Industrial Production Using Continuous Flow Technology – applications in the pharmaceutical sector

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Topics

Introduction

Processing principles

- Plug flow *vs* Continuous Stirred Tank Reactor (CSTR)

Obstacles

- Are they real?

Benefits

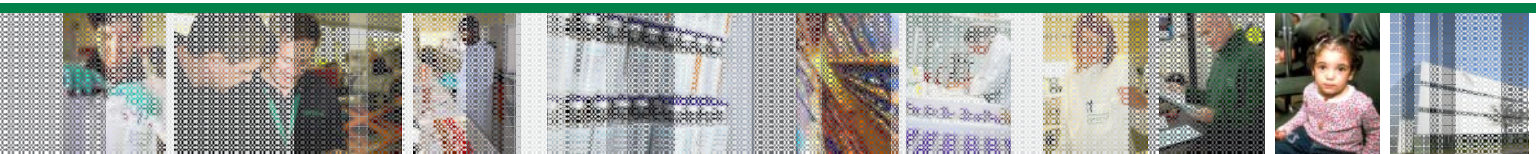
- Cost, size, speed

Practicalities

- Validation
- Deviations
- Batch size

Conclusions

Acknowledgements



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Introduction

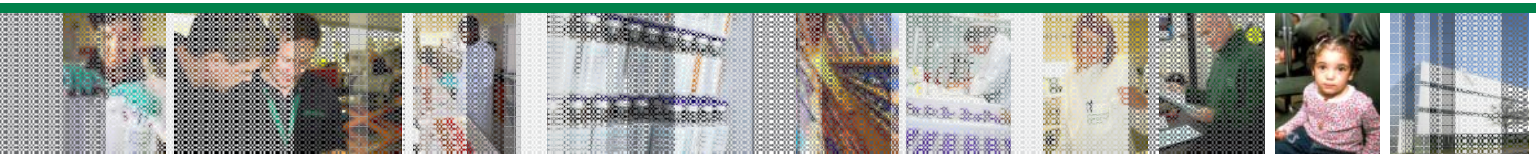
Genzyme has developed a multi-stage, PAT enabled API synthesis for hundreds of tonne scale production

Capacity increased from ~ 26 TPA to 560 TPA within 3 years (and several hundred tons more over past 8 years!)

Use of organic solvent reduced by >90%

Inspected multiple times by MHRA and FDA (two inspections each)

Conventional regulatory filings (not QbD, PAT, *etc.*)



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Processing principles

What is the scale of scrutiny?

- At what level does variation matter?

What is the effect of variation?

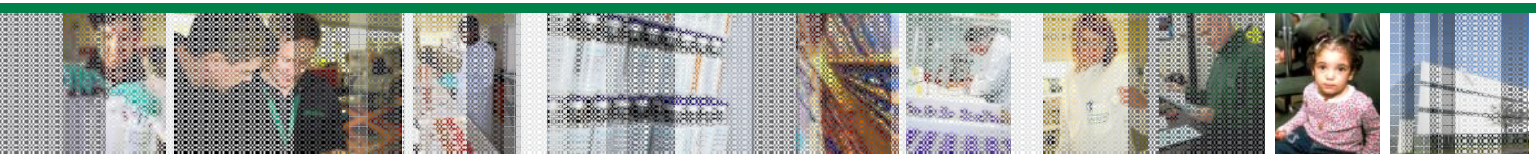
- On the patient?
- On the filing?
- On the business?

Batch processes

- Gross properties measured
- Transient differences are not easily seen or recorded

Continuous processes

- Can be continuously monitored
- Can give data that are “difficult”



