Case Study 5

The compliance revolution:

the impact on the rôle of the QP and the Quality function

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Presentation overview

- Understanding the evolution which is occurring within pharmaceutical manufacturing and the associated product development programmes and commercial strategies
- General (Quality and Regulatory) implications, especially as we move towards continuous processing by first intent
- Quality by Design aspects
  - CQA's and CPP's
  - Design Space, Process Signature etc
  - Continuous (Process) Verification
  - Real Time Assurance / Real Time Release
- Processing equipment qualification; measurement systems qualification; verification of control algorithms etc

Development and commercial strategy

- In general, R&D has traditionally developed products and processes using a batch-wise approach. Continuous processing is viewed as an 'add-on', either because there is no perceived need or because Manufacturing is deemed to be ill-equipped to operate continuous processes
- Manufacturing generally fails to provide the commercial drivers for continuous processing by First Intent in R&D
- Significant benefits are now being recognised by R&D, however, in using continuous processing for rapid, responsive and resource-efficient development programmes
- From the Quality perspective, this means that 'fitness for purpose' can embrace vastly different situations

Continuous processing by First Intent

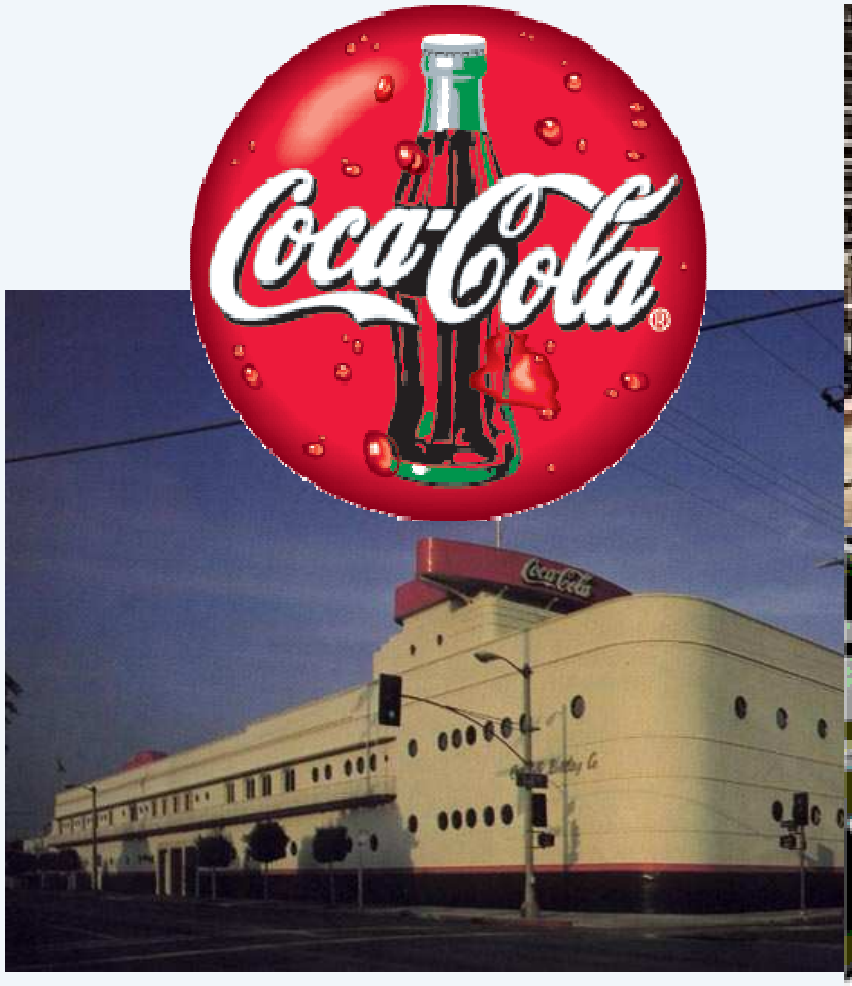
Commercial strategy – potential considerations

- Predicted sales volumes (3, 5, 10 year forecasts)
- Required manufacturing capacity
- Sites of manufacture; opportunities for rationalisation
- Product diversity; opportunities for rationalisation
- Preferred manufacturing equipment
- Potential third party suppliers

Continuous processing by First Intent

Weetabix is exported to over 80 countries throughout the World (including the Middle East, South America and South East Asia)

Coca-Cola manufacturing plant



Coca-Cola manufacture

- *Coca-Cola* manufacture is a ten-stage continuous process (including bottle rinsing, filling etc)
- Input raw materials at Stage 1 are described as Bottles and Cans, Caps, Carbon Dioxide, Sugar, Labels and ‘Secret Formula’
- Syrup blending process is continuous and finished product is coded to establish manufacturing date, shift etc
- Quality of locally-sourced input raw materials becomes critical

General (Quality and Regulatory) implications of continuous processing

How is ‘continuous’ different to ‘batch’?

