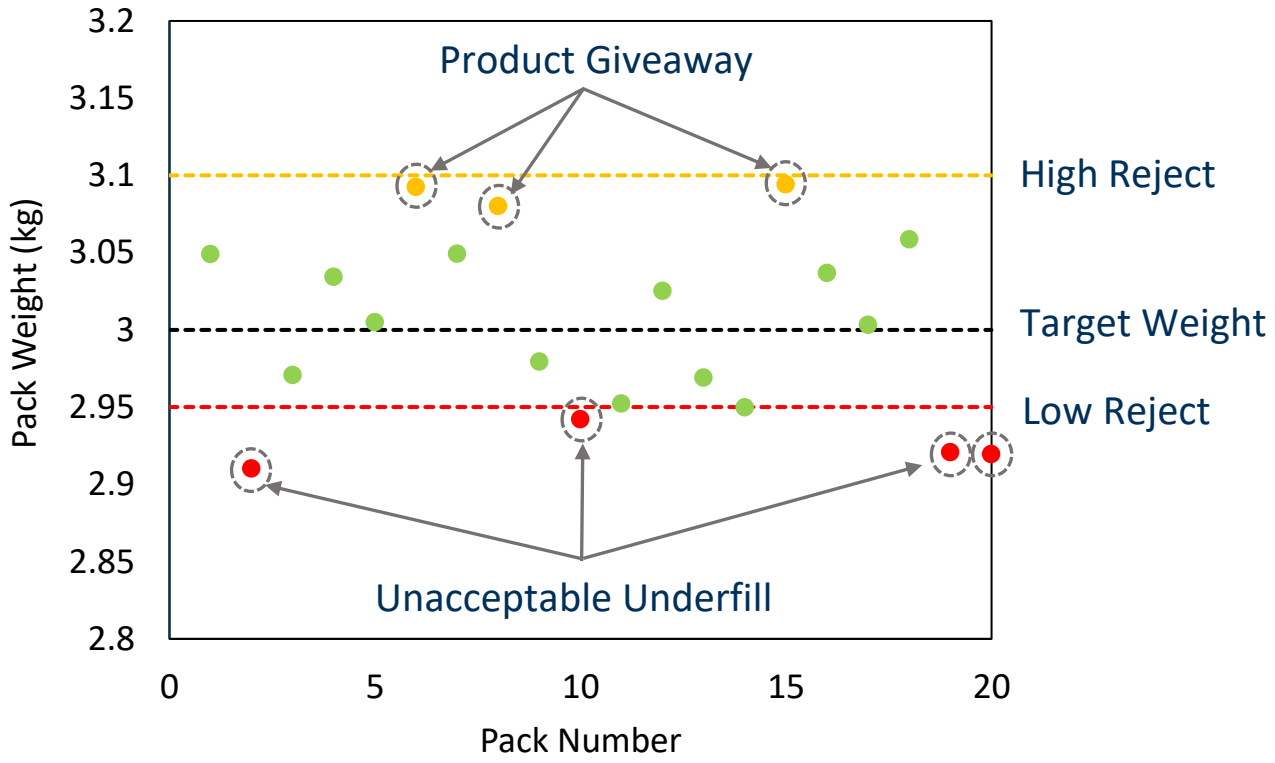
**Packing Problems:**

- Variable pack-to-pack quality
- Variable fill level and packed weights (weights and measures legislation)
- Poor reliability and frequent stoppages
- Long change-over times between products
- Lengthy trial runs when introducing new products

**How can CPI help?**

Open access research facility for:

- Feasibility testing of new products or processes
- Optimisation of packing processes to reduce variability and product giveaway
- Optimisation of process monitoring and control strategies, including PAT



