Process digitisation

Formulation 4.0 / 26 July 2024

Dr. Carlota Mendez Torrecillas
Secondary Manufacturing & Formulation Technical Lead
CMAC National Facility / University of Strathclyde

CMAC

CMAC

CMAC & the lab of the future

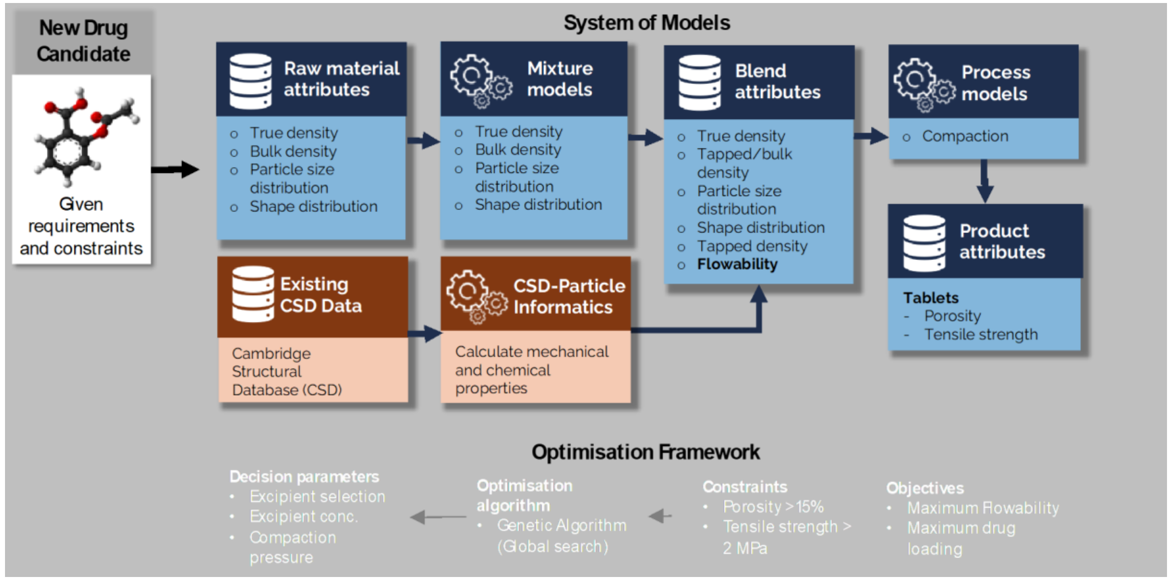
Research Excellence & Intensity | Outstanding Skills Development | World Class Facilities | Exemplary Translation to Industry

- CMAC is a world Leading Centre for Medicines Manufacturing Research, Skills, Facilities and Translation based in the University of Strathclyde (Glasgow).
- **Main focus** is to deliver manufacturing technologies that enable industry to **deliver better products**, quickly, economically and sustainably. This meets the industry demand for reduced time and costs for pharmaceutical development.

