An industrial perspective on product development activities supporting the QbD framework

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Agenda

- Scope
- The QbD framework and concept of collated data
  - Understanding the risks and acting upon them
- Application examples
  - Developing in-depth process understanding
    - Applications 1&2
  - Supporting the Control Strategy
    - Applications 3, 4 & 5
  - Monitoring and Control (Batch and Continuous process)
    - Applications 6, 7, 8 & 9

Scope

- GSK has integrated the Quality by Design framework to develop all its new products

- Presentation of development activity examples integrated to the Quality by Design Framework
  - Generating ***Process Understanding*** to address the Risks identified on project (via TRA/FMEA)
  - Supporting the definition of the ***Control Strategy***
  - Demonstrating ability to ***Monitor & Control*** established processes

- Applications presented are using either Multivariate Analysis (MVA) or Process Analytical Technology (PAT) approaches

Use of the QbD framework as back bone of the development activities

Start with the end in mind:

- Requires to understand the QTPP that defines the CQAs
- Driven by Risk assessment:
  - Derive Process Understanding to define CQAs
- Develop the control strategy

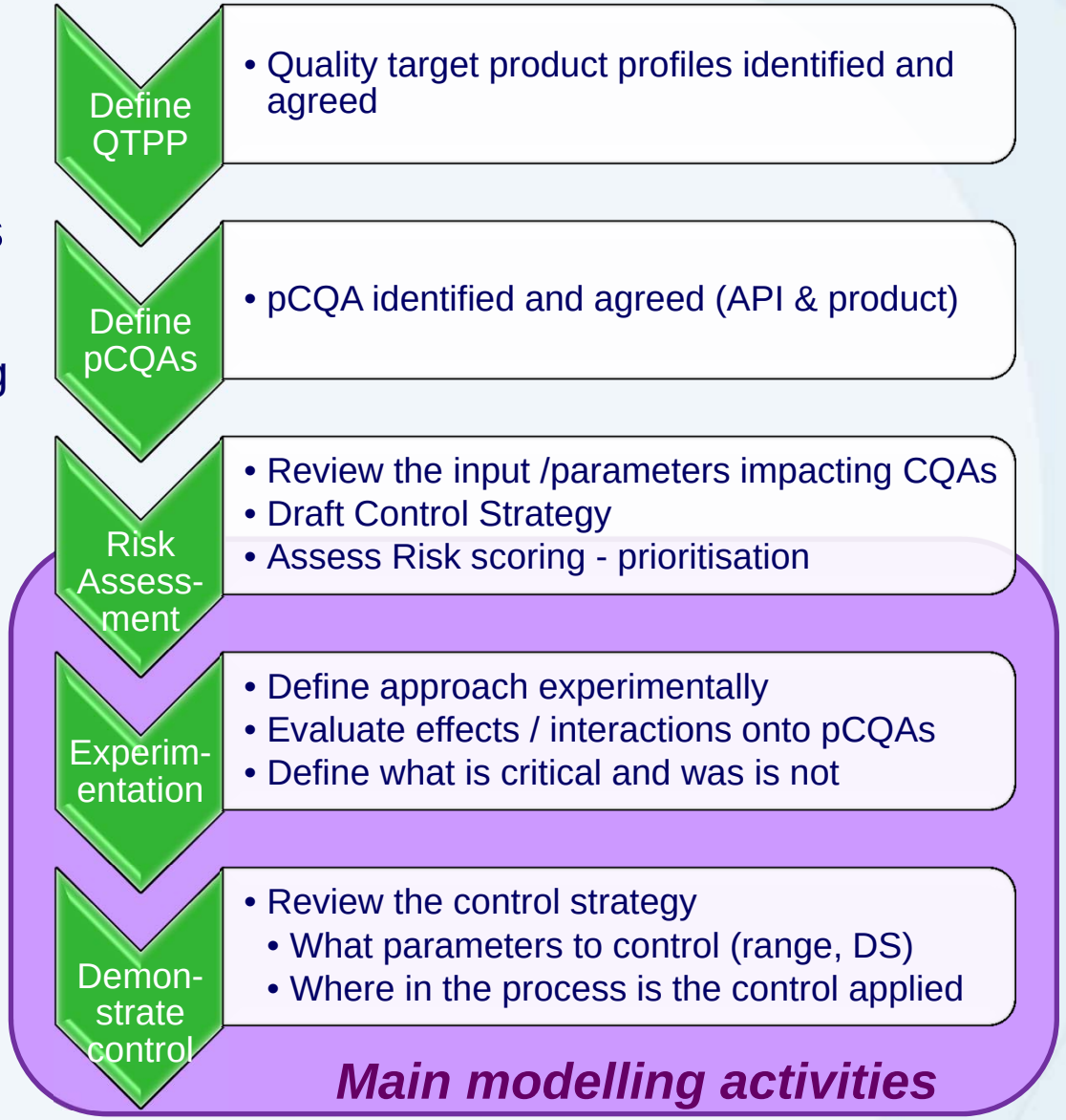
Application examples:

Process Understanding

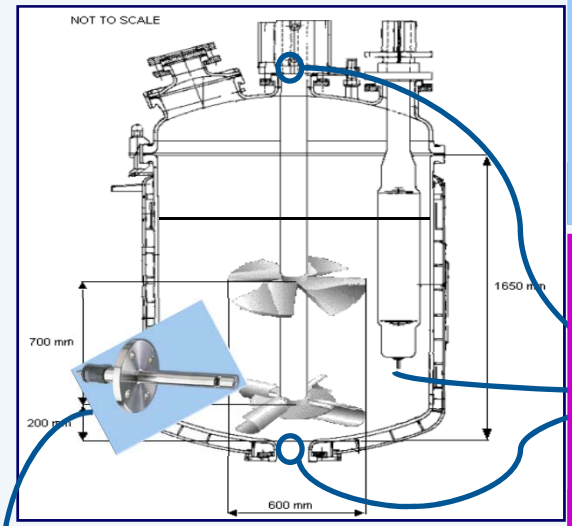
improvement

Support development of Control Strategy

Process Monitoring & Control



Multivariate, cross-functional approach to data analysis



Analytical data

LIMS

PhysProps data

LIMS

Process data

IP21

PAT data

SiPAT

Cross functional approach on data analysis

Analyst

Prop sci

eers

Reported to project team

Reported to project team

- Holistic da review
- Pattern in dataset(s)
- Outlier identificati
- Interaction between d sources