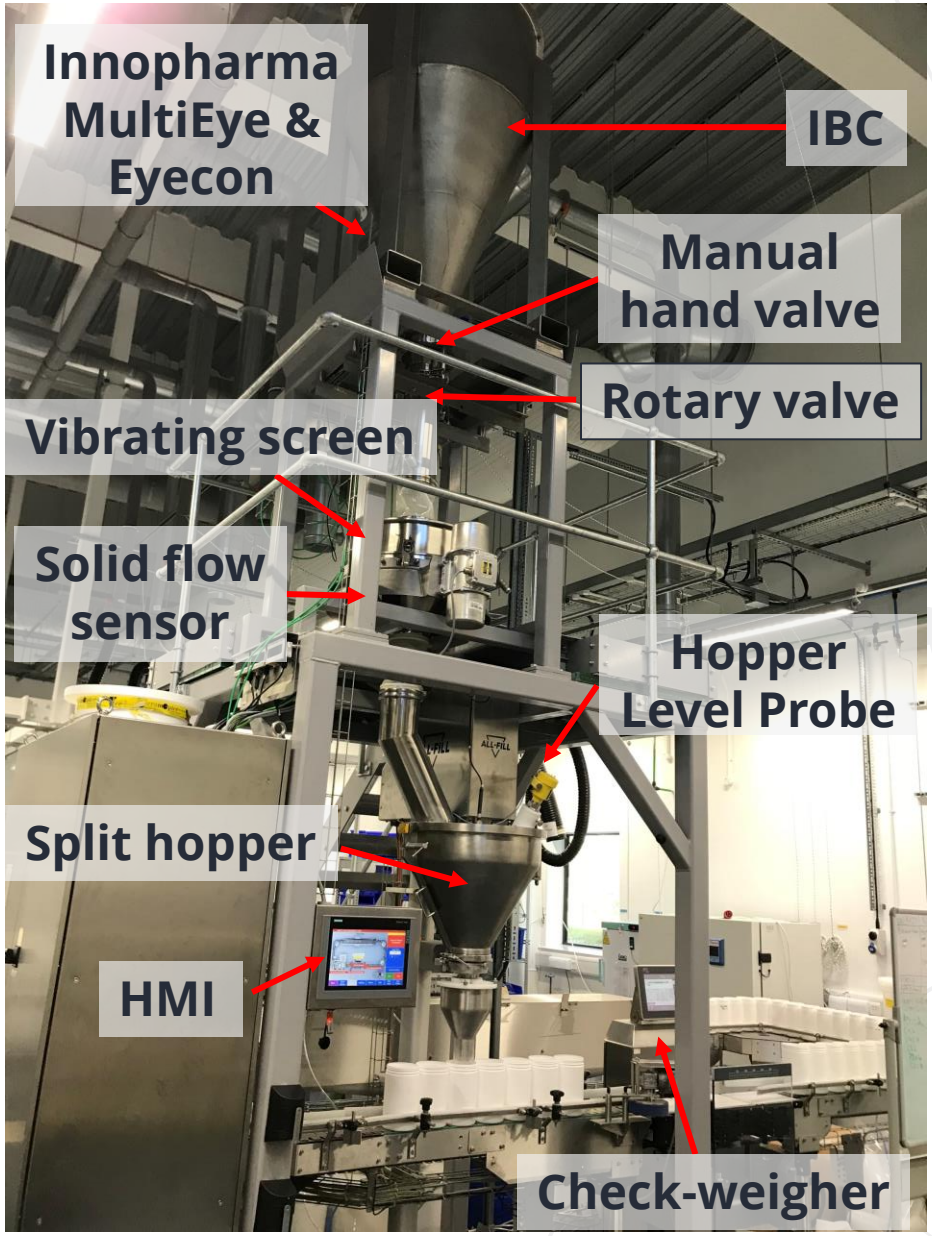
# Capability Overview

**Flexible, open-access platform** can be optimised for a range of packing processes:

- Auto and semi-auto operation
- 4  fill modes (2 volumetric, 2 gravimetric)
- Exchangeable Screens
- 3 tooling types
- Built-in checkweigher and conveying system

Various **process optimisation and control** technologies:

