Approaches to regulatory engagement and filing for continuous manufacturing

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FDA-AIChE Workshop on Adopting Continuous Manufacturing, March 2016

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Disclosures

- The speaker is solely responsible for the content of this presentation unless otherwise acknowledged
- The views presented here do not necessarily represent the views of GSK

Acknowledgements

The following people contributed to the ideas expressed in this presentation

– Andy Scott, GSK

– Mike James, GSK

– Hannah Robinson, GSK

– Lindsay Wylie, GSK

– Matt Popkin, GSK

– Gurjit Bajwa, GSK

Continuous Technology Adoption

Continuous Manufacturing is gaining momentum...

API Continuous Manufacturing

NOVARTIS

Lilly

CONTINUS pharmaceuticals

BAYER

gsk

Pfizer

AstraZeneca

OSD Continuous Manufacturing

VERTEX

MERCK

Pfizer

GRANULES

Abbott
A Promise for Life

APRECIA PHARMACEUTICALS

CONTINUS pharmaceuticals

J&J

TEVA

NOVARTIS

Shasun

AUROBINDO
Committed to healthier life!

gsk

PAT and Real-time Release

(most companies use PAT but these ones stand-out in terms of application to continuous)

VERTEX

BAYER

Pfizer

gsk

Disclaimer: identification of company activity in continuous manufacturing has not been verified and is based on press releases and publications

Purpose of a File

Patient centric view...when doing something different it is good to get back to basics

New Drug Application (NDA)

The New Drug Application (NDA) is the vehicle through which drug sponsors formally propose that the FDA approve a new medicine in the U.S. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA.

The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:

- Whether the drug is safe and effective in its proposed use (as described in the label) and whether the benefits of the drug outweigh the risks.
- Whether the drug's proposed labelling (package insert) is appropriate, and what it should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/

Tiered Approach to Regulatory Engagement

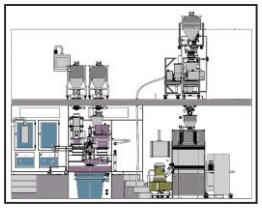
Ensure consistency of message

Industry

- MIT Conference 1
- 2015 DIA/AAPS CMC Workshop
- IFPAC 2014
- DIA 2015 51st Annual Meeting
- AIChE FDA -PD2M conference

Platform

- ISPE China Annual Spring Conference
- 50th AAPS Arden Conference
- QbD meeting at PMDA
- QbD Case Study Group meeting at PMDA
- Pharmaceutical Quality Forum
- INTERPHEX Japan
- APS Pharm Sci Conference, UK
- Invitations to regulators to GEMBA platforms



Project

- Initial FDA meeting
- FDA-ETT
- Direct regulatory engagement related to filing strategy

– Acknowledgements: Andy Scott and Mike James, GSK

Topics for Platform / Project Regulatory Engagement

Different levels of feedback from simple to more complex

Spectrum of regulatory feedback

Definitions

- Process Summary
- Equipment for Continuous Process
- Batch Definition
- Yield
- Raw Materials and Intermediates
- Traceability
- Specifications
- Comparability
- Process Validation/Verification
- Lifecycle Management