Currently most pharmaceutical products are manufactured in batch mode

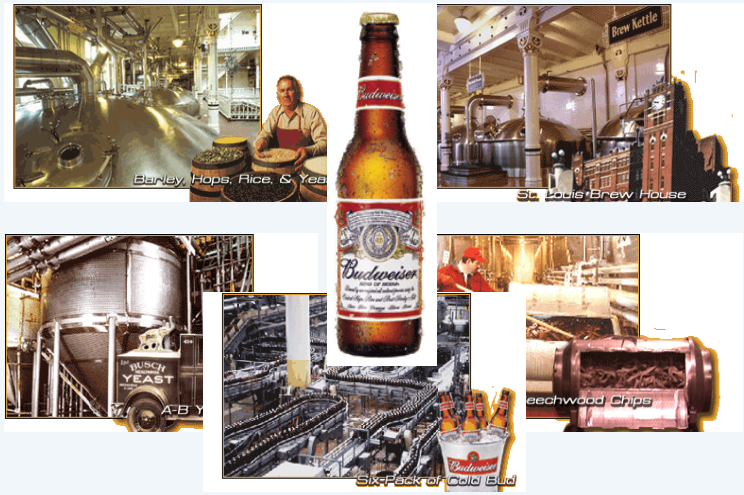
From the Quality perspective this offers a number of apparent advantages:

- Clear definition of what constitutes ‘the batch’ - with benefits of easy traceability and expiry dating
- Ability to sanction the batch quality against finished product specification using laboratory-based ‘end product’ testing
- Discrete batch records can be compiled

General (Quality and Regulatory) implications of continuous processing

- If there is no discrete beginning and end to the manufacturing process, how is ‘the batch’ defined – and how are expiry dates calculated and how are ‘definitive’ batches designated?
- What replaces the batch records?
- If there is no ‘end product’ testing, how is quality demonstrated?
- Conventional testing or novel analytical measurement technology - and development of associated reference standards?
- More sophisticated data treatment techniques
- Increased probability of ‘out-of-specification’ results

Definition of ‘the batch’



The production of a *batch* begins on Monday morning and ends on Friday evening

Cleaning procedures are very well-established

Important to establish ‘steady-state’ conditions

Analytical monitoring is carried out (using relatively simplistic methodology) at extremely frequent time intervals

A very rapid turn-around of results allows product quality to be confirmed or non-compliant time-windows to be identified

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Control and traceability of input materials

- Within a defined time-period, we are likely to have different batches of input materials, so the extent of ‘carry-over’ needs to be understood

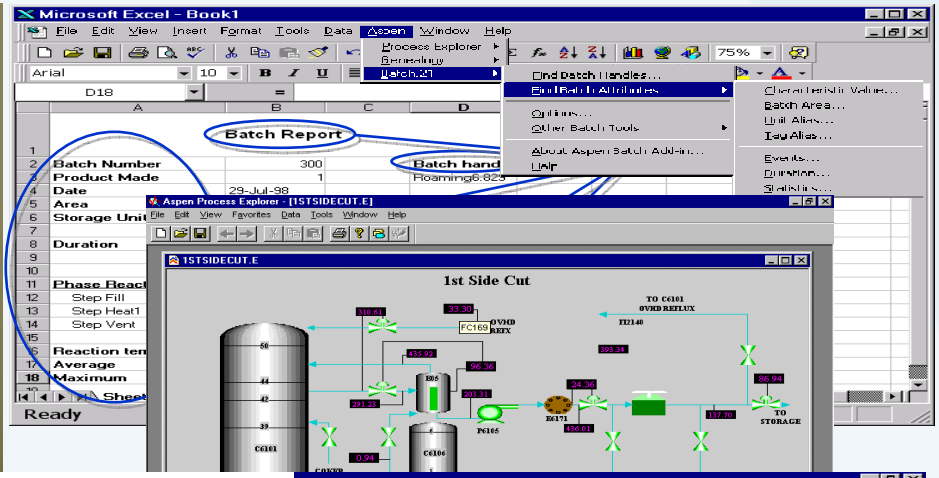
- This will necessitate tighter control, traceability and rationalisation of input materials. The Quality System for continuous processing needs to embrace this and the QP must be assured of compliance