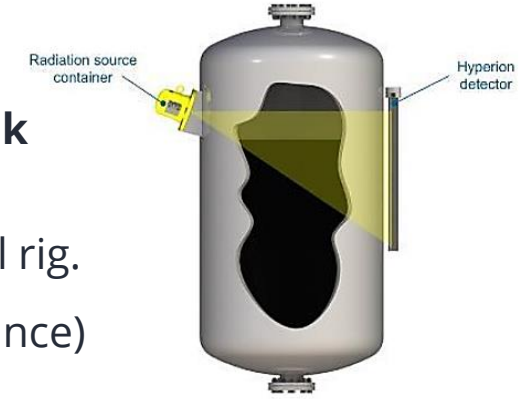
- Solid flow sensor & hopper level sensors
- Three PAT sensors



# PAT Integration

**PAT tools are interchangeable** between the granulation rig and Pack & Fill rig (except Raman, for safety reasons)

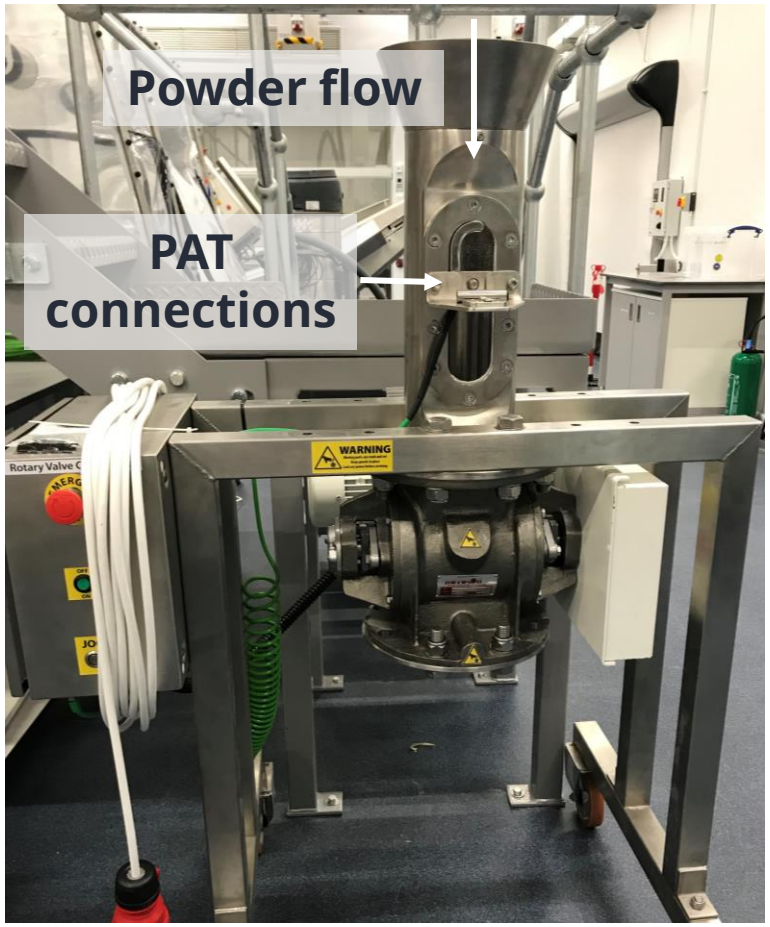
- MultiEye2 NIR probe
- Eyecon2 particle analyser




Tracerco Hyperion **bulk density probe** also available on Pack & Fill rig.

(Beta/gamma absorbance)

Mobile powder rig is a fully PAT-enabled **portable solution** for small scale or in-situ experiments




**Mobile powder rig**

**NIR**

- Segregation
- Moisture sorption/loss

**Eyecon**

- Particle breakage
- Aggregation

**Tracerco**

- Segregation
- Compaction

# Summary

**CPIs open access research facilities can be used to de-risk innovation in powder process control.**

**The oral solid dose pilot line contains digitally-enabled granulation, tabletting, and dissolution equipment, with predictive models to facilitate Quality by Design.**

**The Pack & Fill pilot line, and mobile powder rig, provide a test bed for the development and optimisation of digital control strategies to increase efficiency and minimise waste.**

# Thank you

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