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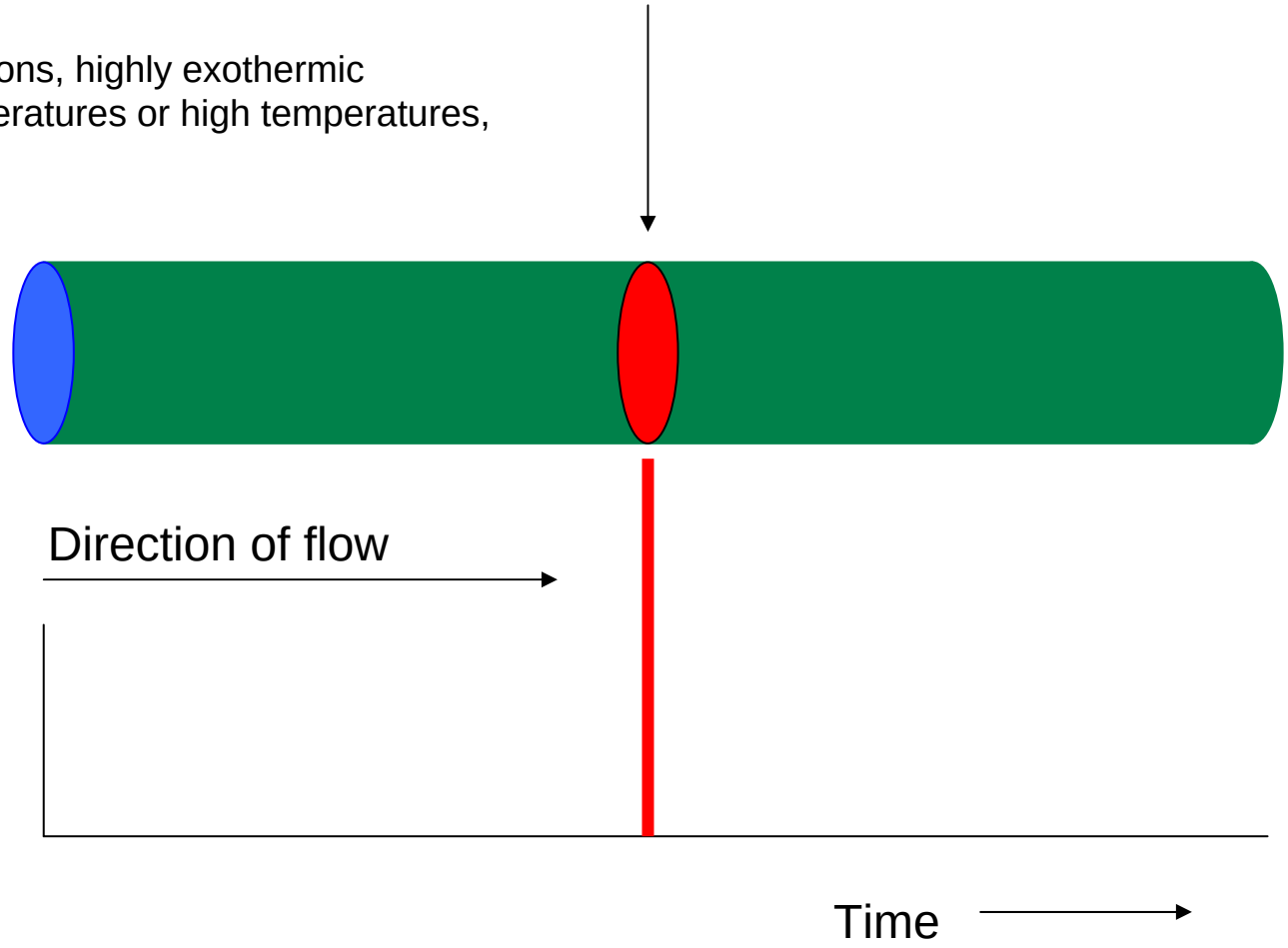