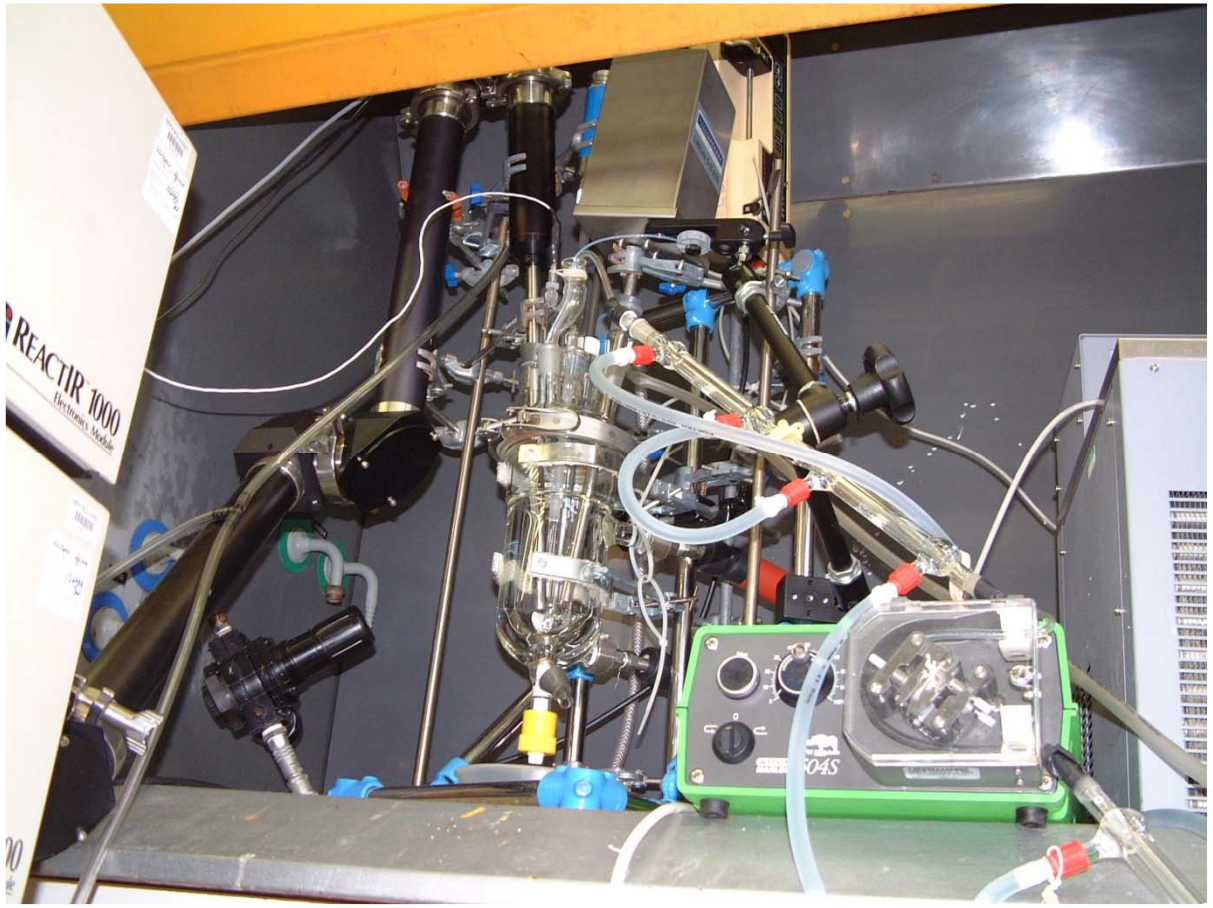
Reported to project team

Capability for integrated data analysis

Also apply multivariate analysis

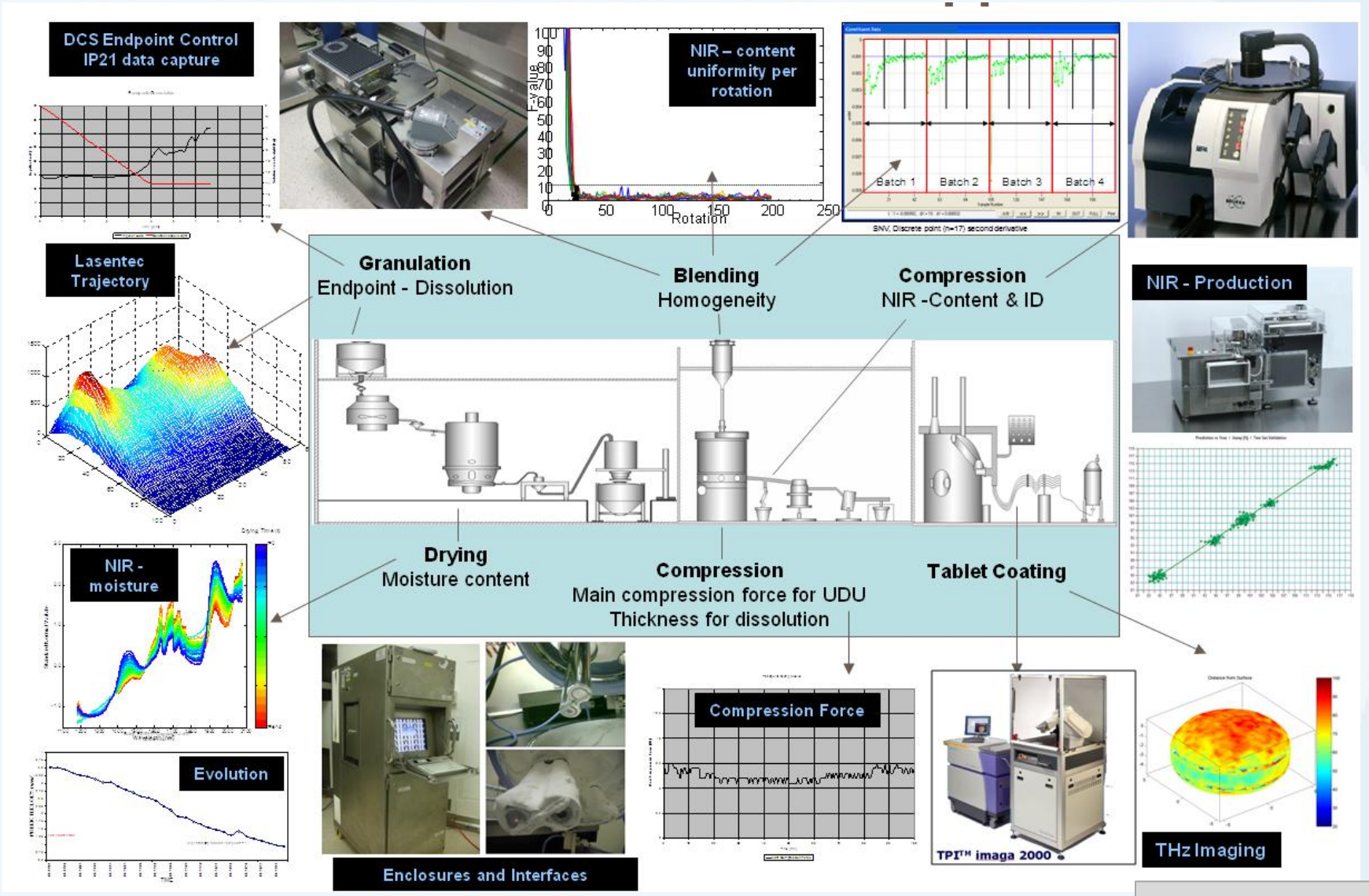
Multivariate

New information / new tools



- 200ml reaction volume…
  - 200kg of instrumentation for monitoring!!
  - 200MB of information generated per hour