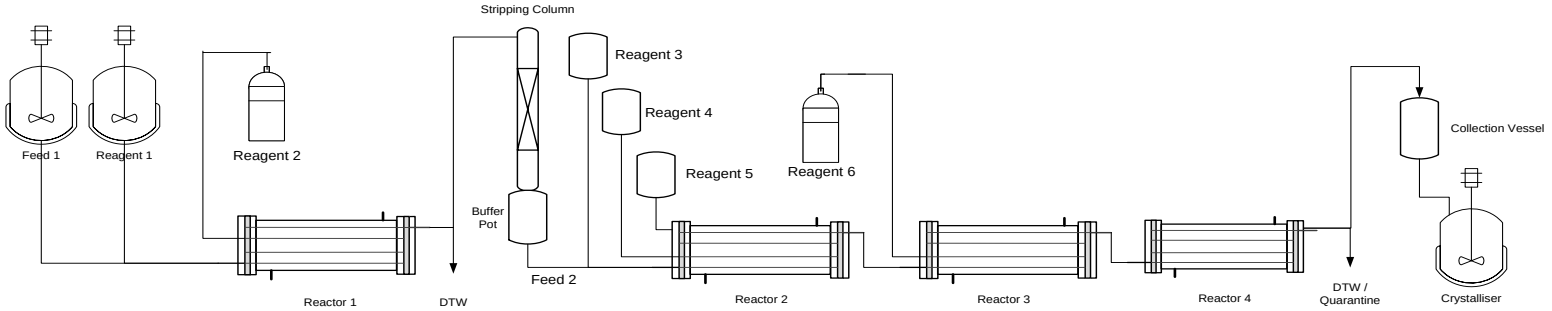
Clarifications

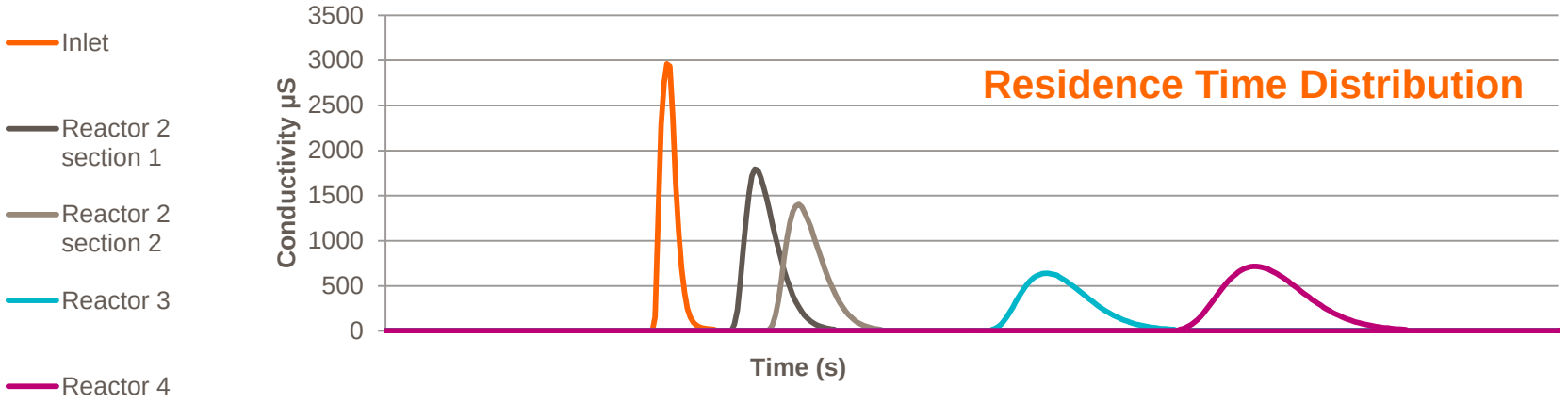
- Equipment Design
- Control System Interface
- Characterisation
- R&D Development Campaign
- Residence Times and Dispersion
- State of Control
- Product Collection or Rejection
- Process Monitoring (PAT) and Sampling
- Process Dynamics