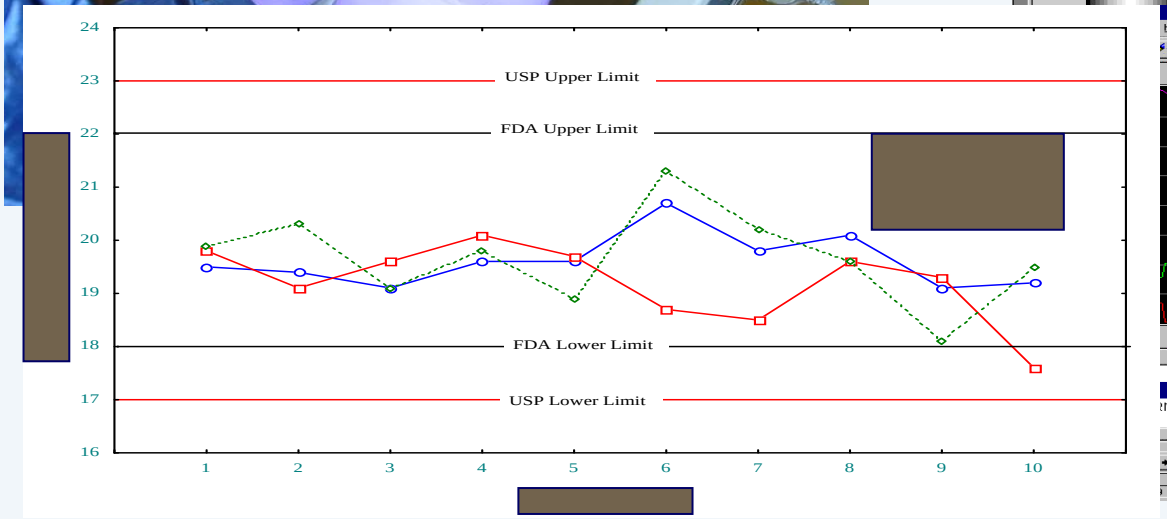
- Longer term, could we envisage that the continuous process automatically identifies differences in input materials (within a previously defined raw material specification) and deals with those differences appropriately? If so, the manufacturing control strategy and its associated quality aspects need to reflect this opportunity and ensure that input raw materials and processing conditions are confidently and demonstrably correlated

Designation of ‘definitive’ batches / materials

- In truth, the requirements of materials produced using continuous processes are no different to those produced in batch-wise mode
- Commercial material needs to be to shown to be ‘representative’, ‘typical’ or ‘equivalent to’ material used in pivotal clinical programmes
- Maybe it’s a simple as demonstrating that ‘steady-state’ conditions have been achieved during manufacture?
- The criteria by which these materials are assessed may be different to those arising from conventional batch-wise production, but the principles remain the same. Hence, the designation of ‘definitive’ materials may require a review of existing requirements to embrace the way in which continuous manufacturing technology is employed

Batch records





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Multivariate statistics ... on the beach

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Certificate of Analysis…..or Certificate of Conformance?

Typical analysis (mg/L) is shown on every bottle:

Calcium	35.0
Magnesium	8.5
Sodium	6.0
Potassium	0.6
Bicarbonate	136.0
Chloride	7.5
Sulphate	6.0
Nitrate	<1.0
Fluoride	<0.1
Iron	<0.01
Total dissolved solids at 180°C	136
pH at source	7.8

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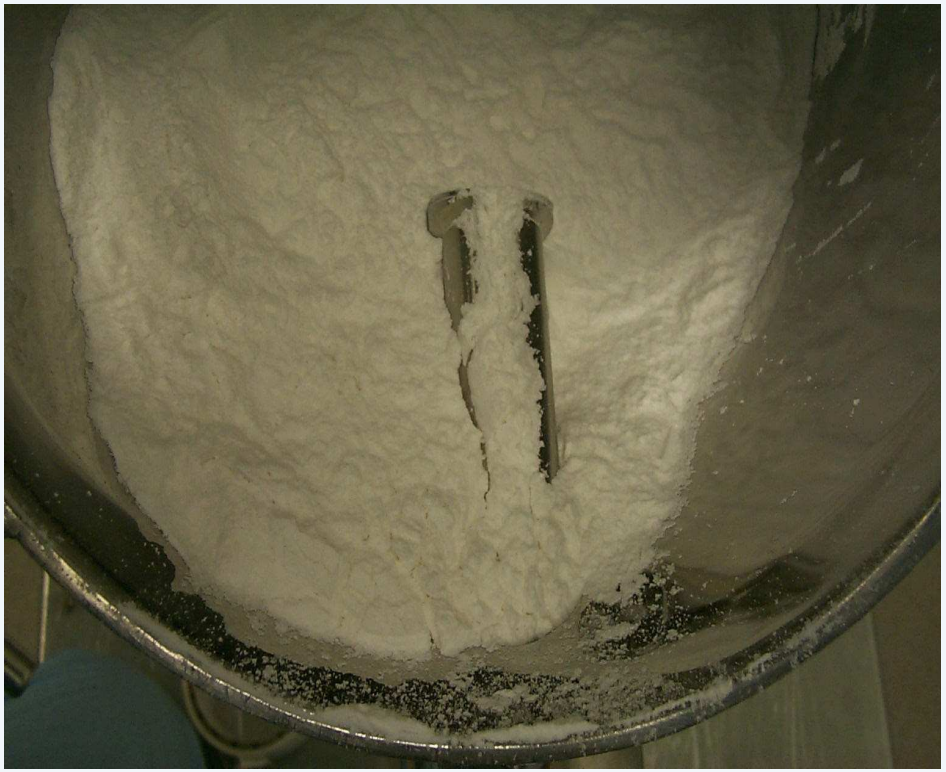
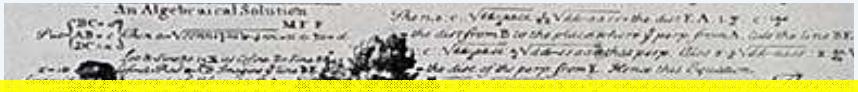
Novel analytical measurement technologies