1. Accelerate Development
2. CMC Digitalisation
3. Advanced Manufacture & Supply
4. Materials & Products

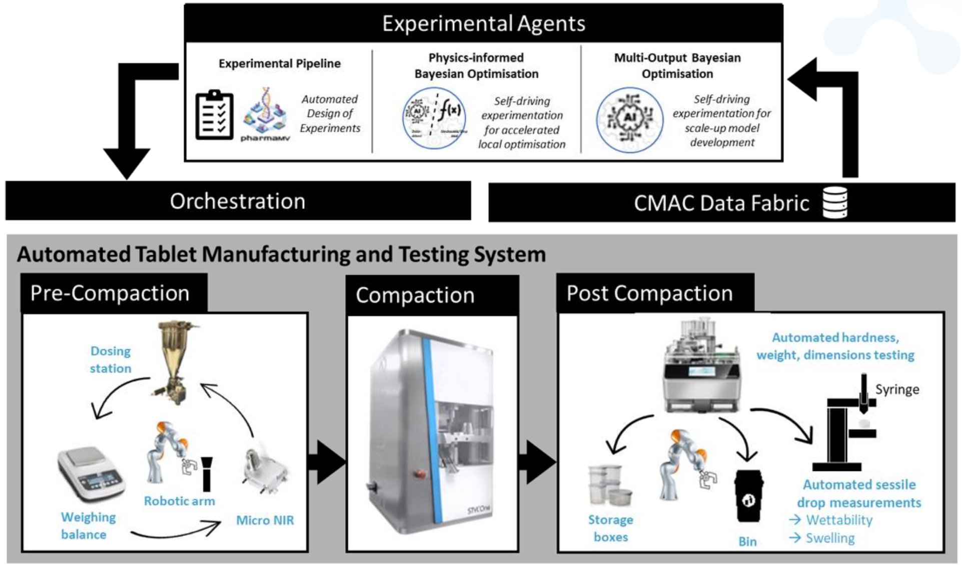
CMAC & the lab of the future

	Material-sparing predictive formulation development	Material-sparing, predictive process development	Material-sparing, predictive scale-up assessment	CDC E2E and Predictive Scale-up	Predictive product performance	Predictive product stability
Focus	•Excipient selection •Excipient concentrations	•Process configuration •Process parameters •Lubricant extent •Micro- and macromixing •Chemometric model development	•Lamination risk •Sticking risk •Strain rate sensitivity •Polymorphic transformation risk	E2E Digital Twin Validation at pilot/production-scale	•Dissolution models for development and RTRT •Multi-modal dissolution testing	•Accelerated stability assessment •Shelf life predictions •Automated stability assessment