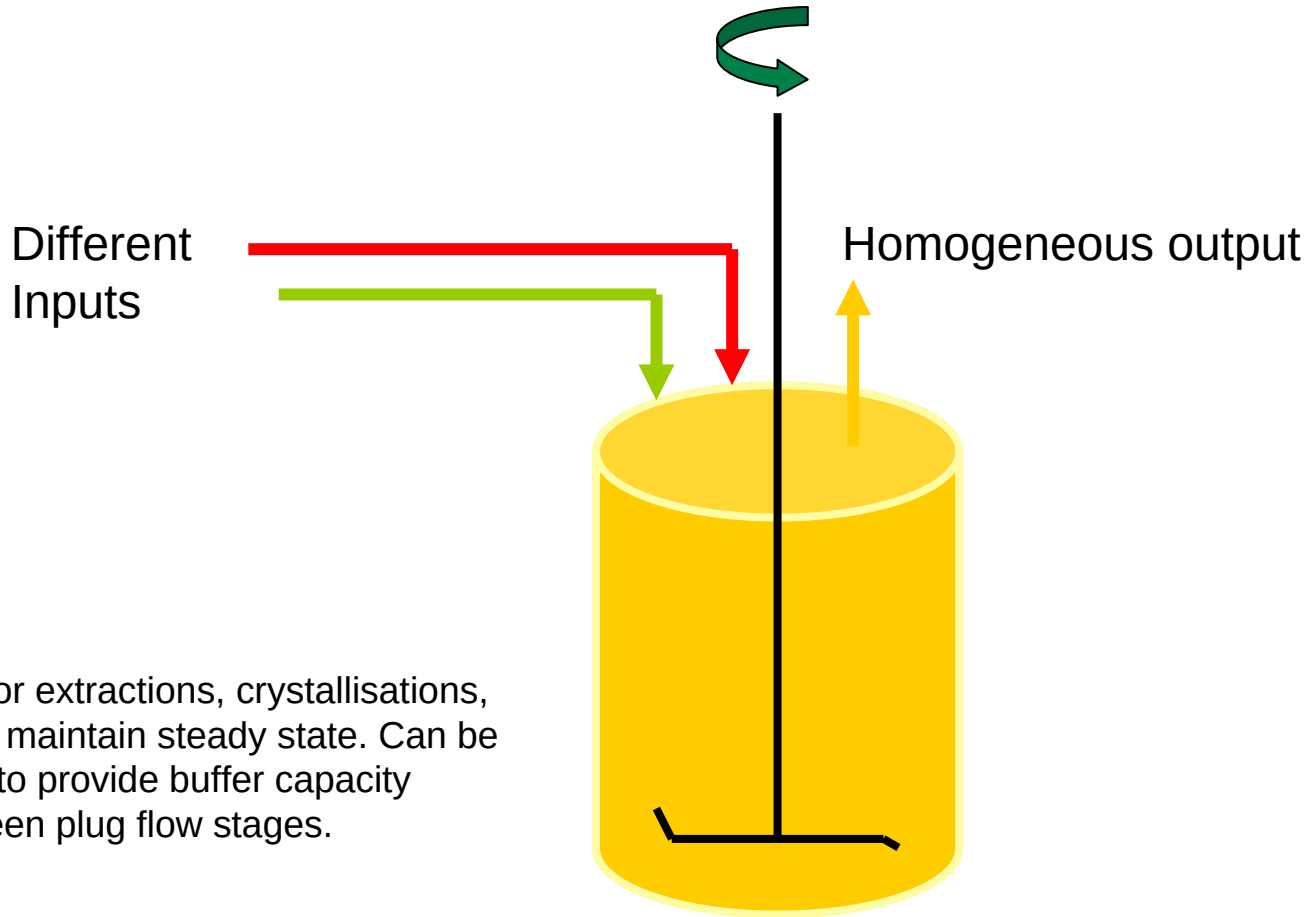
Idealised plug flow

