2016 International Symposium on Continuous Manufacturing of Pharmaceuticals
Massachusetts Institute of Technology
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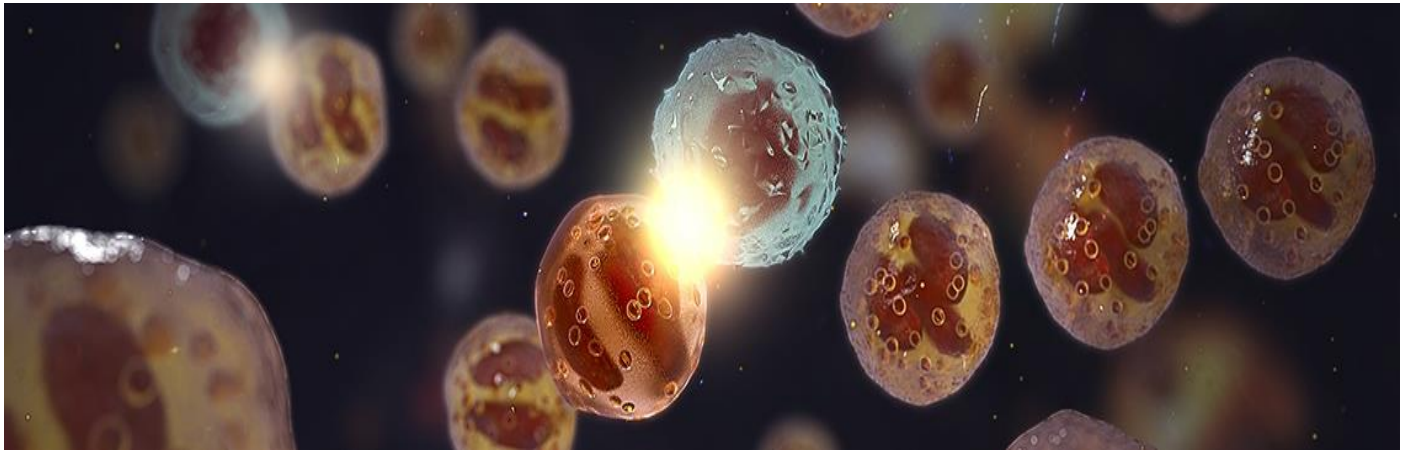
AstraZeneca

New Technology Session 1: Small Molecules Technologies

Philip Shering (AZ) Mark Buswell (GSK) Joel Hawkins (Pfizer)

Commentaries on New Technologies Presentations



Commentators and Commentary Themes

Philip Shering

AZ Global Engineering

Leading AZ Small Molecule Factory of the Future initiative

Industrial Chair for CMAC Technical Committee

Mark Buswell

Joel Hawkins

Pfizer Worldwide R&D

- *Pathways to Industrialisation*
- *Keep It Simple*
- *Chemical, Technical and Business Drivers*

Commentary

Pathways to Industrialisation

- How Flow Chemistry is Changing Small Molecule Manufacturing by Expanding the Reaction Toolbox – Aaron Beeler, PhD, Boston University
  - Great examples of “beautiful” chemistry, “forbidden” chemistry - Doing this in Conti is the best way and in AZ we are beginning to do so….research helps us find shorter more efficient routes etc
  - Still many issues as we scale up. When does Conti become unsafe? What then? How do we manage everything else – storage, leaks, accumulation, abnormal events
  - we need more examples @ relevant scales, we need to *make it real* – address the practicalities of implementing in industry. Want to support development chemists and engineers by having decision trees and workflows in place
  - Opportunity to work closer with academia - building in Pharma (and other chemical) industry knowledge and expertise in assessing and managing risks and other manufacturing issues, – make research more relevant

- Status of and Challenges in End-to-End Synthesis of APIs – Klavs Jensen, PhD, MIT
  - AZ approach is to go into flow where there are clearly identified benefits, then stay in flow until batch is better again. Driving towards end-to-end makes things more complex, expensive, difficult to control – with more difficult experimental work to satisfy regulator
  - Robust continuous separation remains a challenge – do you need to do it in conti? Automation and control in end-to-end, yes we can do it but it may take years. How to qualify, validate?
  - How do we make end-to-end a practicality? We want our Control Strategies to be equipment independent – to make TT easier and so regulators can understand. Can we achieve end-to-end with truly independent simple, simple to control modules?