Monitoring in Drug Product



Jonathan Hammond

Applications 1&2

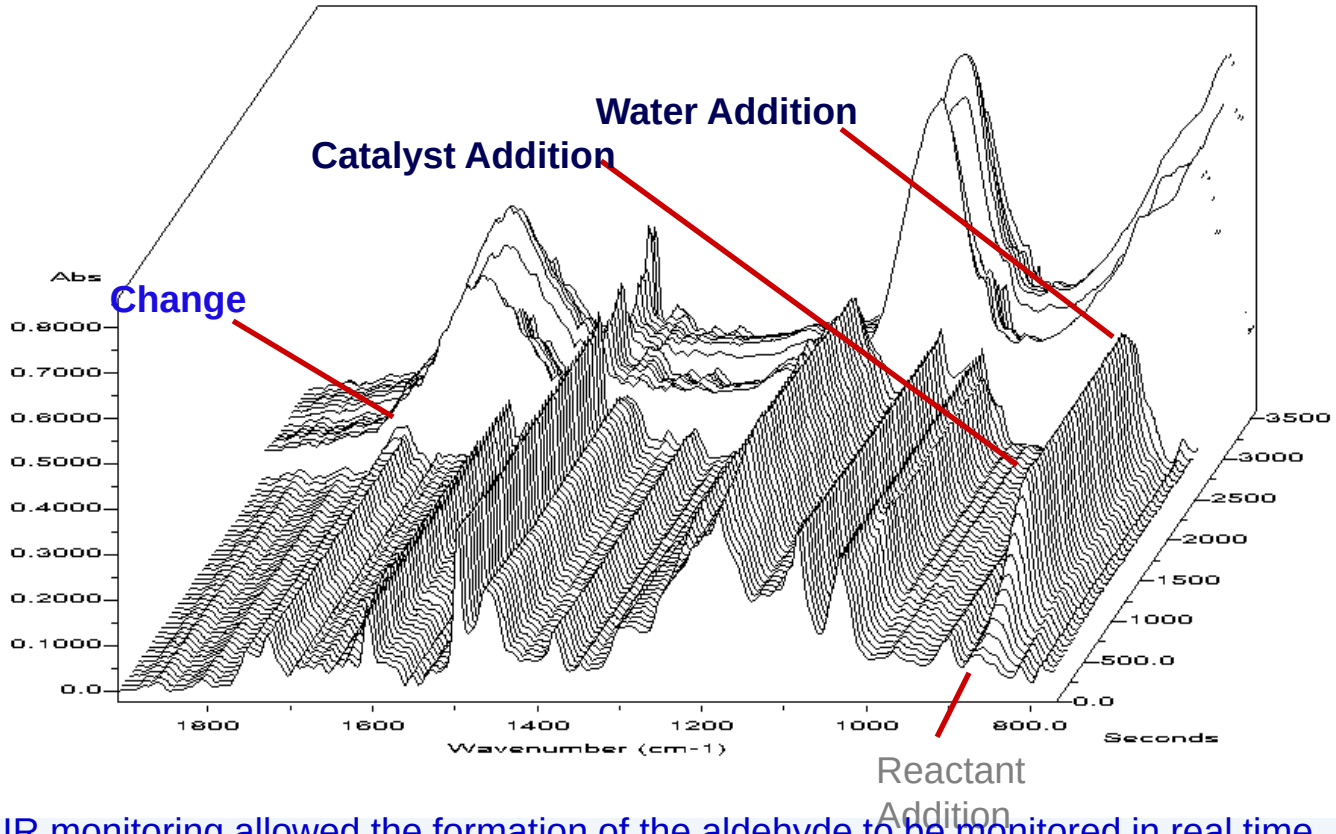
Process Understanding

Process Understanding - PAT

Why using PAT to measure in-situ and on-line:

What we thought we knew!

Monitoring by HPLC, using an aqueous mobile phase, gave the opposite conclusion !!



Real Time IR monitoring allowed the formation of the aldehyde to be monitored in real time which led to the conclusion that

*Addition of the catalyst did not lead to formation of **compound 1**. Only on addition of water did the reaction occur to give the aldehyde*

Jim Rydzak

Post-campaign review – Process Understanding - MVA

Review of complete analytical profiles

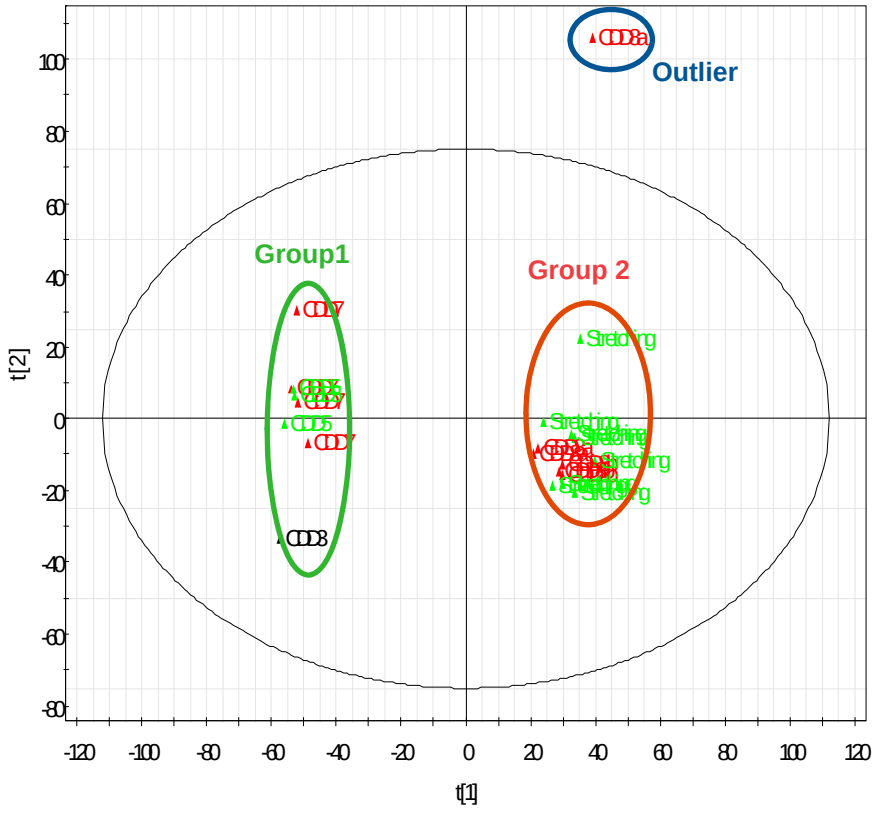
- **Target:**
  - Summarise data from 6 campaigns (24 batches), for 19 impurities
  - Provide a simple overview of the development campaigns

Step 1: Identify differences and similarities between batches with simple 2D plots
PCA Scores plot:

- Each point represents 1 batch
- Identify groups and outliers
- Batch colour coded by manufacturing sites

- Special cause identified between Group 1 and Group 2
- No pattern relating to manufacturing site was identified

Scores plot: pattern between batches



Post-campaign review – Process Understanding - MVA

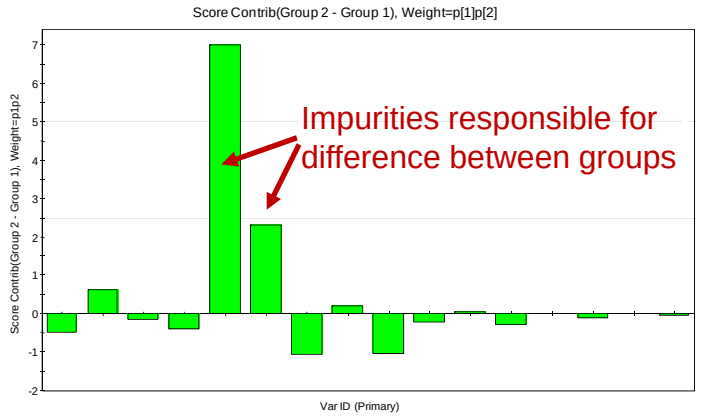
Review of complete analytical profiles (continued)

Step 2: Identify impurities associated with the group differences

Contribution plot:

- Each impurity represented by a green bar
- Larger bars indicate impurity significant in the difference between the groups

Contribution plot:
difference between Groups 1&2



Deliverables:

- Identified two distinct groups
  - Root cause: Change of raw material supplier used in process
- One atypical batch identified
  - Root cause: higher solvent residual, linked to a documented process deviation
- Process is shown to be site independent
- Route changes during process development were shown to have no impact on impurity profile
- Analytical data summarised for easy discussion and communication