Fundamental

- Deviation management
- Control Strategy
- State of Control

Equipment Characterisation

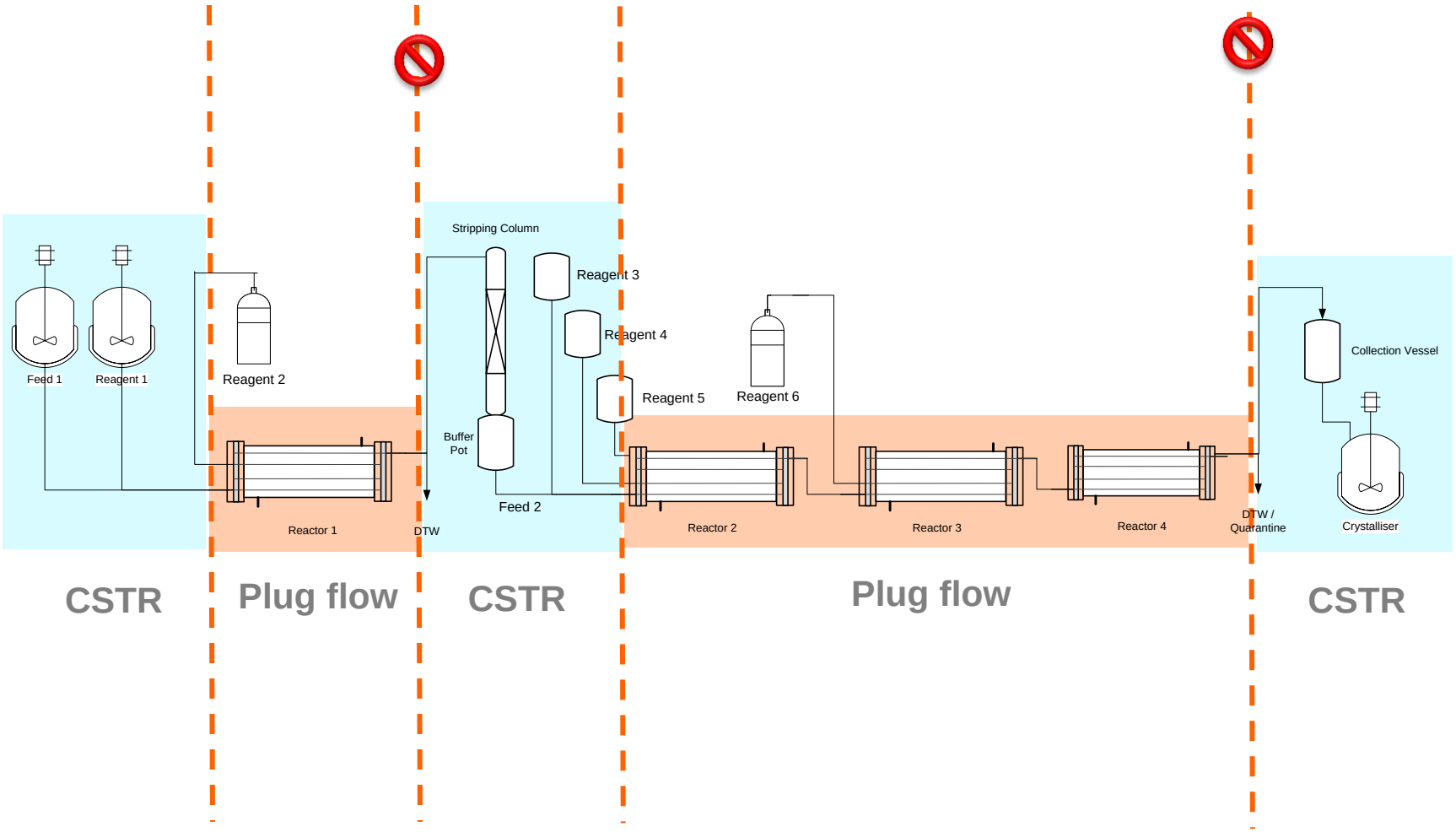




- Mixing intensity and Re
- Reactor volumes and surface area
- Heat transfer capability
- Residence time distribution

Acknowledgement: Hannah Robinson, GSK

Traceability in a Synthesis Flow Process



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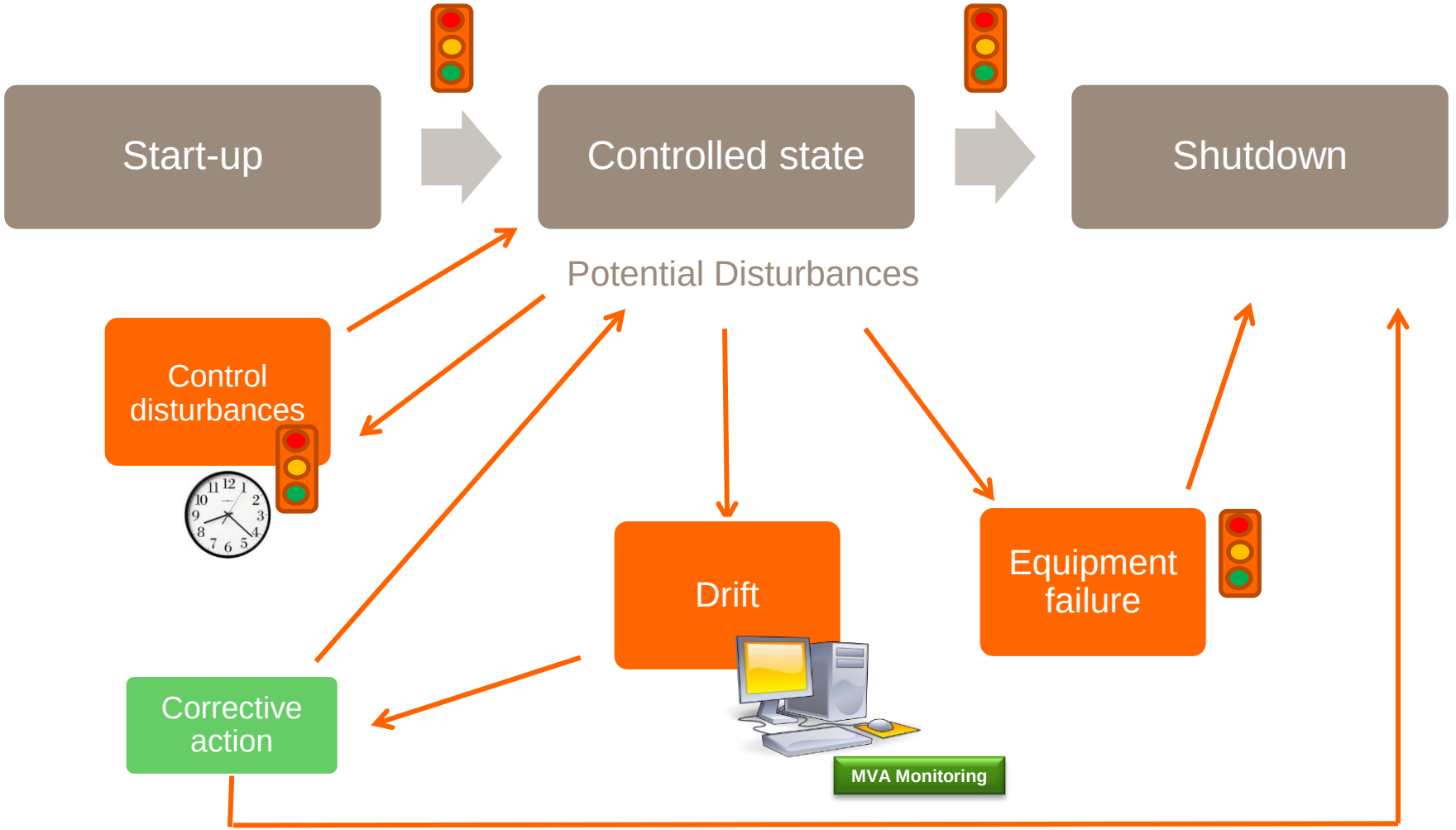
Control phases