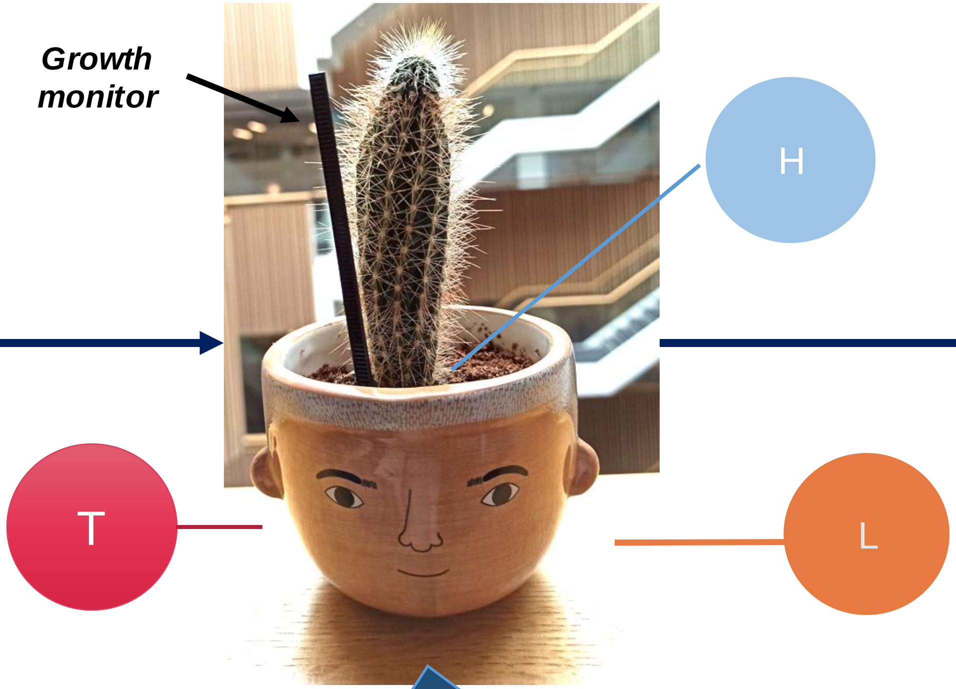
Tableting DataFactory

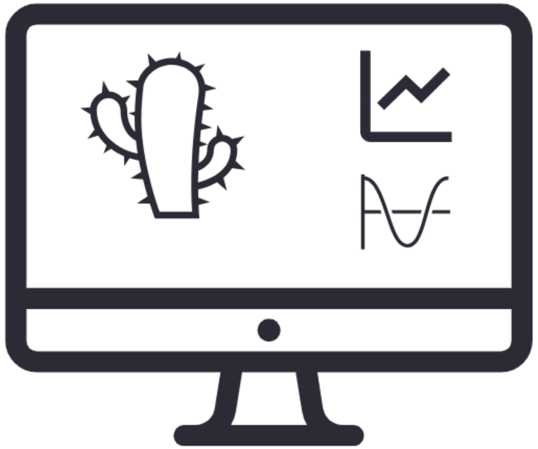
Self-driving Manufacturing and Testing



Process digitisation

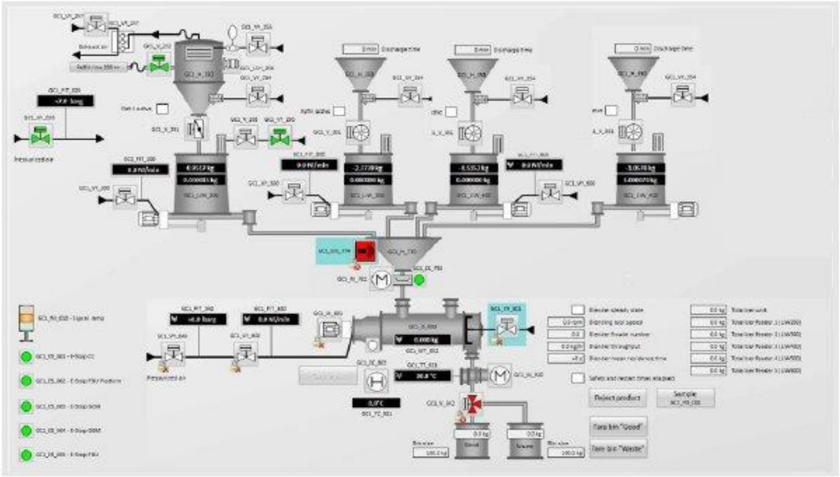
Traditional Care	Process Digitization (Monitoring with Sensors)	Digital Twin (Virtual Plant Model)

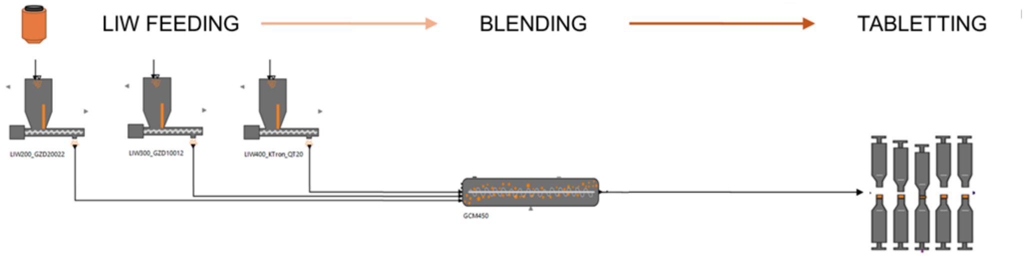




Case study: Process digitisation & Digital Twin

- **UK Grand challenge:** CDC Rapid Development using Digital Twin Workflow
- **Continuous direct compression:** streamlined manufacturing method with only three main units (feeding, blending and tableting) that directly compresses ingredients into tablets, offering increased efficiency and consistent product quality.
- **Physical CDC line :** 5 feeders to produce a throughput up to 50 kg/hr with two possible blending options (continuous and mini-blend)





Case study: Process digitisation & Digital Twin

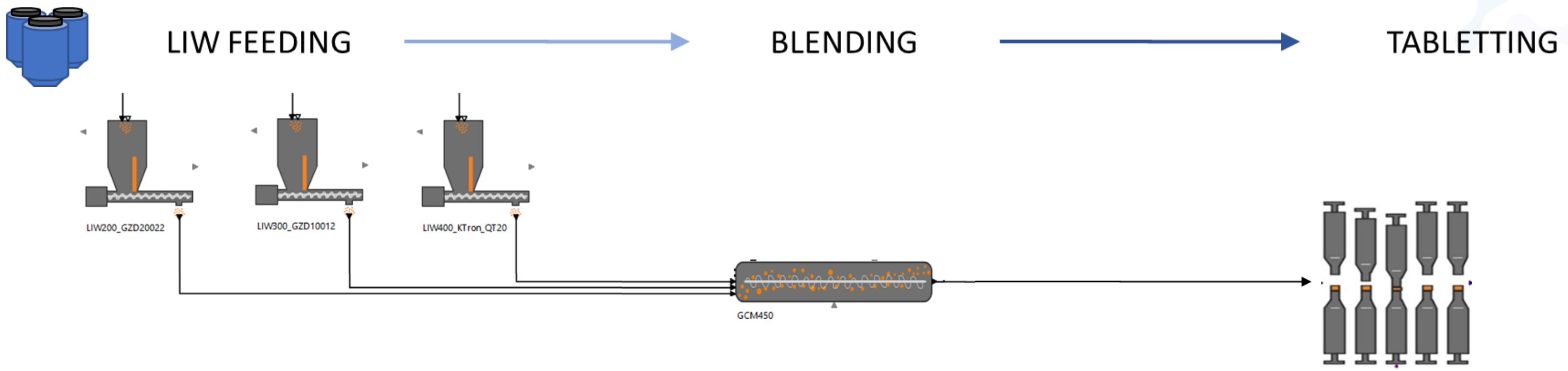
How much material did we use for characterise the CDC digital twin units?