Control strategy options

- Direct
  - The Critical Quality Attributes are measured (end-point control)
- Indirect (or inferential)
  - We establish the model which relates process parameters and input variables to the Critical Quality Attributes of the process output – this is **Process Understanding**
  - We monitor and control these key process parameters and inputs

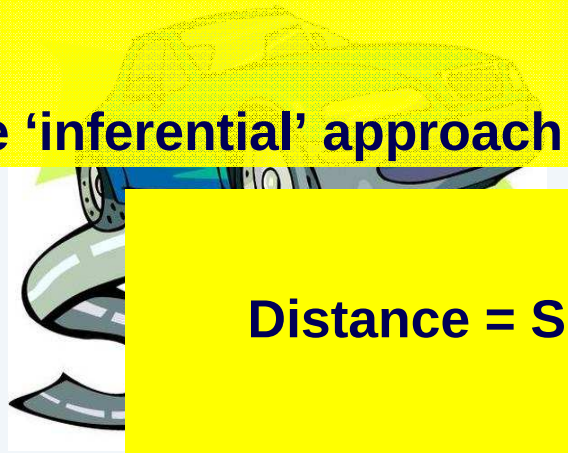
Control strategy options



If we want to know the distance from London to Heidelberg...

...we can use the 'direct' approach….that is, measure the distance

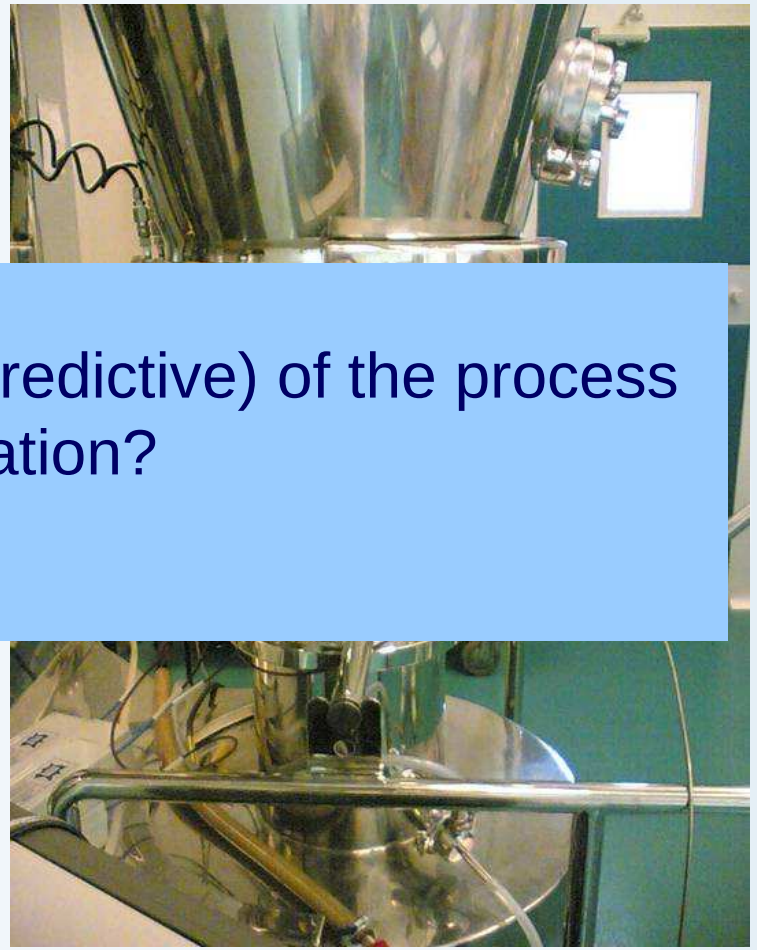
...or use the 'inferential' approach….based on the following model:



Distance = Speed x Time

d = st

Interfacing of measurement systems



- Location of sensors

Is our sampling representative (or predictive) of the process under investigation?