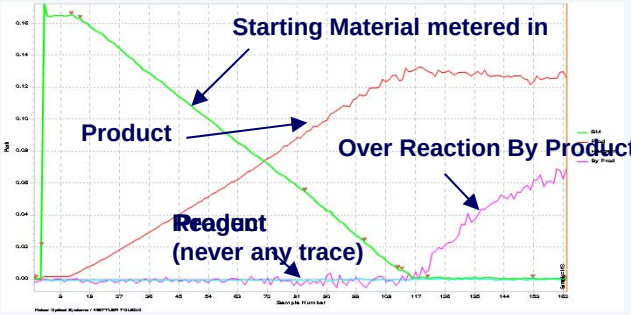
Applications 3, 4 & 5

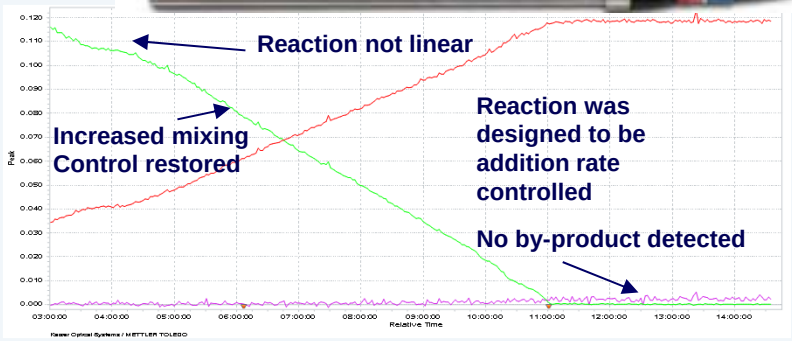
Support development of Control Strategy

Support Control Strategy Definition - PAT

Raman Reaction Monitoring

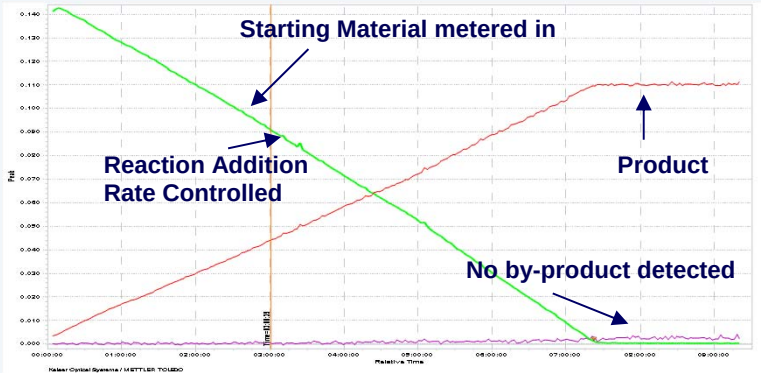
- **Scope:** Real time Raman method achieving the less that 0.1 unreacted specification
- **Situation:** The starting material in stage 1 can break down. When that happens you have less than a stoichiometric amount to react and can stall the reaction and leave unreacted material 1. If material 2 is overcharged it is difficult to remove and produces a color problem and high impurity levels. If the reaction proceeds too long it can produce a thiocarbonate that will interfere with stage 3.





- **Measurement:** In-situ Raman was used to monitor both the starting materials and see any formation of a thiocarbonate impurity (see trend above)
- **Result:** Real time data allow correction of the agitation rate saving batch 1. All batches met 0.1 unreacted spec
- **Conclusion:** A successful transfer of real time monitoring Raman method was achieved by a team effort meeting all expectations and saving at least one batch.

Typical of remaining batches



Jim Rydzak

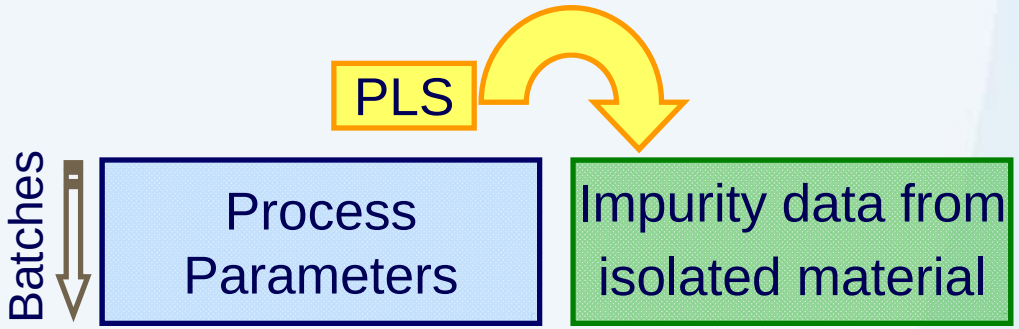
Support Control Strategy Definition - MVA

Impact of Process Parameters variability on CQAs

- **Target:**
  - Identify any potential relationships between variability in Process Parameters and variability in Attributes
  - Identify the process parameters which impact the impurity levels

- **Dataset:**
  - X block: Process parameters from a Pilot Plant campaign
  - Y block: Associated attributes from isolated material

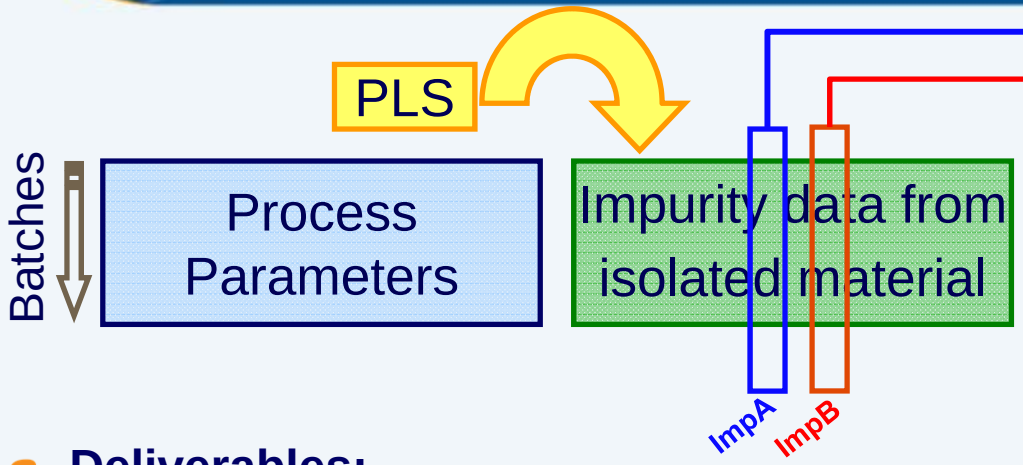
- **Methodology:**
  - PLS regression modelling between the two blocks of data, to identify / assess parameter-attribute relationships



Related article: J. Gabrielsson, H. Jonsson1, C. Airiau, B. Schmidt, R. Escott, J. Trygg *J. Chemometrics,* 2006 (20), 362–369

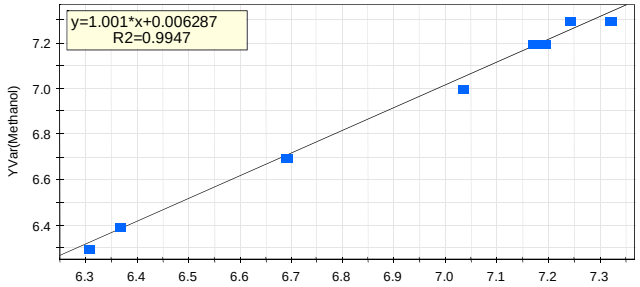
Support Control Strategy Definition - MVA

Impact of Process Parameters variability on CQAs (cont'd)