Discrete slice of material with zero axial mixing and perfect radial mixing

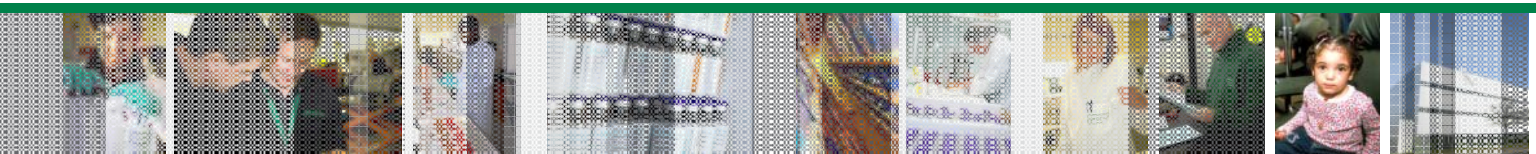
Use for faster reactions, highly exothermic reactions, low temperatures or high temperatures, high pressures



Idealised CSTR regime



Use for extractions, crystallisations, etc to maintain steady state. Can be used to provide buffer capacity between plug flow stages.



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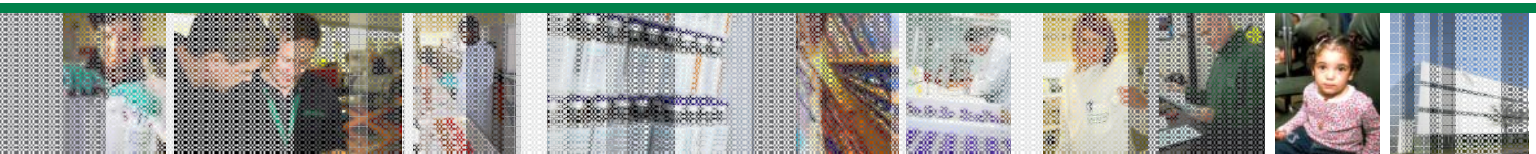
Flow regime characteristics

Plug flow

- Used for fast reactions, *etc.* Kinetic control predominates.
- Highly dynamic and responsive to change
- Susceptible to process “spikes”
- Needs PAT that is fast

CSTR behaviour

- Equilibrium (thermodynamic) control
- High buffering capacity and slow response time
- Insensitive to process “spikes”
- PAT needs to be stable



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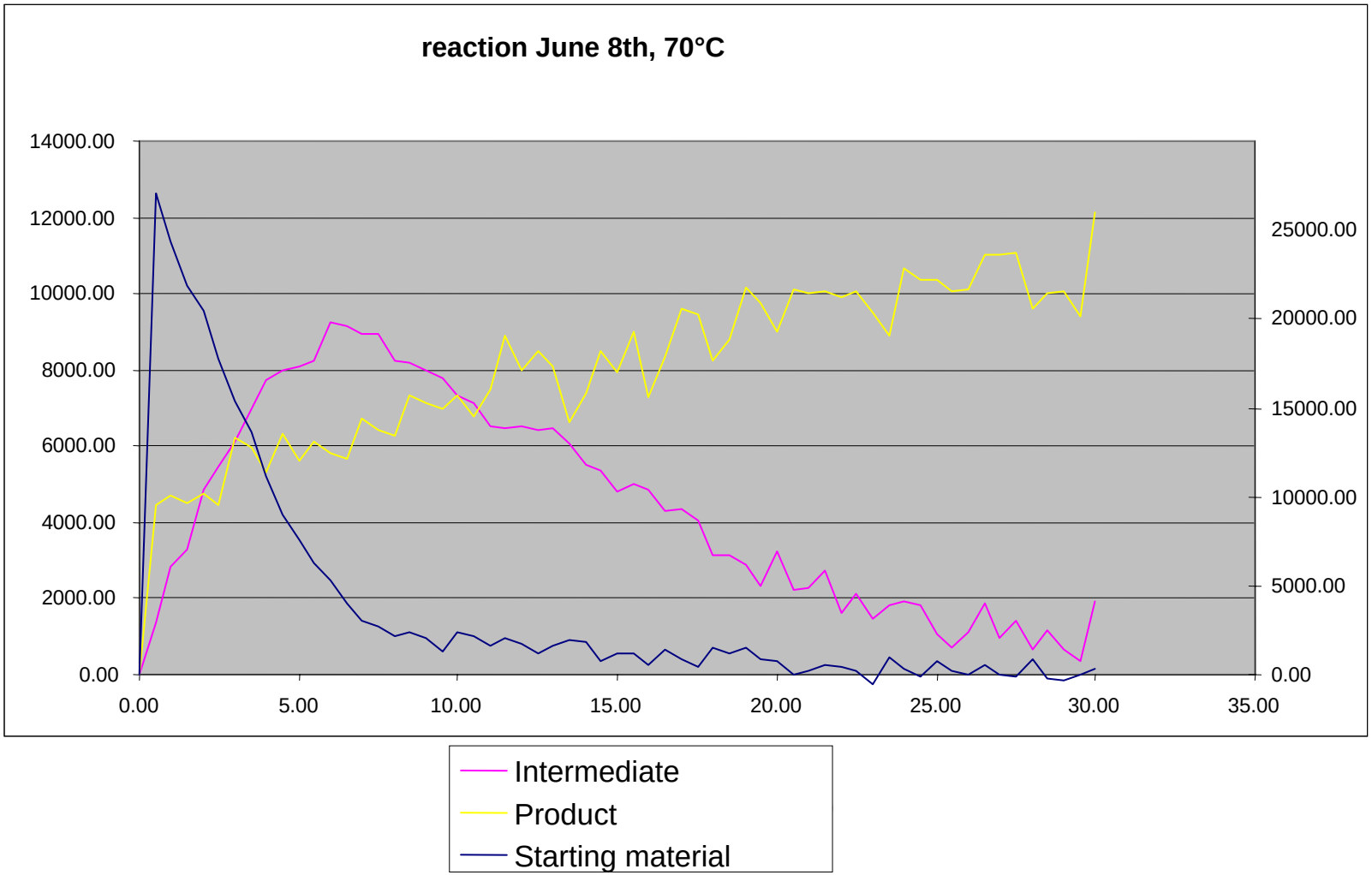
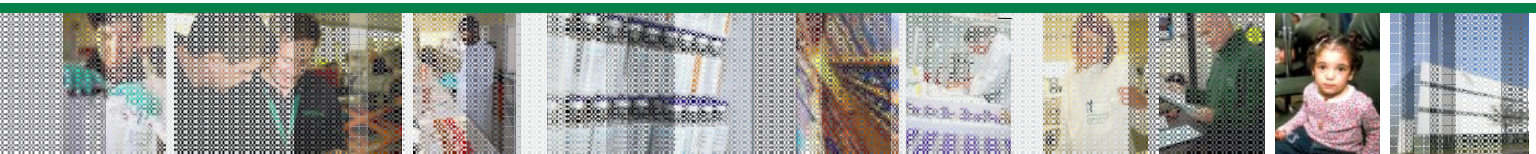
Process understanding is needed