- Mechanical interfacing

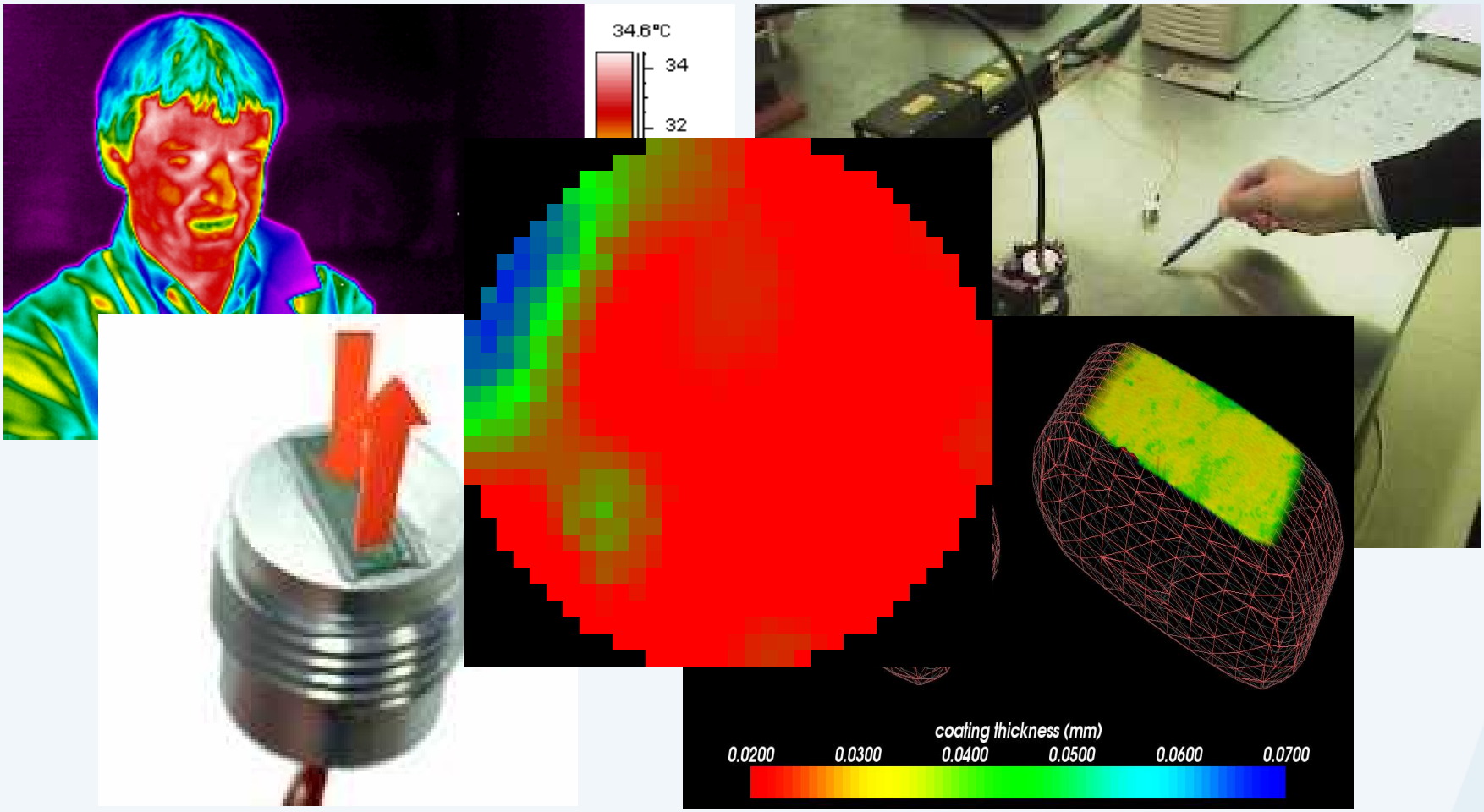
Process measurement considerations

On-line and in-line process measurement applications generally will not involve physical ‘sampling’ of the system or process

Nevertheless, all such process measurement techniques are effectively sampling from the bulk of the material under investigation

- Effective sample size (ESS) needs to be estimated
- Suitability of level of scrutiny needs to be demonstrated
- Measurement cycle time must be established in the context of the time-frame of the process

Reference standards



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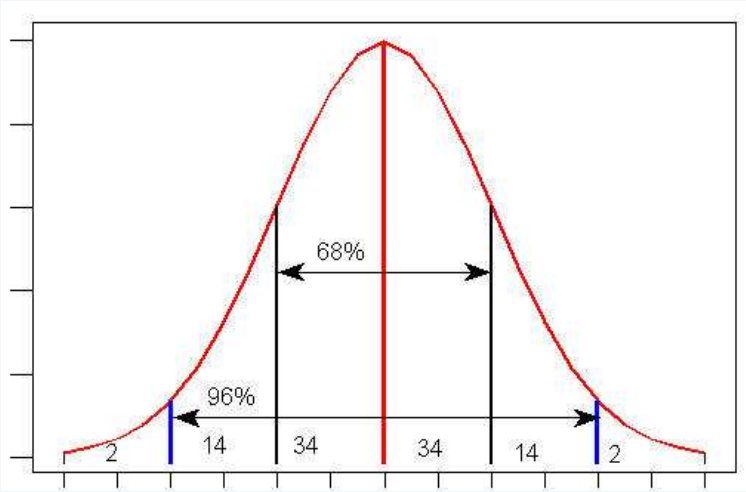
Probability of outliers



$$p(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

Where a small number of outliers are acceptable during ‘end product’ testing (eg tablet content uniformity), revised specifications need to be developed to reflect the vastly increased number of data points which real-time process measurement produces

Current ‘Out-of-specification’ investigative procedures need to be re-thought

Should Industry be trying to lead the regulators more actively ?