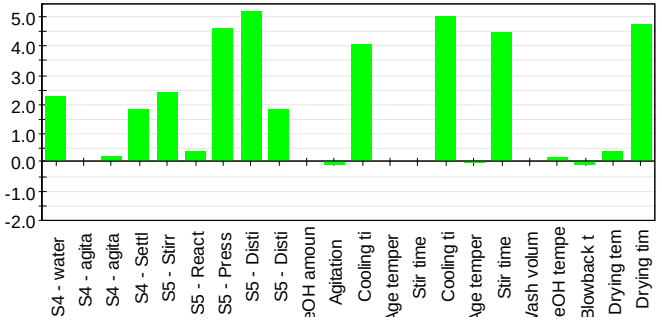


- **Deliverables:**
  - Understanding of parameter- attribute relationships at manufacturing scale:
    - Identified Impurities affected by the process parameters
    - Identified which process parameters are most influential
    - Identified impurities not affected by the process parameters
  - Confirmation of the Control Strategy
  - Supports robustness studies and Design Space knowledge

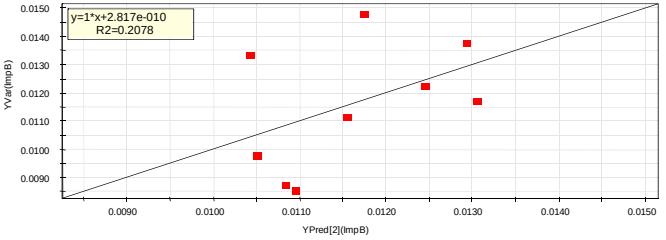
ImpA well modelled: influenced by parameters variability



Parameters associated with ImpA variability

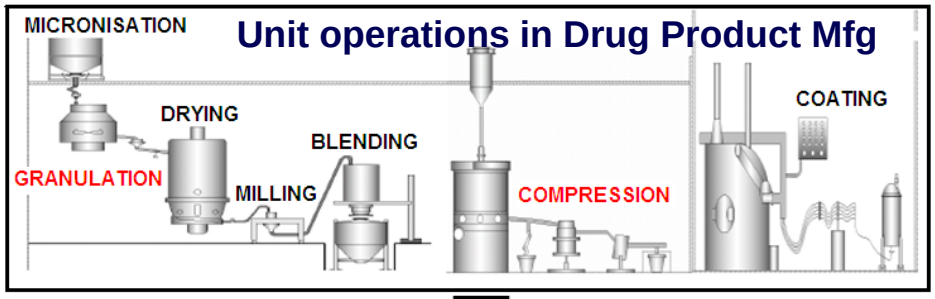


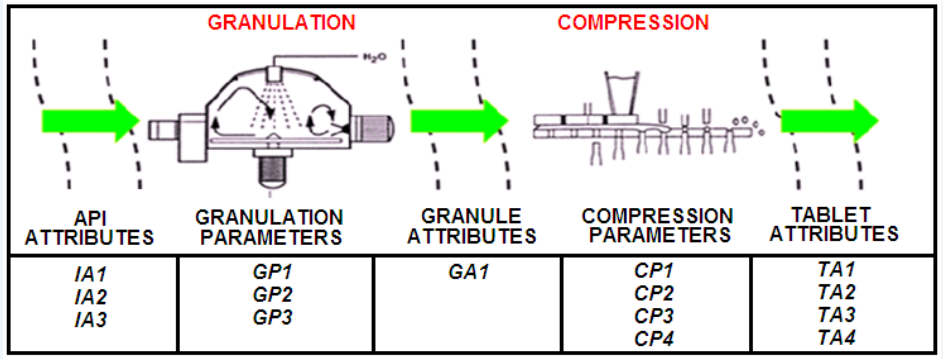
ImpB has no significant model: not affected by PPs



Support Control Strategy Definition - MVA

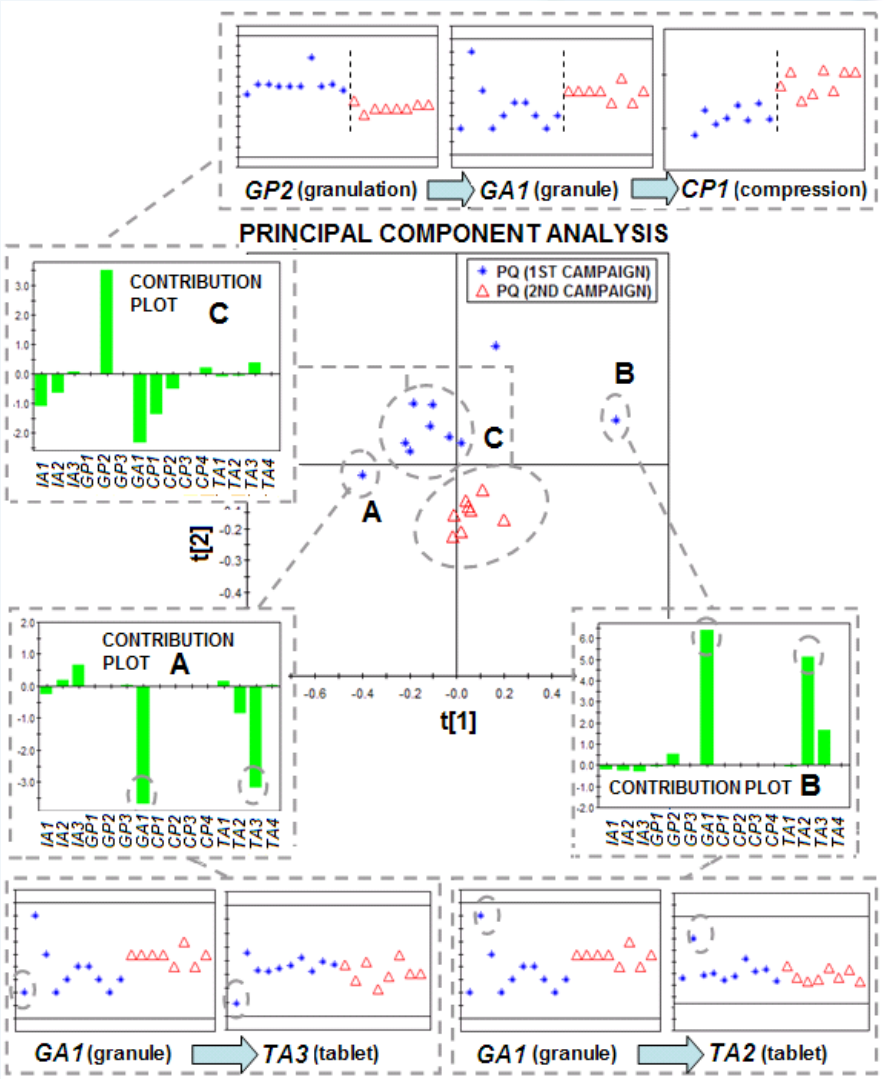
MVA & Solid dose – Control Strategy verification at Scale





Focus on the material attributes from API, granulation and compression, and processing parameters which deliver those attributes

Question addressed by MVA: Post technology transfer *is there any shift / onset of patterns in the finalised manufacturing process?*