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Perceived Obstacles for introduction of continuous processing into Pharmaceutical manufacturing

Needs new filing strategy

- QbD
- PAT
- Internal RA barriers
- FDA/EMA resistance

Existing installed capacity

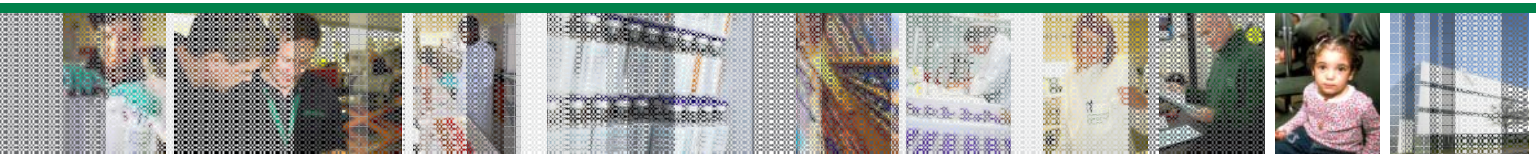
- Excess batch based capacity exists in many big pharma companies

Specialised or dedicated plant required

- Needs high levels of assurance of forecast accuracy for demand
- Not easily made multi-purpose
- Needs early investment in process engineering
- Turn down ratios need to meet demand
- Creates single points of failure

Plant becomes redundant at end of period of exclusivity

- High level of dedicated plant (not multi-purpose)



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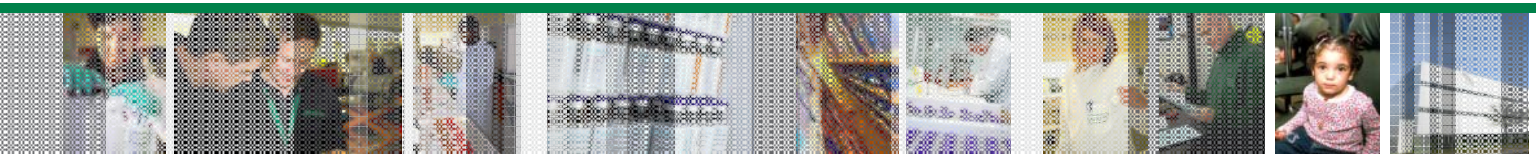
Benefits