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Quality by Design (QbD) aspects

- Identify and agree the CQA's of the process output
- Establish the CPP's which can most significantly affect these CQA's
- For newly-designed processing equipment, we need to ensure that this design provides appropriate control capability of these CPP's
- Establish the Design Space
- Agree the manufacturing control strategy
- Demonstrate the conformance of the process on a continuous basis

Continuous verification approach

Traditional validation approach

Development

PQ

VMP VSR

Commercial supply

Periodic review

Periodic review

Continuous verification approach

Development

PQ 1

VMP IVSR

Commercial supply

PQ 2

On-going verification

VSR

Periodic review

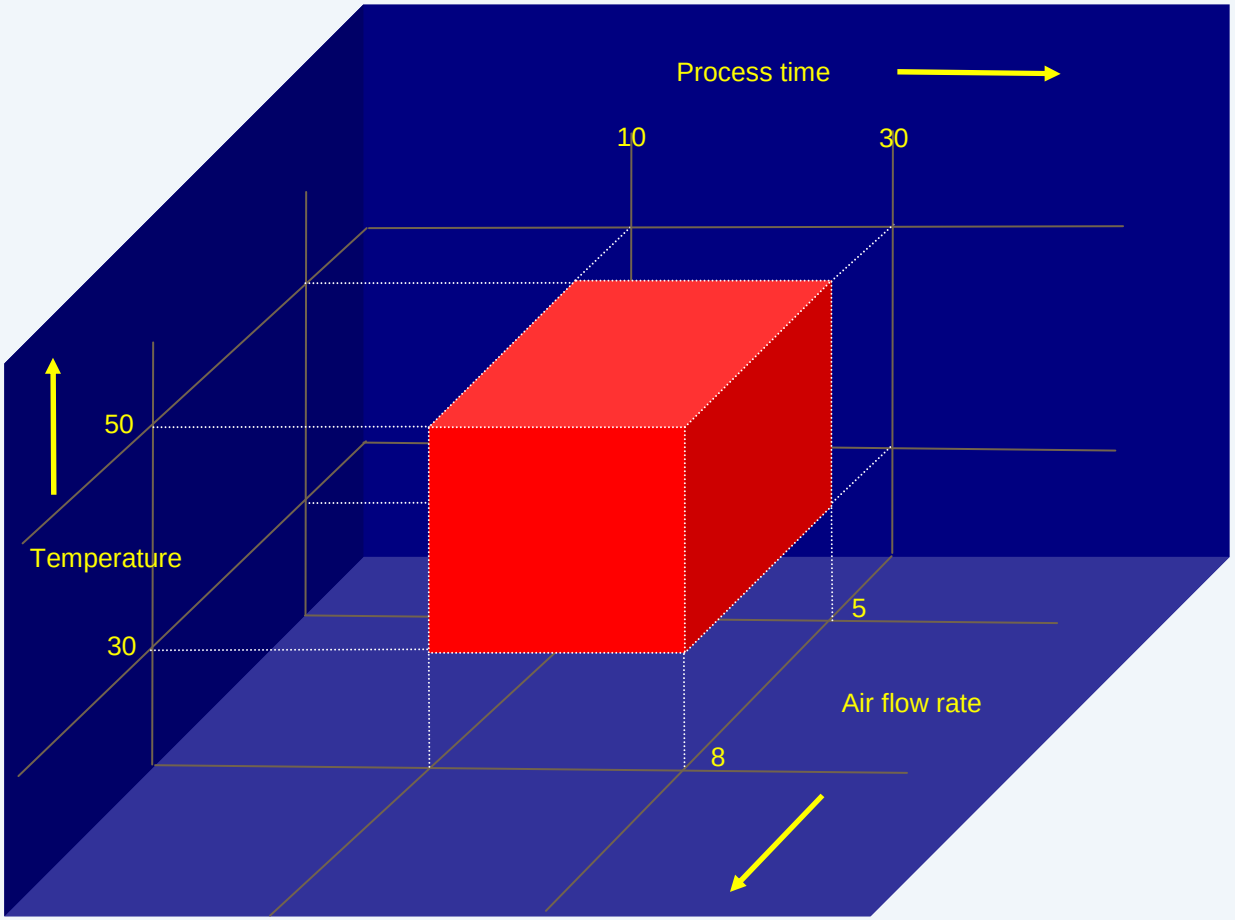
CQA's for granulation process

- Uniform Content (in particular API homogeneity)
- Appropriate granule size and tight mono-modal distribution
- Consistent (good) flow properties
- Consistent crushing strength
- Consistent porosity, density, wettability, solid fraction etc
- Consistent moisture content of granule at start of drying stage