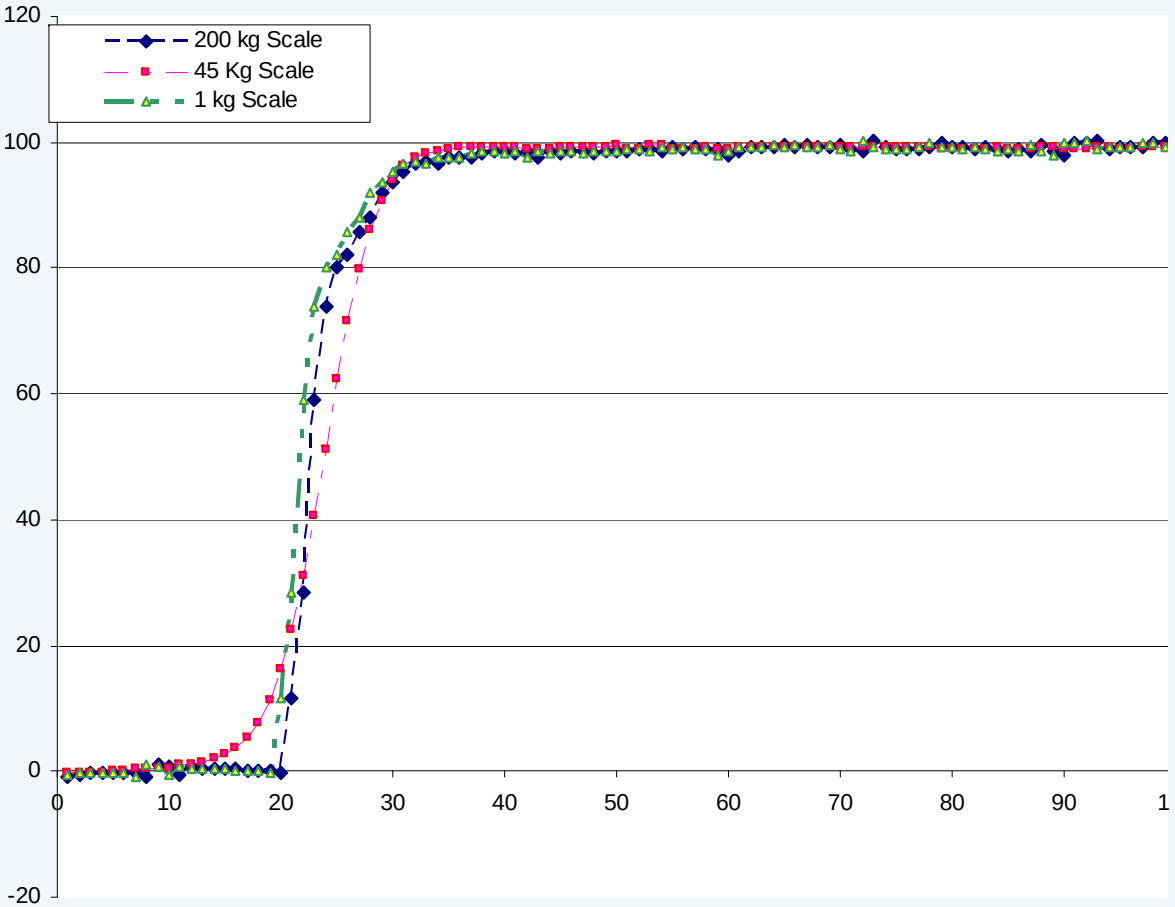
S. Zomer, M. Gupta, A.Scott,
Journal of Pharmaceutical Innovation 2010 (5): 109-118

Applications 6, 7, 8 & 9

Process Monitoring & Control

Process monitoring / control - PAT

Scale comparison of Form conversion



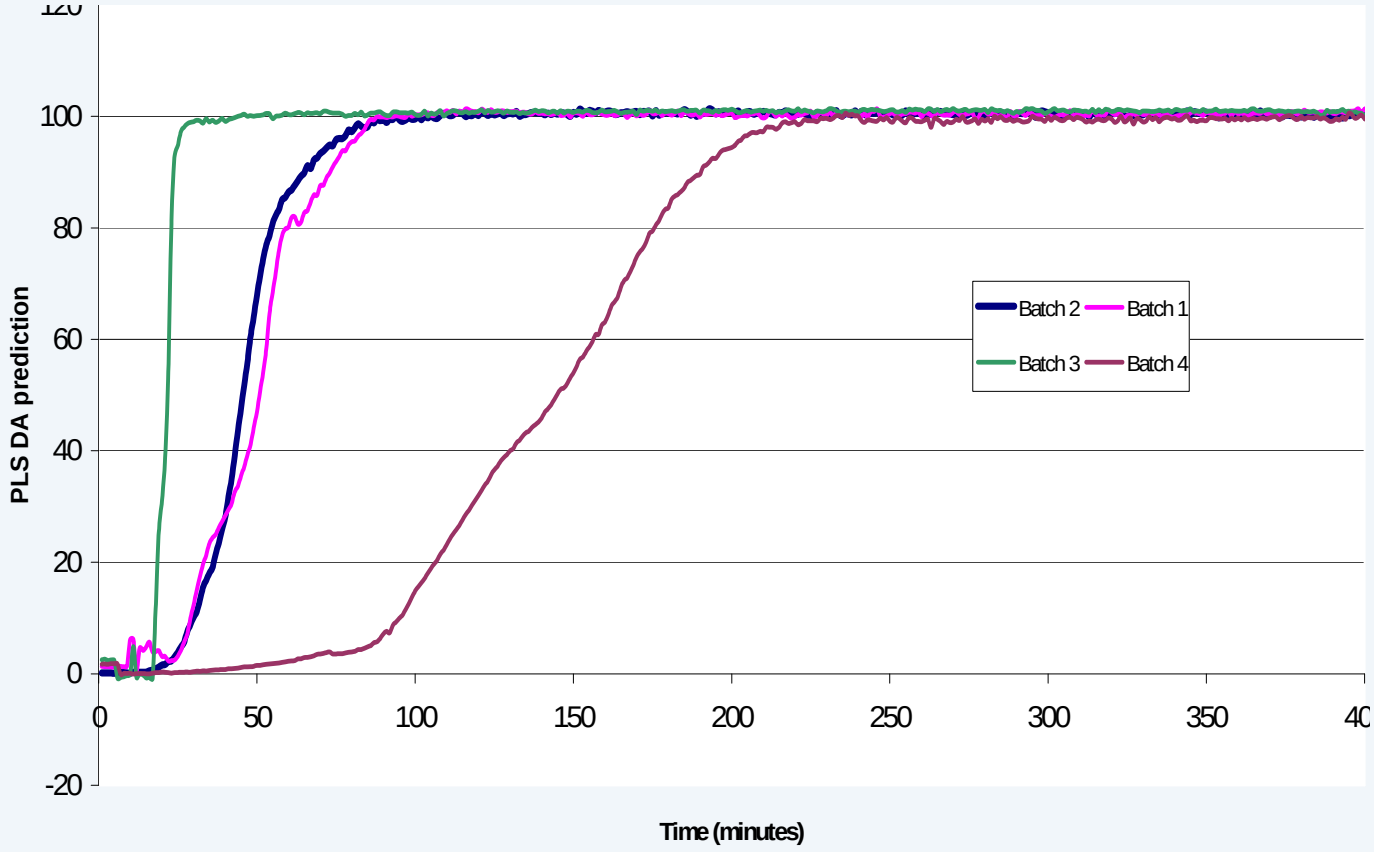
- Done at Lab, PP and Manufacturing scales showing scale independence for similar process conditions

Jim Rydzak

Process monitoring / control - PAT

Reaction end point detection

Overlay of NIR PLS-DA predictions of form conversion for 4 different batches



- Process conversion rates can be seen when process parameters are varied
- Real time monitoring can insure full completion of conversion and save cycle time in the plant