- Accelerated development possibility
- Implicit QbD requirement
- Will require continuous verification (not validation)
- Reduced Capital Expenditure
- Faster build – possibly with disposables
- Smaller footprint
- Scale out/number up approach can address demand uncertainties
- Easily replicated in other plants
- Modular build possibilities
- Offers the possibility of continued lower cost manufacturing beyond loss of exclusivity
- Enable some high energy processes to be run safely
- Can limit inventory of highly toxic materials



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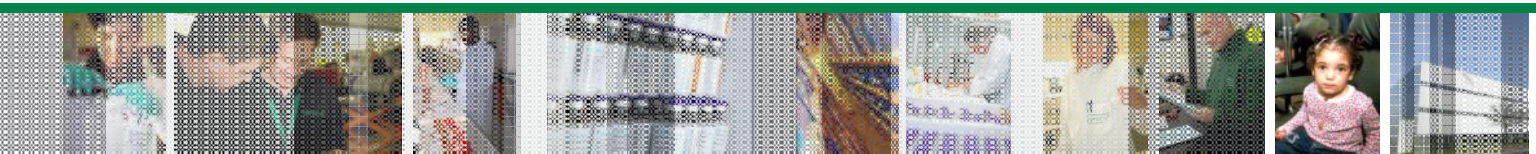
Validation

Continuous processing requires a move away from traditional three batch validation

- Continuous verification that the process is in control
- Control system requires validation, as does control philosophy

Aim to maintain steady state

- Demonstrate the control system's ability to respond to perturbations
- Have agreed way of dealing with discrepancies
  - Continue
  - Stop
  - Divert



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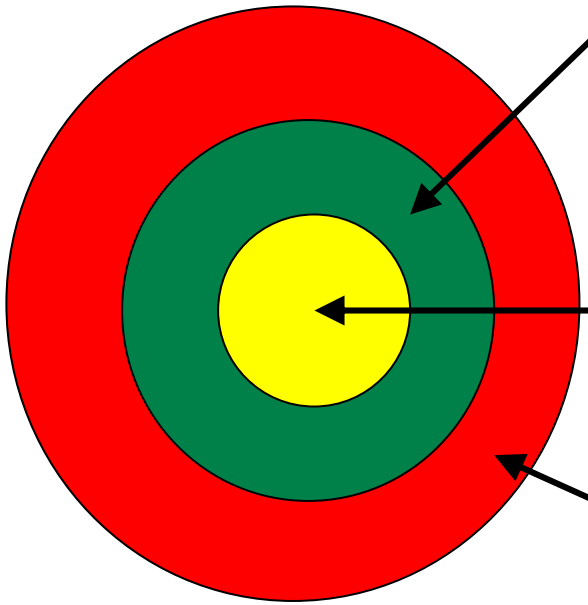
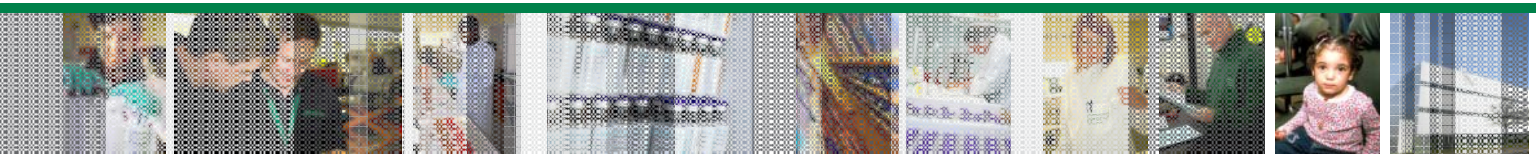
Design space and alerts/alarms



Design Space
Action alarm

Control space
(Set point range)
Out of trend alarm

Knowledge space
(or subset) Control
system takes over to
avoid regulatory
non-compliance