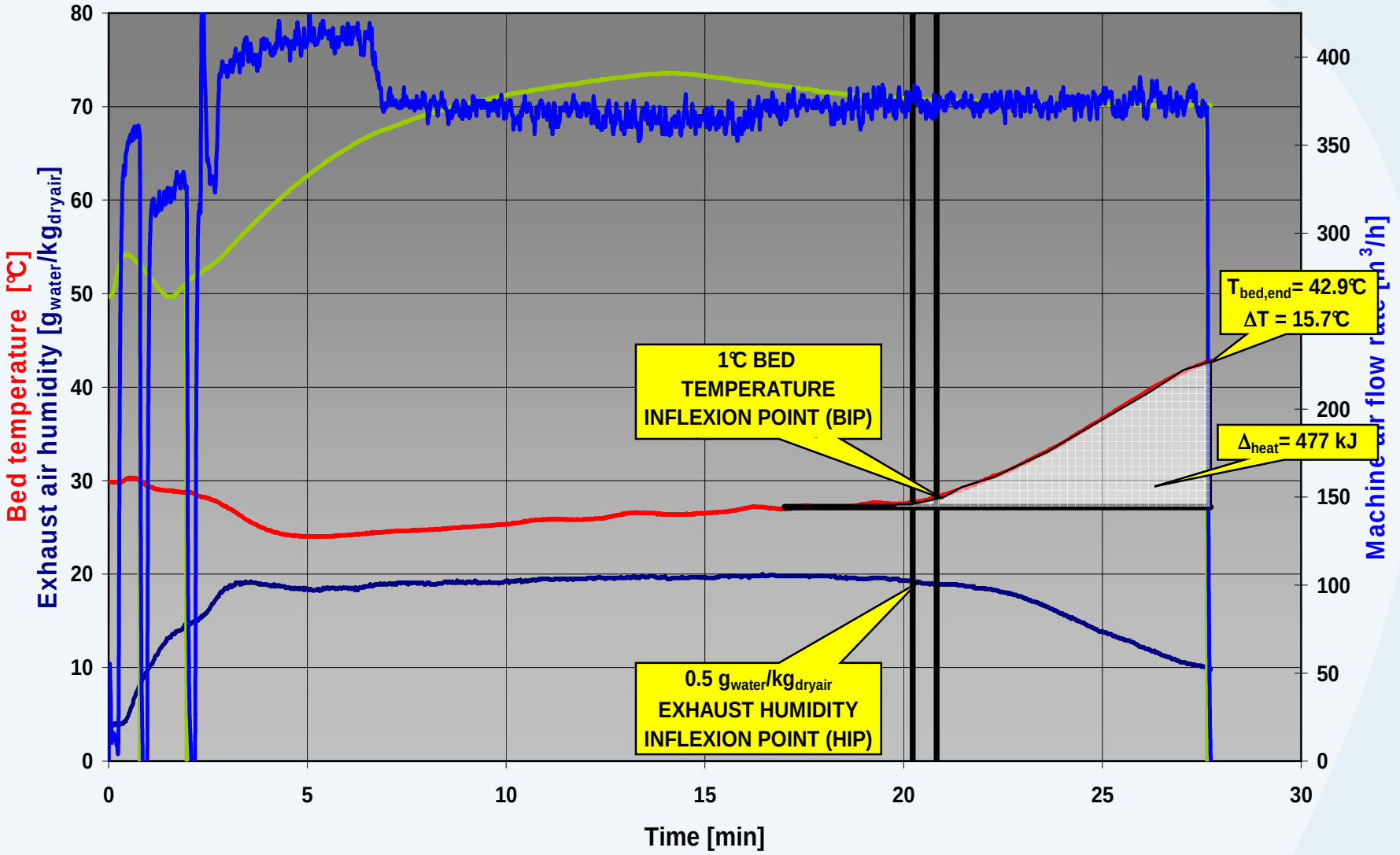
CPP's for granulation process

- Load (fill height)
- Spray addition rate
- Spray droplet diameter and velocity (ie pressure, nozzle type, distance)
- Binder addition method (wet or dry)
- Dry blending time
- Main Impellor speed and Side Impellor (Chopper) speed
- Granulation endpoint (relating to granulating time and amount of liquid added)
- Temperature (powder and liquid)
- Ambient RH