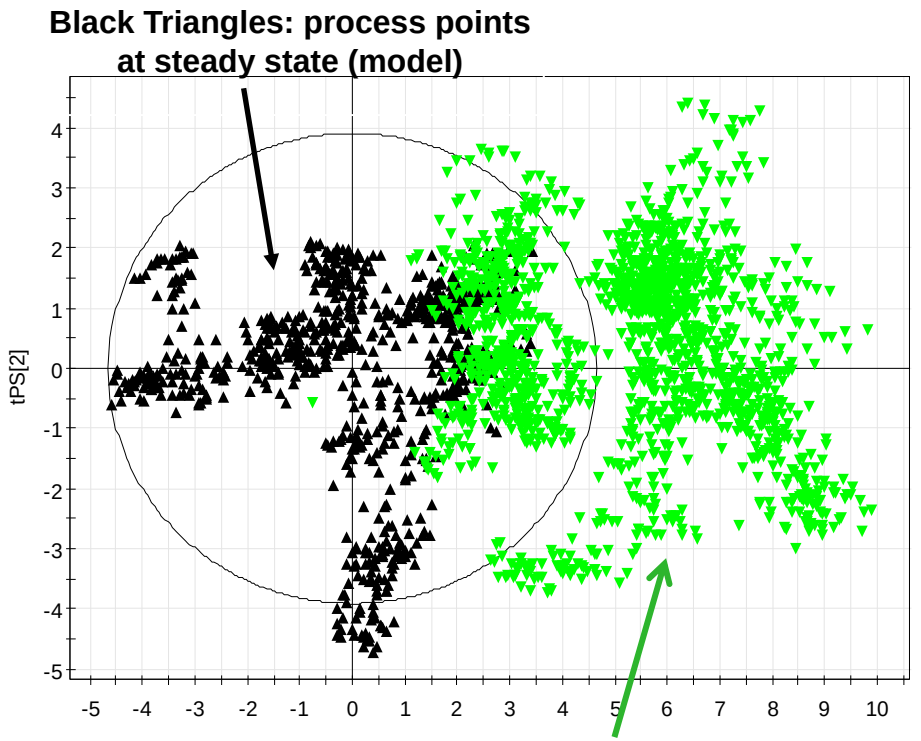
Jim Rydzak

Real-time MSPC for process monitoring & control

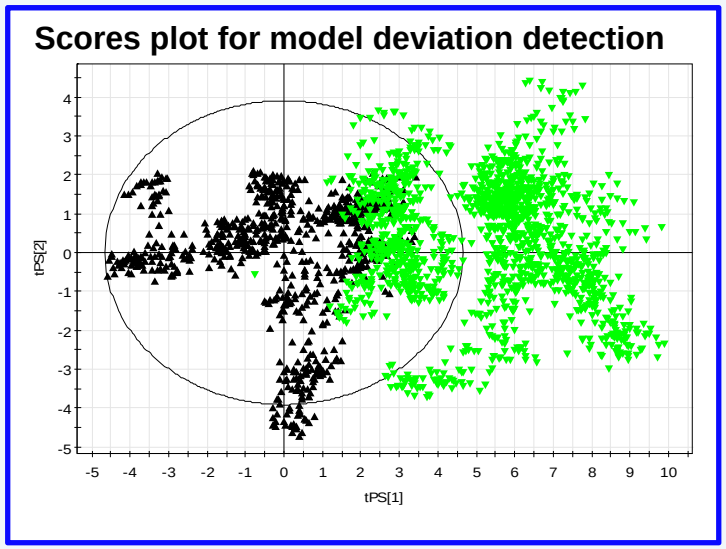
- **Target:**
  - Apply real-time Multivariate Statistical Process Control (MSPC) to process parameters during continuous processing
  - Early fault detection, allowing manual control to keep process running

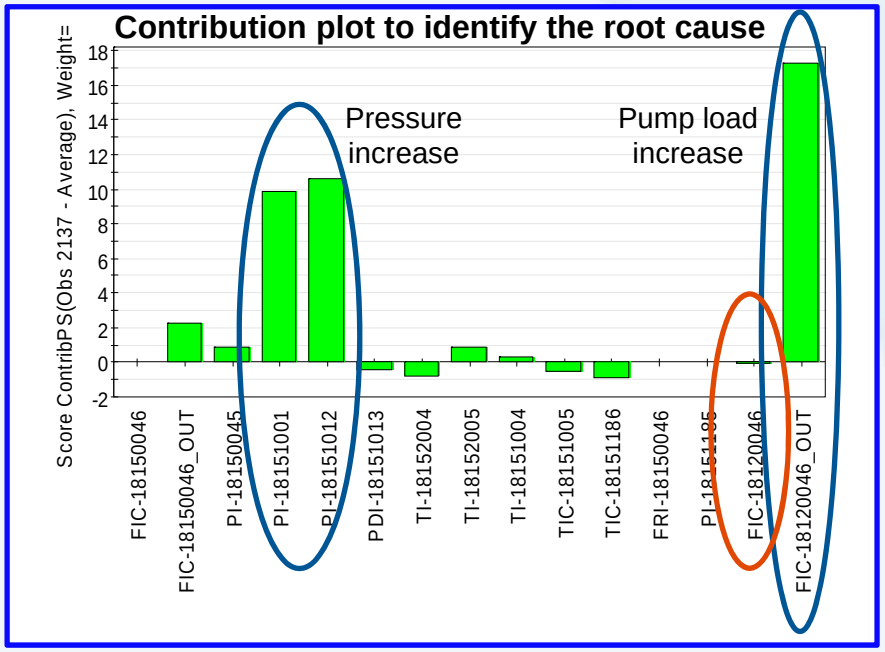
- **Methodology:**
  - Data: 15 process parameters (from plant historian)
  - MSPC model: 12hrs at steady state
  - Summarised onto Scores plot
  - Monitor process performance in real-time

- **Application:**
  - Identify any deviation from the steady-state model
  - Information available in the control room for plant operators/engineers