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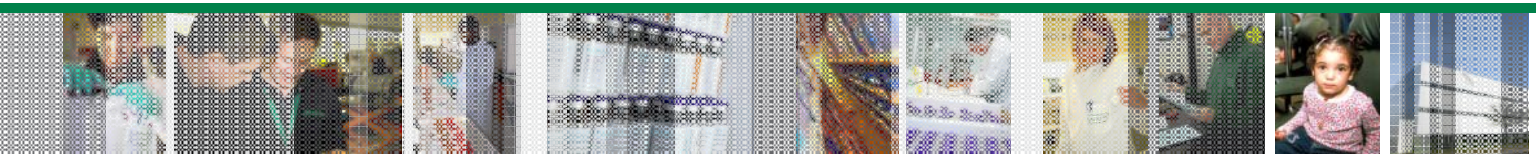
Deviations

Use risk assessment techniques prior to event if possible

Write regulatory filings carefully to avoid regulatory non compliance which would have no adverse patient affect

- Example:
  - A spray dryer indicates an outlet temperature of 123ºC for 1 minute 17 seconds. The NDA/MAA filings state that the product is dried below 110ºC. What do you do?

  - What temperature is the product?
  - Is primary drying over?
  - How long is the exposure?
  - What is the effect of the exposure?
  - Each particle is exposed for a very brief time – however long the excursion lasts.
  - When does a dryer ever show the actual product temperature?



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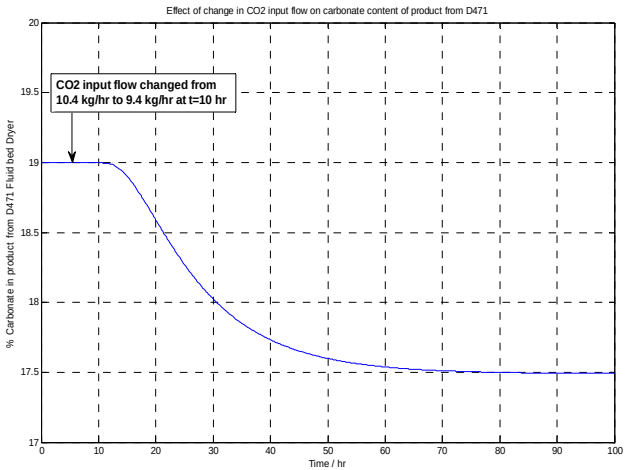
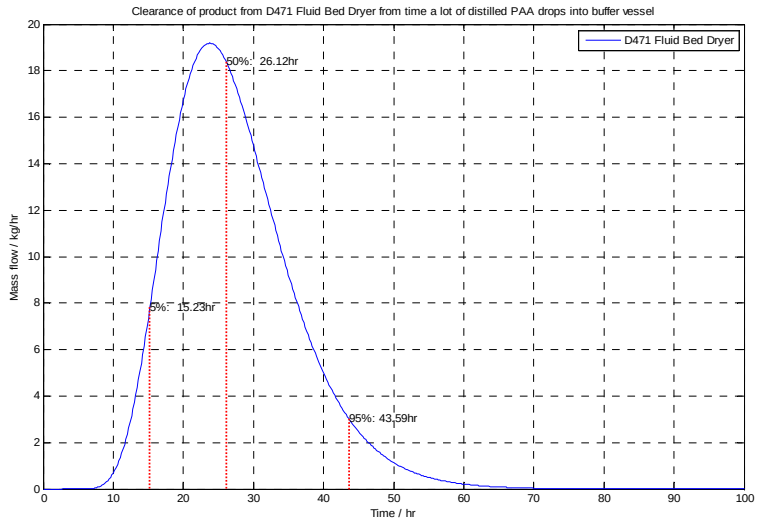
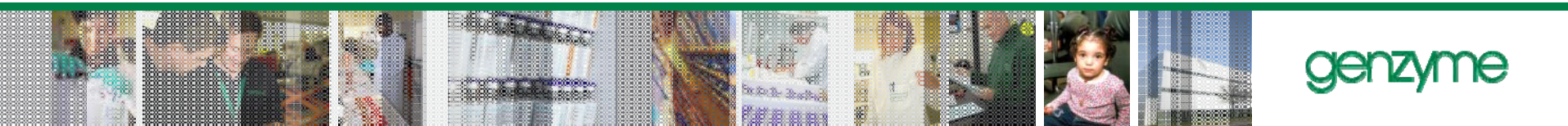
Coping with interruptions