Operation	Type of experiment	Material used
Material Characterisation	Density, Flowability, Particle size & shape	50 kgs
Feeder characterisation	Volumetric, gravimetric and batch dispense	500 kgs
Blender characterisation (only continuous blender)	RTDs, RSDs, extent of lubrication, material hold up	3000 kgs
Tablet press (Fette 102i & Korsch X3)	RTDs	1500 kgs

Over 5 tonnes of materials used

CMAC

Case study: Process digitisation & Digital Twin



Sub processes :

- Feeding
- Multi mixer types
- Compaction
- PAT interfaces & controls
- Lubrication sensitivity

1 Feeder models	2 Blender models	3 Tablet press models
1a Feedfactor prediction *Inputs*: Material properties, Equipment configuration *Outputs*: Decay model parameters	2a Blender macromixing (RTD) *Inputs*: Blend properties, Equipment configuration *Outputs*: RTD model parameters	3a Feedframe macromixing (RTD) *Inputs*: Blend properties, Equipment configuration *Outputs*: RTD model parameters
1b Feedfactor variability prediction *Inputs*: Material properties, Equipment properties *Outputs*: Estimate of variability	2b Blender micromixing (RSD and strain) *Inputs*: Macromixing, Equipment configuration *Outputs*: Micromixing as variability	3b Tablet compression/compaction *Inputs*: Tablet composition, Equipment configuration *Outputs*: Tablet specifications
1c Batch dispense prediction *Inputs*: Feed rate, Data filtering approach *Outputs*: Batch feeding accuracy	2c Extent of lubrication *Inputs*: Targeted small scale *Outputs*: Transferable blend CQA insight	

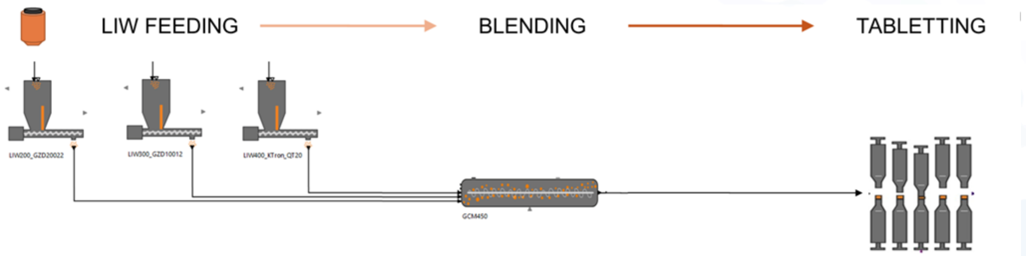
Case study: Process digitisation & Digital Twin

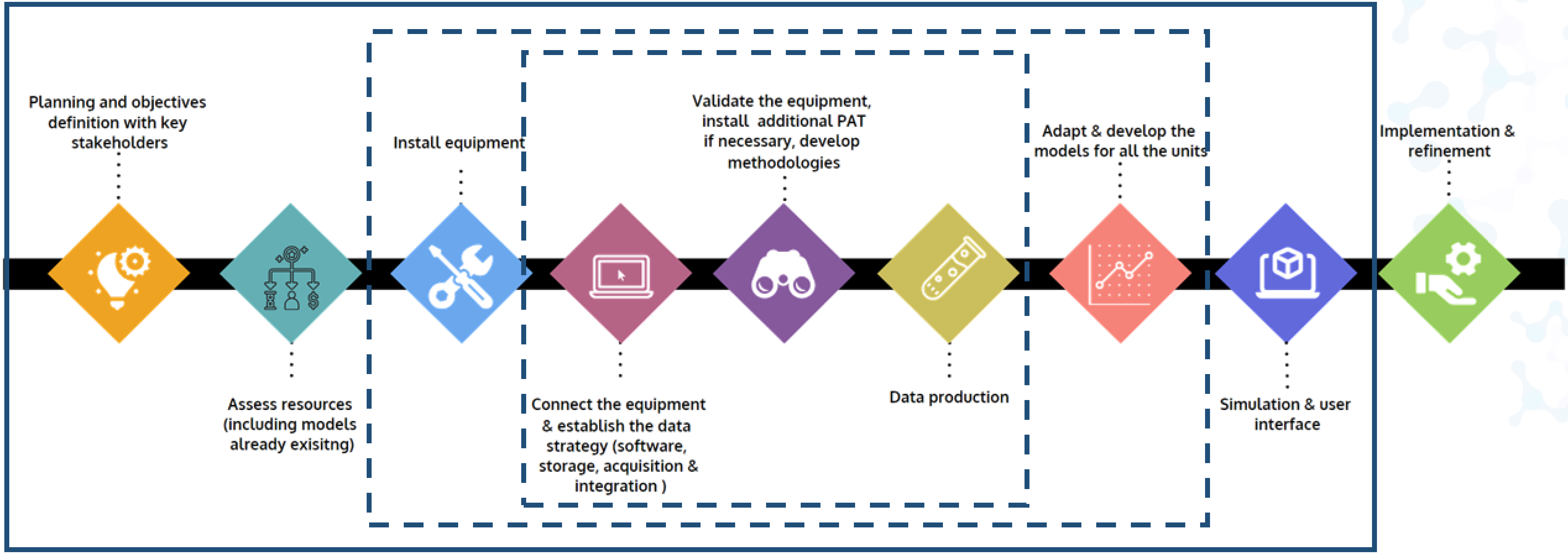
Key model developments & project outcomes:

- **Material Properties**: A database was created to store physical, process, and product properties of relevant materials.
- **Feeder Performance Prediction**: An ML model can predict the performance (weight loss) and variability of feeders from different vendors.
- **Content Uniformity:** Another model predicts how blending properties affect the uniformity of content in both continuous and batch systems.
- **Residence Time Distribution (RTD):** Models were developed to understand how long materials spend in each unit operation (feeding, blending, compression) and the entire production line. This information can be used to optimize control strategies.
- **Lubrication Impact**: A model was created to predict how blending and feeding properties affect the final tensile strength of the product, considering lubrication sensitivity.
- **Compaction and Compressibility:** These models can be used to set up and monitor tablet presses.
- **Advanced Process Control (APC):** Data-driven models were developed to implement APC methods across the entire production line.

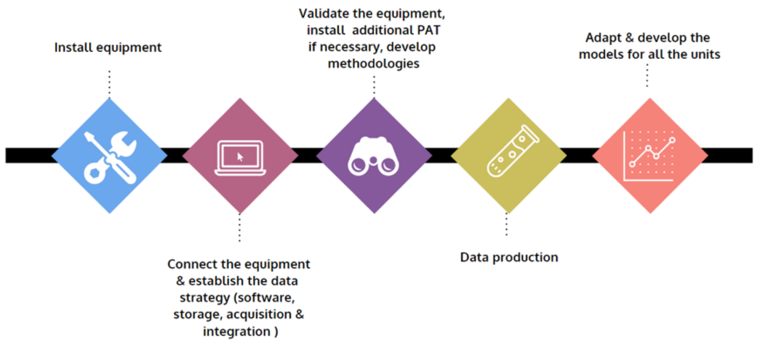
CMAC

Case study: Process digitisation & Digital Twin



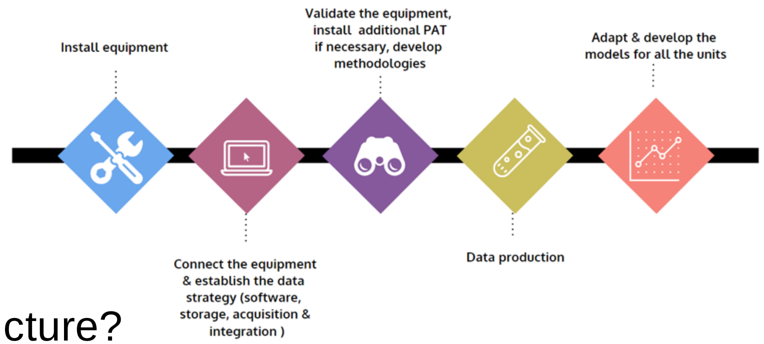


The real “nitty gritty”: Before you start generating data



- **Data Acquisition** and Integration
  - Do you know **exactly** where your data comes from?
    - Equipment range of operation
  - What do you actually need to monitor and acquire?
    - Difference between using parameters for control, measurement, and data modelling.
    - Real-time vs. Batch Acquisition
  - How are you going to validate the data you acquire is correct?
  - Do you have previously generated data/information to guide you?
  - How do you ensure you are generating high quality data?
  - Are you actually prepared for the amount of data that is about to be generated?