How will disturbances be handled?



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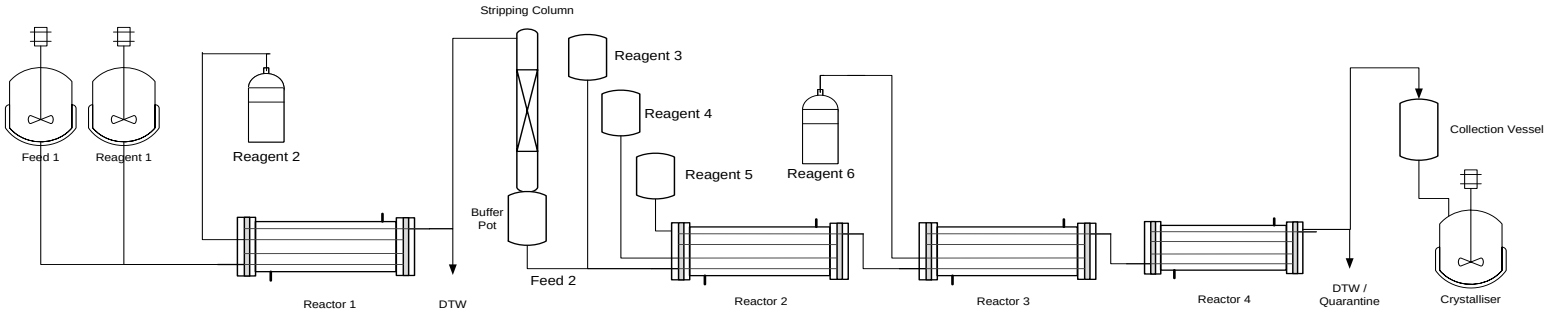
Some thoughts on Control Strategy

Deviations, process dynamics, control loops, consistent output



Deviations

- In both batch and continuous deviations need to be investigated and managed – challenge in continuous is that this will need to happen in real-time (at least for process deviations)

Process Dynamics and Control Loops

- "If the process control system is having to actively adjust process parameters to remain within design space or state of control, isn't that a sign of a non-robust process?"
- Reality is that pharma continuous processes will be better understood and controlled – mainly as disturbances related to changes in raw materials will be managed out through the control strategy and equipment configuration; e.g. loss in weight feeders will adjust rpm to deliver desired target throughput rate

Consistent Output

- Precision and accuracy
- Process parameter trends and MVA modelling can demonstrate "precision" – consistent output (whatever that may be)
- PAT enabled as a key component of the control strategy leading to RTRT

Moving from Engagement to Filing

Communication and knowledge management

- Important to link Industry and Platform level engagement to Project level engagement and filing.
- It is at the Project filing level that the fundamental debates need to crystallise unambiguously
- Most issues are around the Product Control Strategy, the role of end-product testing and practicalities of product release

“Tested and complies”

- Batch paradigm
- Assumes uniformity of product which relies on fully blended nature of a batch
- Straight forward to file
- Practically for a QP it is unambiguous and straight forward to release

“If tested will comply”

- Continuous paradigm
- Need to demonstrate uniformity of product and complies with specification
- Less clear how to file
- Need to clarify regulatory expectations of both assessment/review and inspection

Conclusions

Continuous Manufacturing is gaining momentum...

- Best practise is to create a framework for regulatory engagement that covers Industry, Platform and Project levels
- Need to actively manage the link between regulatory engagement and filing to drive consistency; early and continued dialogue with regulators is important
- The most important thing to crystallise is approach to Product Control Strategy and the shift in paradigm from “Tested and complies” to “If tested will comply”
- There shouldn't be any regulatory hurdles to implementation of CM; only points for clarification
- From industry perspective it is important to harmonisation of regulatory, filing and inspection approach