International Symposium on
Continuous Manufacturing of Pharmaceuticals
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White Paper # 1

Achieving Continuous Manufacturing: Technologies and Approaches for Synthesis, Work-Up and Isolation of Drug Substance

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Session #1 structure

Panelists:

Ian R. Baxendale (Durham, UK),
Alastair J. Florence (CMAC, Strathclyde UK),
Klavs F. Jensen (MIT, US),
Martin D Johnson (Eli Lilly, US),
Paul Sharratt (ICES, Singapore),
Jon-Paul Sherlock (AZ, UK)

Agenda:

• Introduction:	A. Florence	20min	(9:15-9:35pm)
• Open discussion:	All	45 min	(9:35-10:20pm)
• Closing remarks:	A. Florence	10min	(10:20-10:30pm)

- Break
- Seated for next session by 11am

White Paper #1: Contributors

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Consultants / Reviewers:

Philip Dell'Orco, (GSK, US); Ian Houson, (CMAC, UK); Jim Cashman, (Eli Lilly S.A. Irish Branch, Kinsale); Zoltan Nagy, (CMAC, UK/Purdue University US); Tim Jamison, (MIT, US) and Brian Glennon (UCD, Ireland).

Welcome inputs to final whitepaper during and after symposium!

White Paper #1: Contents

Abstract

Introduction

1. Reactions: The wider adoption of continuous flow strategies in pharma

- **1.1 Flow chemistry equipment (*types and principles*)**
- **1.2 Translation of flow protocols from the laboratory bench to the plant (*Hit – Candidate; Clinical Development; Manufacturing*)**
- **1.3 Reaction classes (*where can benefits be obtained*)**

2. Workup and Isolation *(technologies and challenges, particle control)*

3. Quality Assurance and Control (*challenges and needs*)

4. Safety (benefits and new concerns)

5. People Skills and Culture (*intellectual and structural needs*)

6. Conclusion / Recommendations

Key Points

- Synthesis
  - Flow chemistry capability developing; access broad chemical space; enhance selectivity – consider downstream
  - Integrate multiple steps – balancing kinetics and flows
  - Need for rapid development / understanding – when/how to deploy?
  - Achieve economic, consistent and scalable supply
  - Multipurpose or custom plant
- Work-Up and Isolation
  - Selective chemistries can help simplify
  - Solid/liquid separations are challenging
  - Particle attributes currently key link between substance and product
  - Improved / alternative purification techniques – avoid particles?

Key Points

- Quality Assurance & Control
  - Operation in controlled state (vs theoretical steady state)
  - Opportunity to exploit automation
  - Need for plantwide control expertise
  - Implement PAT to remove need for offline testing
  - Challenges for modelling/simulation e.g. process effect on attributes
- Safety
  - Benefits clear e.g. reduced inventories; headspace removal; containment
  - Pumps / material transfer methods become key - pressure and pressure relief
  - MoC – corrosion testing
  - Fouling, encrustation, blockage will occur

Key Points

- People, Skills & Culture
  - Move beyond ‘hand-over’ between chemists and engineers
  - Analysts and chemometrics
  - Chemistry, engineering and analytics convergence
  - Lack of experience of new processes/technologies a barrier – training
  - Needs senior level support to ensure continuous considered at right time

Discussion Points

- Estimates 40% of existing batch chemistries could benefit from flow (more can be delivered in flow)
  - Is this right; how to maximise?
- Need to build evidence base
  - Share practical knowledge & demonstration of more examples
- Progress on capabilities
  - Training and equipment – what / how?
  - DoE and automation – are capabilities there?
  - Modelling, PAT, analytics, control, other?
- How to achieve consensus?