The real “nitty gritty” ”: Before you start generating data



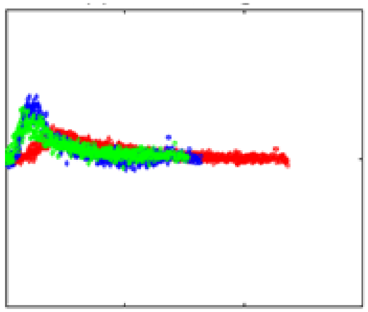
- **Data** Acquisition and **Integration**
  - Do you have data and procedure standards?
    - Do they include software used, format, units, digits, and file naming structure?
    - Do you have written protocols? Are mistakes easy to spot? How long does it take to become compliant? How much manual input do your procedures require?
- **Data transfer:**
    - Is data transfer integration fully automated?
    - Do you need to transform or filter the data?
    - Are you considering the time latency?
    - What are some signs that data transfer might not be happening correctly?

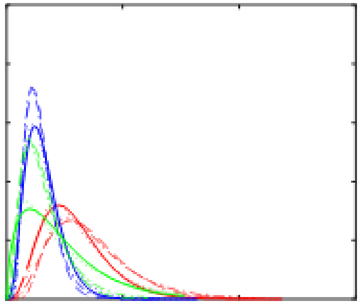
CMAC

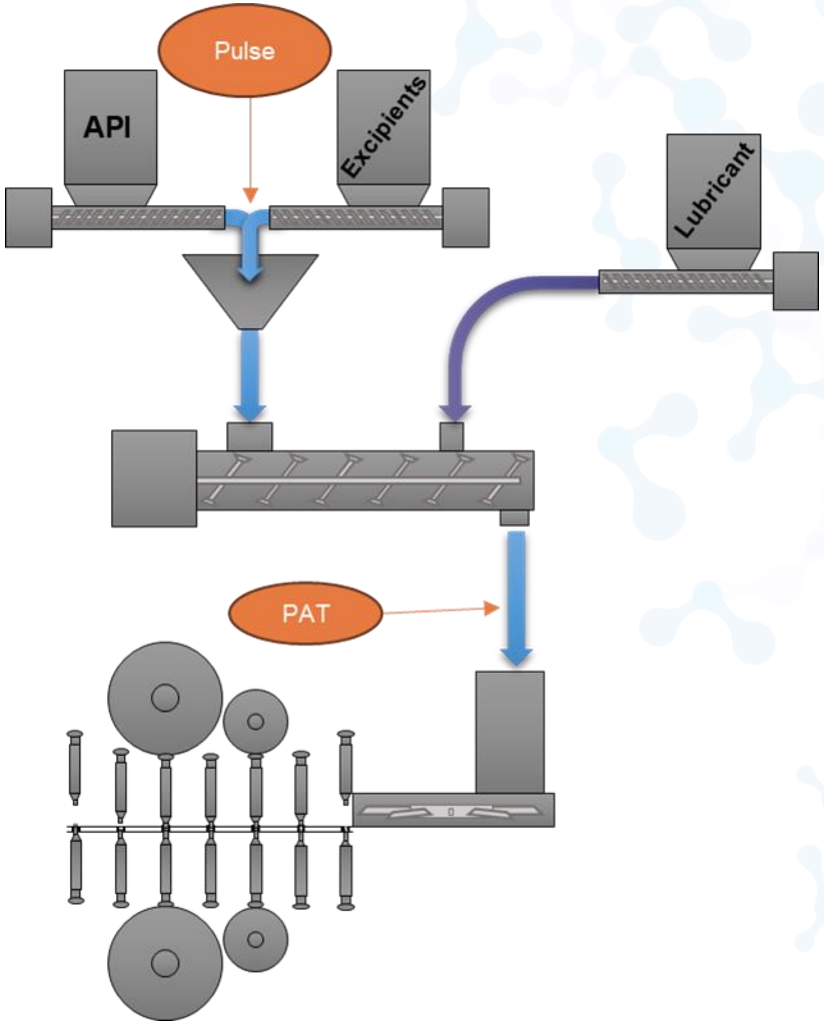
The real "nitty gritty"

Residence time distribution experiments : Blending

- Pulse injection : API
- Monitoring the outlet for the tracer concentrations
- Analysing the shape of the curve generated, we should be able to understand blender and flow behaviour as well as dead zones
- The continuous blender had different weirs available to change the mass hold-up of the blender.
- Goal : Understand the effect of material properties and equipment configuration.