Real-time MSPC for process monitoring & control



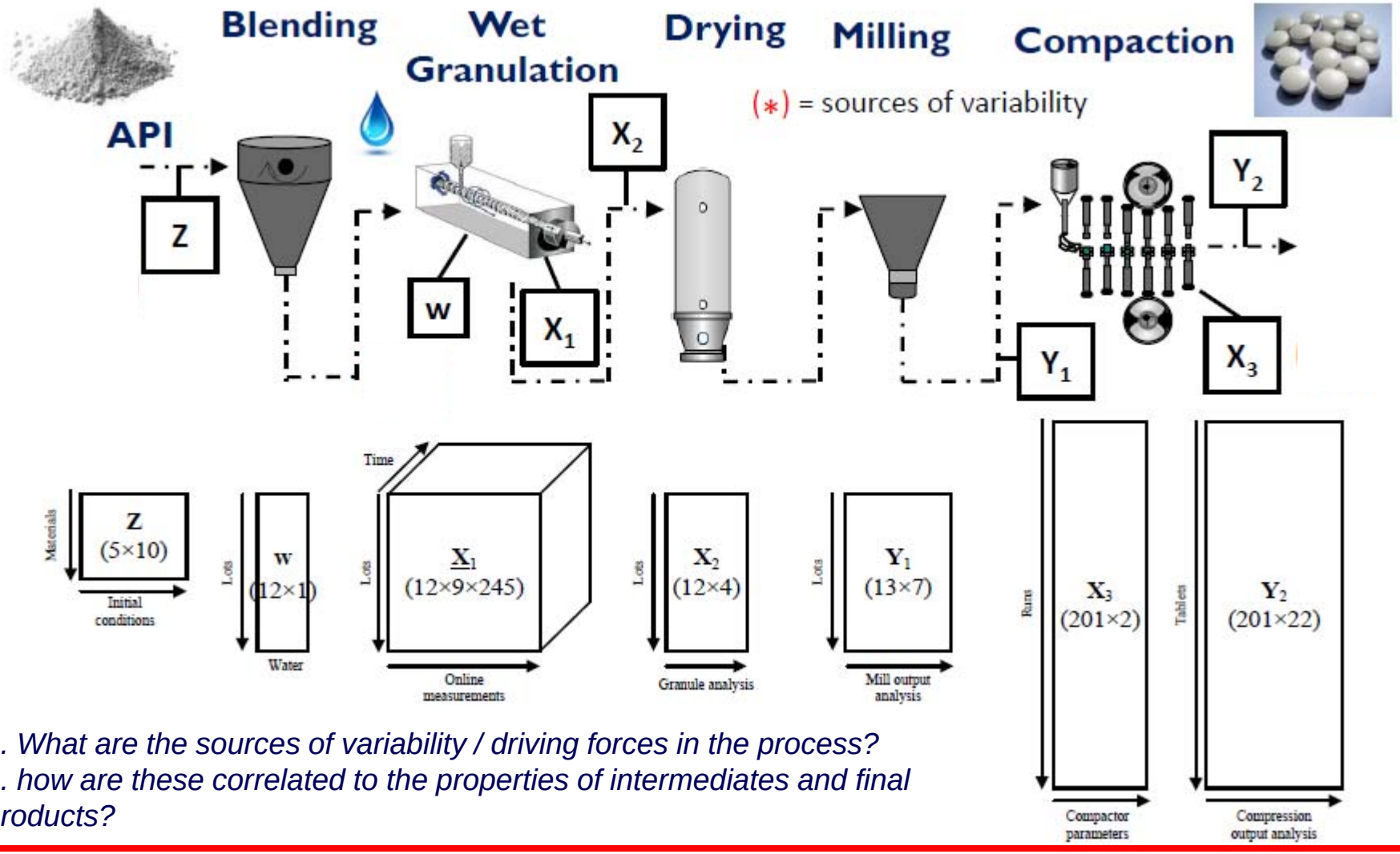


- **Deliverables:**
  - Real-time identification of process deviations
  - Process control (manual):
    - Real-time action to address a pump issue
    - Minimise loss of product by avoiding unnecessary diversion to waste
  - Information available in the control room
  - Real Time Assurance of when process is at steady state

From the contribution plot:

- Early warning of pump failure:
  - Pump load increase
  - Pump flow constant

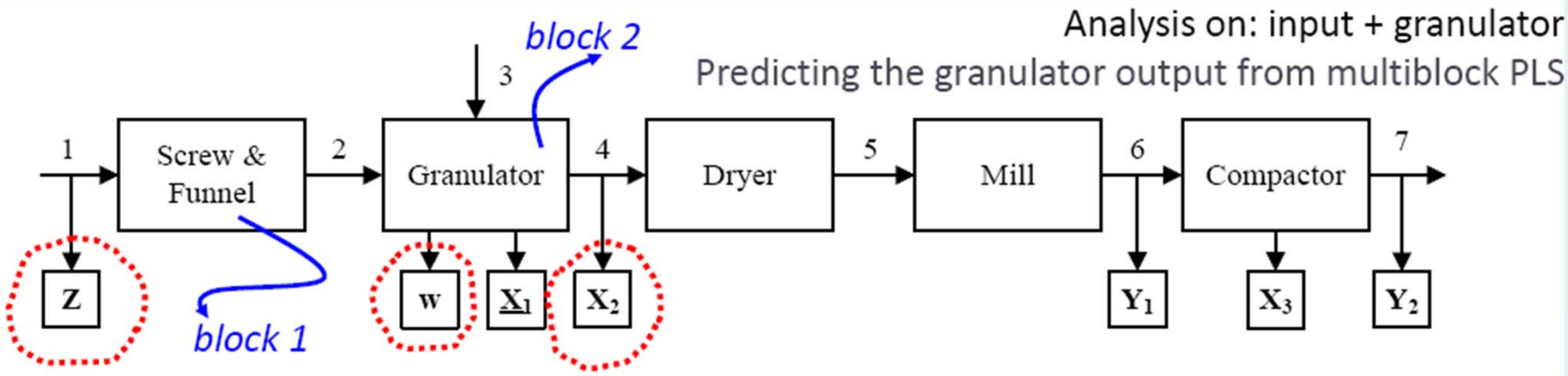
MVA & Solid dose - Continuous processes



1. What are the sources of variability / driving forces in the process?
2. how are these correlated to the properties of intermediates and final products?

E. Tomba, M. De Martin, P. Facco, J. Robertson, **S. Zomer**, F. Bezzo, M. Barolo
International Journal of Pharmaceutics 2013; 444: 25-39

MVA & Solid dose - Continuous processes



- $[Z^* \; w] \rightarrow [X_2]$ *Can the **granulator output PSD** be predicted?*

LV	R^2X	R^2X_{CUM}	R^2Y	R^2Y_{CUM}	Q^2	Q^2_{CUM}
1	32.67	32.67	75.74	75.74	48.78	48.78
2	52.89	85.55	12.07	87.82	35.96	84.73
3	9.68	95.23	2.42	90.24	-1.97	82.76
4	4.46	99.69	3.47	93.71	9.70	92.47
5	0.15	99.84	0.94	94.65	0.34	92.80
6	0.14	99.98	0.08	94.73	-0.40	92.40

Good prediction of granule PSD!

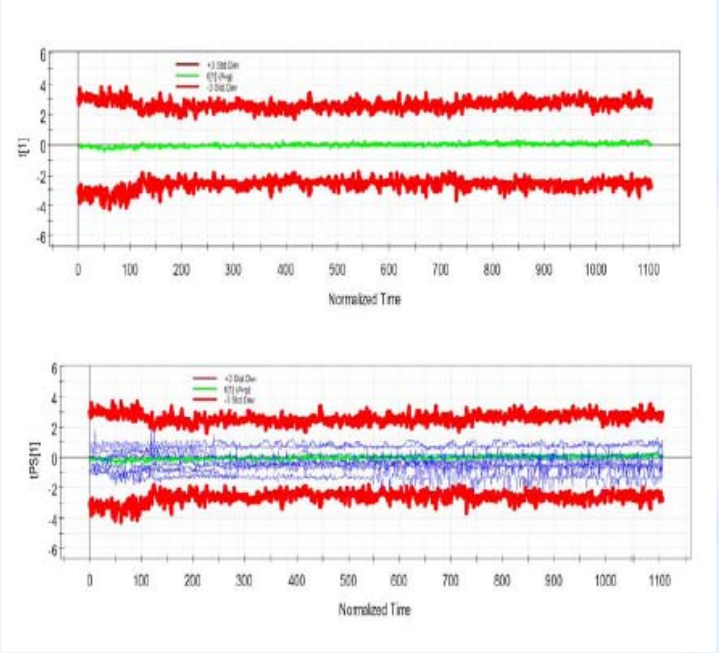
E. Tomba, M. De Martin, P. Facco, J. Robertson, **S. Zomer**, F. Bezzo, M. Barolo
International Journal of Pharmaceutics 2013; 444: 25-39

Process monitoring / control - MVA

Using MSPC to demonstrate state of control – Batch process

- **Objective:**
  - Demonstrate consistency and control of a process unit operation

- **Methodology:**
  - Batch MSPC applied to Compression stage
  - Model built from set of batches of acceptable product quality
  - Process data from subsequent batches projected onto the model showing consistency and state of control



- **Output:**
  - Provide confirmation of state of control of a critical unit operation
  - Included in NDA for this product, part of the confirmation of the control strategy

Patrick Rameas

Conclusions

- Quality by Design framework in place across Product Development activities
- Project Technical Risk Assessment (TRA) is the backbone of the development process
  - Triggers requirements for specific process understanding
  - Drives the Control Strategy
  - Defines the requirements for process monitoring and control
- MVA and PAT are core components of the Product development activities
  - Critical tools to address large dataset complexity, requirement for in-depth process understanding and drive for robust control strategy

Acknowledgements

- Jim Rydzak
- Greg Gervasio
- Jonathan Hammond
- Richard Escott
- Patrick Rameas
- Simeone Zomer
- Andy Scott
- Manish Gupta
- Greg Webber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