- Almost impossible to detect change once product enters CSTR stage
- Need to wait for equilibrium to be attained before the process change is possibly identifiable
- Use development data to confirm that the new conditions have the effect that you anticipate



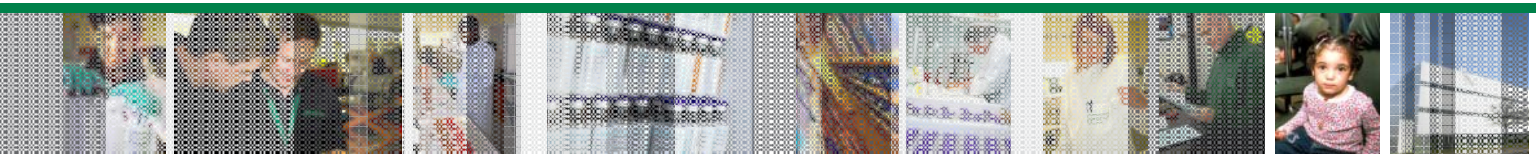




Batch size

Has caused more issues with inspectors and reviewers than any other aspects of continuous manufacturing

- One reviewer was adamant that continuous processing gives a product that is inherently less homogeneous than a batch……..
- Continuous processes can give batches that are defined by a period of time or a fixed quantity.
  - Why?
  - Recent FDA statements supporting continuous manufacturing suggest that a better definition would be to define a batch as lasting for as long as the process is producing material of consistent quality.



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Conclusions

There is a much greater awareness of the advantages of continuous manufacturing in pharmaceutical industry than five years ago

Full adoption is slow and tends to be for one reaction/purification operation at a time

Regulatory path forward is becoming clearer

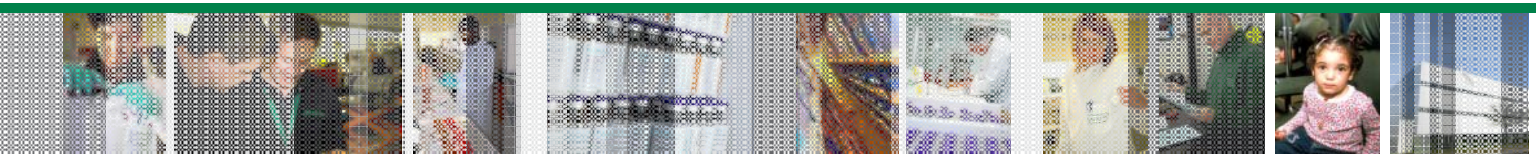
Real time and/or parametric release becoming more common

And next…….

Removal of traditional distinction between primary and secondary manufacture?

Biologics presents interesting challenges

Registration of a platform covering families of compounds for individualised therapy?



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Acknowledgements

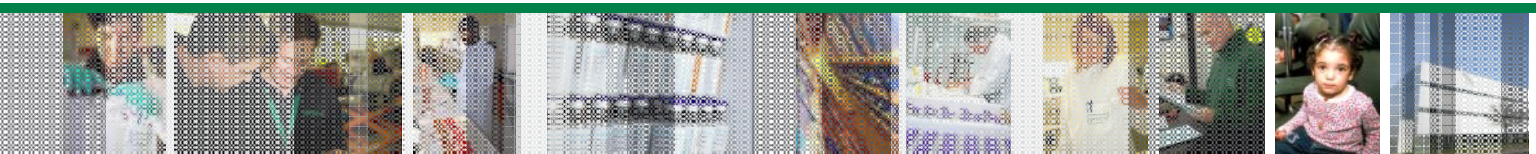
Many Genzyme colleagues over the last ten years, but especially:

Senior Management for believing we could make this happen.

Chemical Development, Haverhill

- Synthetic chemistry, analytical development, PAT group, process modelling, chemical engineering, automation
- Regulatory Affairs, US and UK
- MTS and Manufacturing Groups

And you for listening!



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