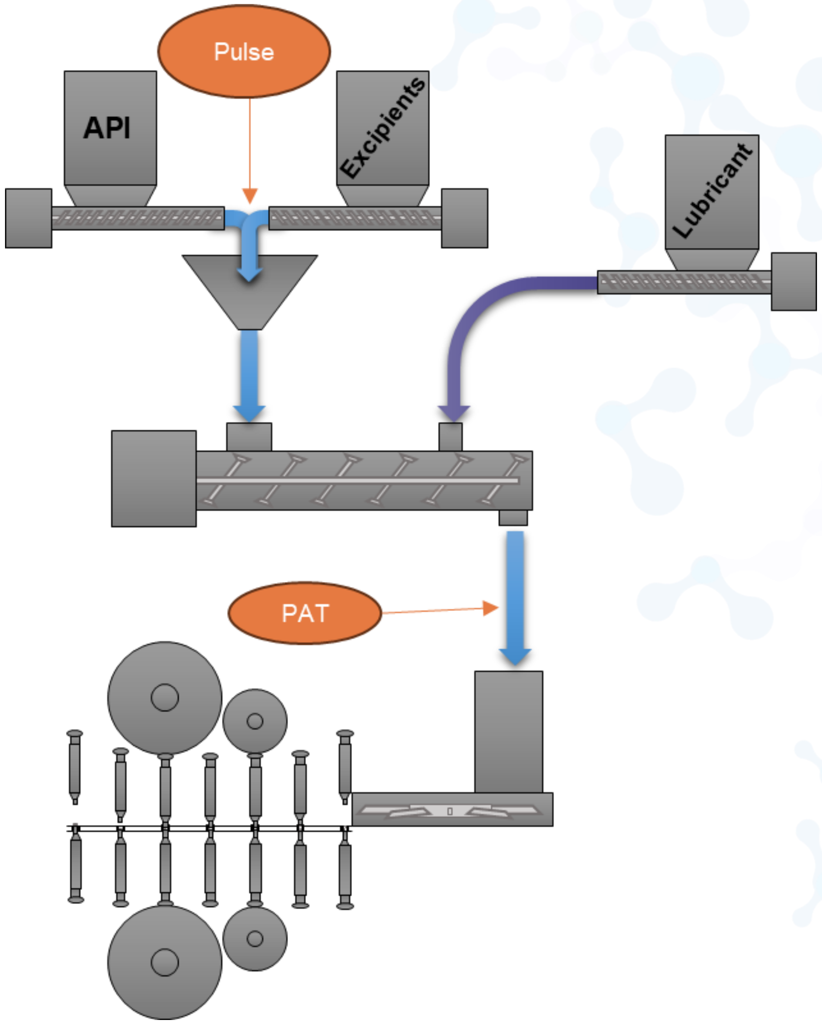




Residence time distribution experiments : Blending

.

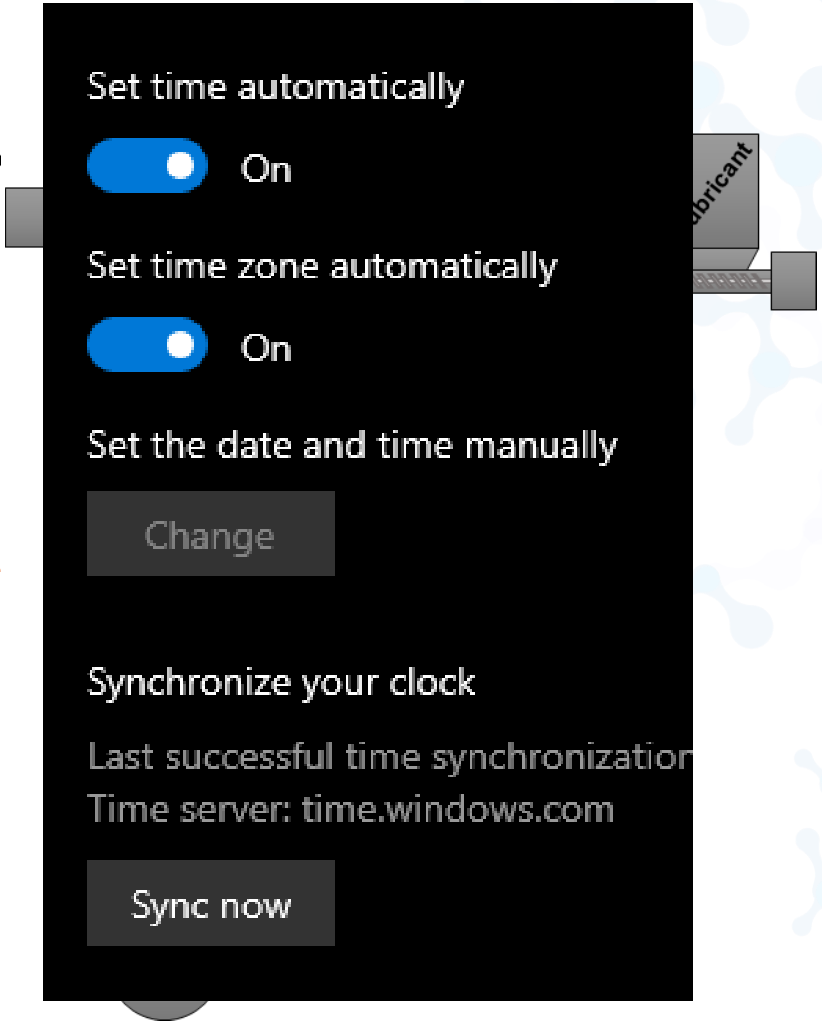
- Time of residence for a blender could be very short (seconds)
- The values did not match the expected (the response was appearing 1-2 seconds after introducing the pulse in the system which was not impossible but incredibly unlikely)
- Started the troubleshooting
  1. PAT (noise / presentation / models)
  2. Equipment control (volumetric vs gravimetric)
  3. Review the experiment itself (pulse)
  4. **Data transfer & signal latency**