Depiction of Design Space



Process signature



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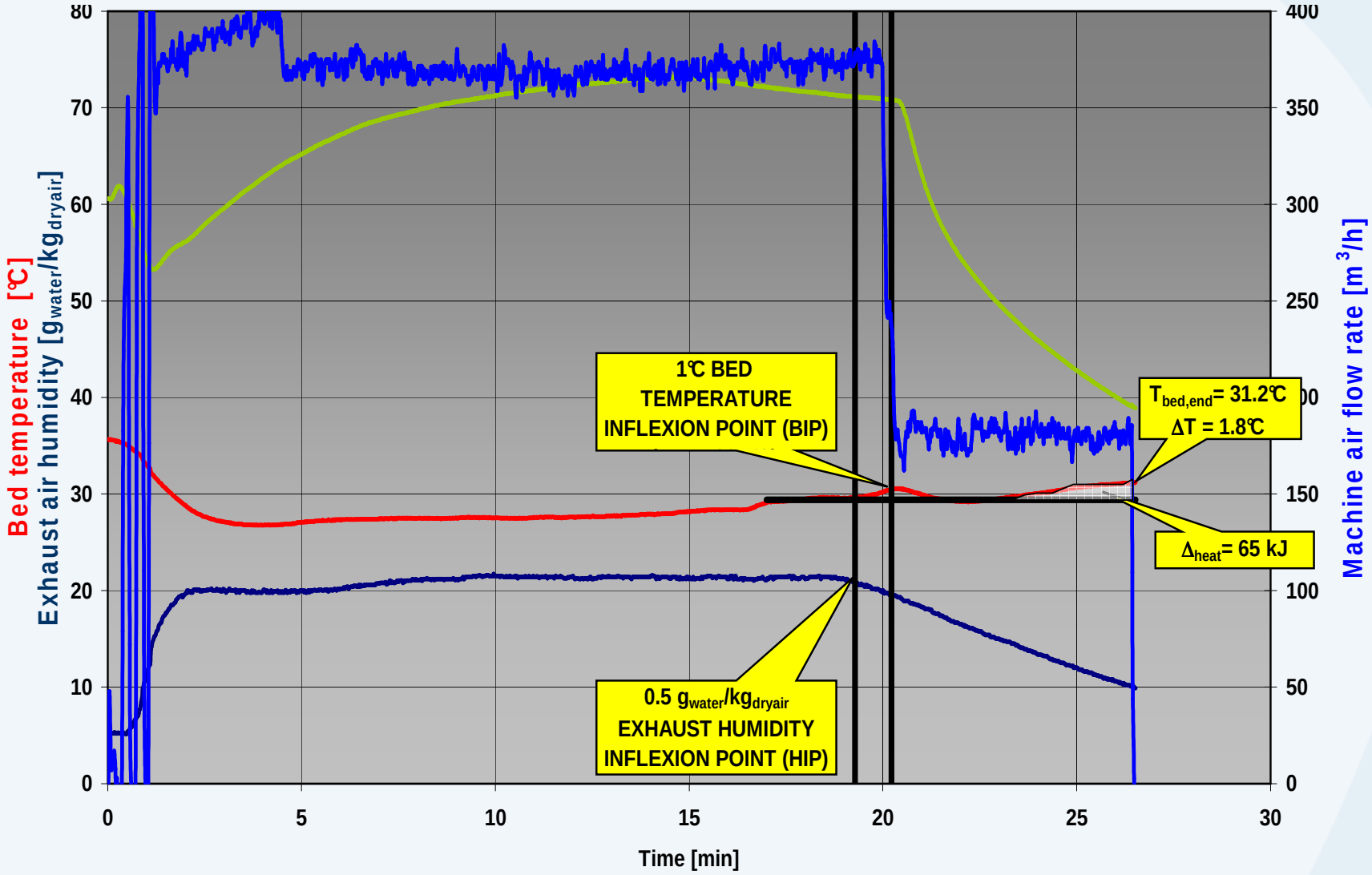

Qualification and verification

- Traditional (stand-alone) equipment qualification and traditional (stand-alone) qualification of process measurement equipment…….but…….

  …….with additional qualification/validation/verification aspects based on the interfacing of real-time measurement systems with the manufacturing equipment
  - representative nature of the measurement
  - influence of measurement system on manufacturing process and *vice versa*
  - influence of external (environmental) factors
  - data collection and data processing

Qualification and verification

Process measurement and control applications are different and potentially novel for certain types of equipment

Issues such as interfacing, PQ aspects, intrinsic safety etc need to be considered more fully

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Summary

- The ‘traditional’ Technical and Quality skill set and expertise needs to be further enhanced – especially in terms of multivariate statistics, modelling and novel analytical measurement techniques
- Quality systems which embrace continuous processing are evolving rapidly and require a broader awareness and appreciation of additional manufacturing factors
- Demonstration of compliance is moving more towards a situation of ‘Pass’, ‘Fail’ and ‘Yet to be classified’. The challenge for the QP and the development scientist is to be clear what additional information and judgement are required in order to deal with the ‘Yet to be classified’ situation
- There are real opportunities and, in fact, a real need for the review and further development of regulatory expectations and standards