Commentary

Pathways to Industrialisation

- Continuous Crystallisation in Pharmaceutical Manufacturing – Allan Myerson, PhD, MIT
  - AZ is interested in continuous crystallisation - manufacturability problems often related to (variability in) physical properties.
  - barriers to implementation – are these barriers even higher than presented? 20g of material might come from 2-3 early development batches (potentially with different synthesis routes) - What are the technologies that reduce the barriers ie less material, shorten development time, fewer experiments?
  - if we want to exploit the recycling technologies - we need to be convinced that they work. What is the impact of degradation when we are keeping things hot for a lot longer, impurity levels are changing, how much more time/characterisation/material will we require?
  - To enable us to exploit these new technologies – we want to see them work. We need to *make it real* – case studies with real APIs that address concerns and deliver demonstrated benefits

- Innovation in Continuous Filtration, Drying and Formulation of Drugs – Salvatore Mascia, PhD, CONTINUUS
  - Improvements and advances in isolation and drying technologies great to see
  - Need to continue development addressing scale up challenges, and have good rationale to decide whether to isolate and dry in continuous
  - Need to understand limitations of equipment, develop beyond prototypes – get to a position where integrated solutions are available to pharma manufacturers – I want to know how to select a piece of equipment, then be able to buy a package.

New Technology Session 1: Small Molecules Technologies

Commentary
Mark Buswell

Commentary

Keep it simple

- How Flow Chemistry is Changing Small Molecule Manufacturing by Expanding the Reaction Toolbox – Aaron Beeler, PhD, Boston University
  - Within GSK flow chemistry is starting to be seen as the technology of choice for fast explosive cryogenic chemistries but the broader tool-box reality still doesn't yet match the potential
  - Key to changing this is accessibility of standard robust flow chemistry equipment at lab scale that is "walk-up" and that has a clear pathway to industrial scale-up and commercial supply
- Status of and Challenges in End-to-End Synthesis of APIs – Klavs Jensen, PhD, MIT
  - GSK are very aligned with concept of modular plant - library of unit operations that can be assembled in a standard architecture
  - Recent experience of scaling up a continuous 3 stage synthesis was that actually the chemistry aspects of the process worked very well – right first time; it was the more physical engineering aspects that have caused some teething problems
- Continuous Crystallisation in Pharmaceutical Manufacturing – Allan Myerson, PhD, MIT
  - Really struggling to pursue continuous crystallisation – as of today GSK do not have a single continuous crystallisation step in active development
  - Not sure trying to produce "traditional" crystalline API continuously is worth pursuing
- Innovation in Continuous Filtration, Drying and Formulation of Drugs – Salvatore Mascia, PhD, CONTINUUS
  - Agree it is time for a re-think around isolation methods related to novel drug product intermediates

Chemical, Technical, and Business Drivers for Flow Chemistry and Continuous Processing

Joel M. Hawkins
Pfizer Worldwide R&D

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Chemical and Technical Drivers	Corresponding Business Drivers
1) Inherently burdensome operations • Gas liquid-solid high pressure chemistry – packed bed columns with high local catalyst loadings, P, and T • Gas-liquid high pressure chemistry – bubble columns	• Simplify operation – especially reactor cleaning and catalyst loading which can be done in parallel off line • Minimize equipment size and cost with low pressurized volumes • Minimize infrastructure costs for safe operation • Hydrogenations common
2) Smaller and more flexible production equipment • Modularize wrt sets of components • Walk in hoods with modules ventilated or N_2 purged based on component needs • Segregate bulk volumes	• Minimize technology transfers by developing and manufacturing on the same or similar equipment, especially for new smaller volume drugs • Minimize plant size and cost • Flexible production scale and plant location to meet business needs

Chemical and Technical Drivers	Corresponding Business Drivers
3) Continuous crystallization, isolation, and drying	• "Dial in" and maintain crystal size, distribution, shape, and polymorph • Especially for APIs – facilitate formulation (including continuous formulation) • Quality from precision and control
4) Continuous reaction monitoring with feedback control	Product quality • Target control with operational simplicity

Chemical and Technical Drivers	Corresponding Business Drivers
5) Streamline workups and telescope reactions • Design chemistry to be simple by minimizing reaction components and byproducts, e.g. by flowing through heterogeneous catalysts or simple thermal processes	Streamline processes by minimizing the total number of unit operations • Link robust steps
6) Continuous extractions	• More efficient • Link continuous steps • Improve downstream crystallizations • Optimize with extraction screening and modeling • Increase throughput in batch processes by using continuous extraction and separation between tanks

Chemical and Technical Drivers	Corresponding Business Drivers
7) Fast mixing with excellent heat transfer • Maintain reagent stoichiometries • Run -78 °C chemistry at -20 °C	Avoid cryogenic tanks • Pump control critical • Avoid extreme scaling out of microreactors
8) Important niche chemistry • Hazardous batch chemistry – flowed only after full hazard review by safety experts • Well controlled high temperature reactions – alternative to microwaves • Photochemistry – especially visible light photocatalysis	Enable shorter synthetic routes by expanding chemical space • Will grow out of Med Chem – need co-discovery with early process