The real “nitty gritty”

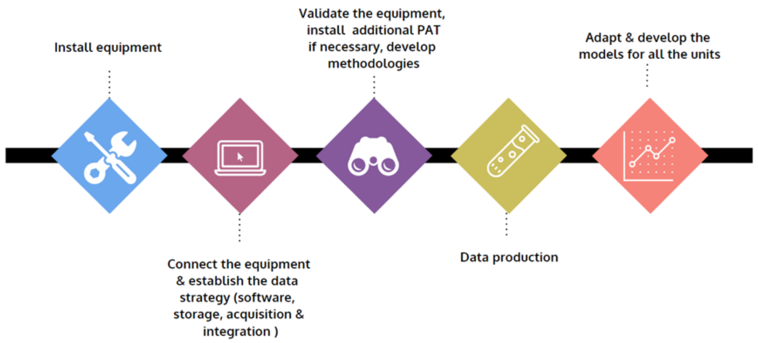
Residence time distribution experiments : Blending

- **Feeders and blenders:** controlled by SCADA & transferred *each second* to a Real-time Process Monitoring Software
- **PAT :** Signal acquisition was triggered in the PAT proprietary software by another Real-time Process Monitoring Software which also collected and transferred the data *each second* to Real-time Process Monitoring Software to apply the model and let us visualise / record real time.
- Different computers & servers all connected through the network
- The first culprit
- The second culprit



The real “nitty gritty” ”: Before you start generating data

- **Other considerations**
  - Do you have the technical expertise in-house for the task?
  - Does the modelling team and formulation team “speak the same language”?
  - Metadata:
    - Standardisation
    - Accuracy and completeness
    - ELNs
  - How much flexibility you have to refine the process using new data?



Other lessons learnt

- To succeed, a thorough understanding of your equipment and its operation is crucial. Make sure you identify the key parameters to monitor and avoid data overload.
- Users need **ongoing** training and support.
- Not all processes need immediate digitisation: Consider the complexity of the process, the availability of technology, and the existing skillset within your workforce.
- By using new models in old data, we can discover hidden patterns, predict bottlenecks, and suggest process improvements.
- People are key to successful process digitization

CMAC

CMAC

https://cmac.ac.uk

Acknowledgements

- **CMAC (main team under Prof. John Robertson supervision):** Dr. Ecaterina Bordos, Dr. Michael Devlin, Dr. Hikaru Jolliffe, Dr. Martin Prostredny and Colette Tierney
- CMAC (the rest of the MMIC team)

GC1 : This work was funded by the Medicines Manufacturing Innovation Centre project (MMIC), UK (project ownership: Centre for Process Innovation, CPI). Funding has come from Innovate UK and Scottish Enterprise. Founding industry partners with significant financial and technical support are AstraZeneca and GSK. The University of Strathclyde (via CMAC) is the founding academic partner. Pfizer are project partners and have provided key technical input and data. Project partners DFE Pharma have provided materials and technical input, and project partners Gericke AG have provided technical equipment support and advice. Project partners Siemens and Applied Materials have provided key software and software/IT expertise.

CMAC

UNIVERSITY PARTNERS:

END USERS / SUPPORTERS

FUNDING & INNOVATION SPOKES