Session II: Top Challenges Faced in Industry based Focus Groups

AIChE FDA Workshop on Adopting Continuous Manufacturing

Topic 2: Applicability of Continuous Manufacuring to a Diverse Pharmaceutical Portfolio

What is a diverse pharmaceutical portfolio?

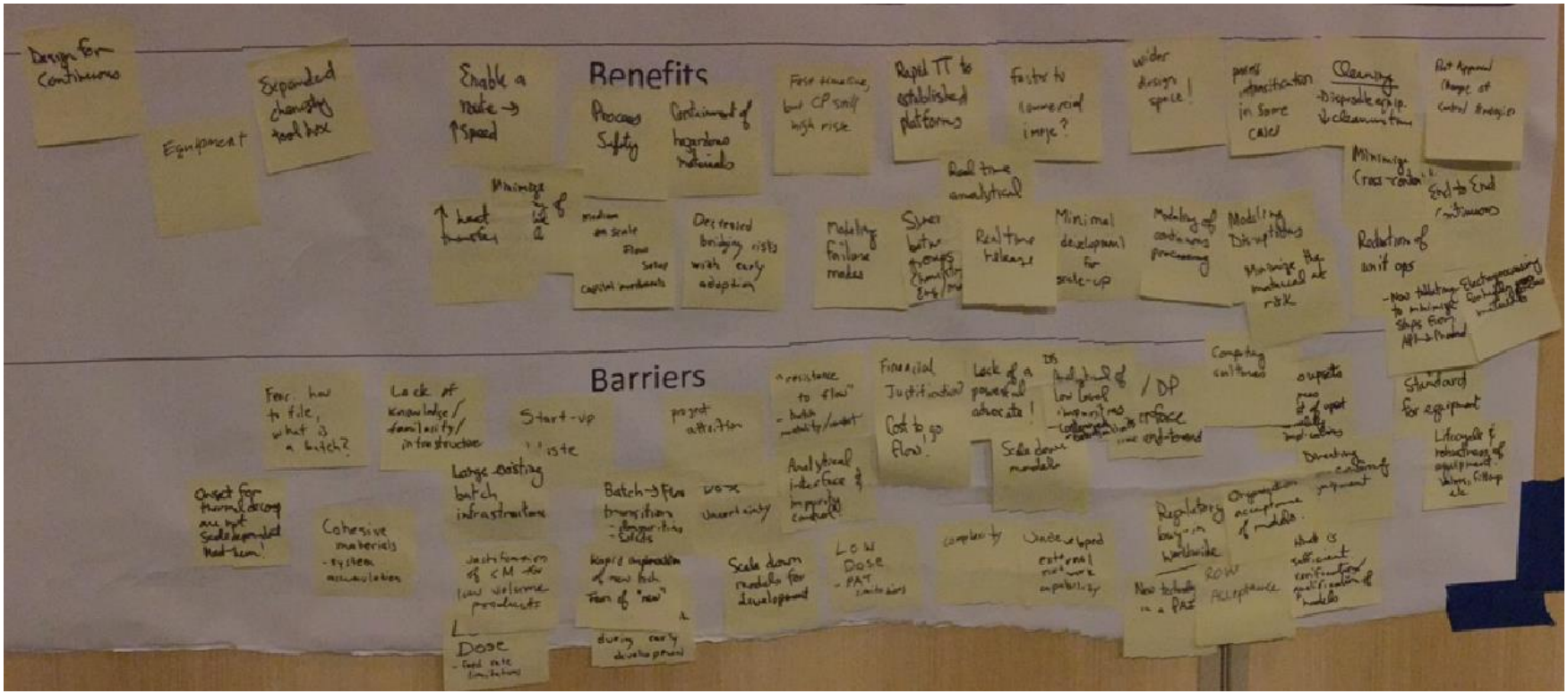
Drug Substance

- Therapeutic area
- Phase of Development
- Production volume
- Containment & potency
- Project timelines and acceleration (breakthrough status)
- Molecular complexity
- Variety of reagents / transformations
- Complex control strategy
- Rate of reaction
- Solid state form
- Physicochemical properties
- Bulk/powder properties

Drug Product

- Therapeutic area
- Phase of Development
- Production volume
- Containment & potency
- Project timelines and acceleration (breakthrough status)
- Route of administration
- Dosage forms / release profiles
- Unit dose strengths
- Manufacturing platform
- Combination products

What are the benefits & barriers of implementation of continuous processing?



Benefits

	DS	DP
Development Efficiency		
Design for continuous early	X	X
Expanded chemistry tool box	X	
Speed to delivery	X	X
Tech transfer to established platforms	*X*	*X*
Faster to commercial image		X
Decrease bridging risks with early adoption	X	X
Minimal development for scale up	X	X
Synergy between disciplines	X	X
Process Safety		
Increased heat transfer	X	
Reduce inventory of energetic material	X	
Containment of hazardous materials	X	X
Minimize material in general	X	X

	DS	DP
Improved Control / Quality Assurance		
Real time analytical	X	X
Real time release	?	X
Reduction of unit operations	X	X
New tableting to minimize steps from API to finished product		X
Modeling of continuous processes	X	X
Modeling process disruptions	X	X
Minimize cross contamination	X	
Minimize unit operations	X	X
Manufacturing Efficiency		
Post approval change control strategies	X	X
Disposable equipment	X	
Reduce cycle time	X	X
Process intensification	X	X
Wider design space	X	X
mInimize material at risk	X	X
end to end CM	X	X
Supply Chain		
Minimize inventory	X	X
Speed	X	X

Barriers

	DS	DP
Lack of experience & uncertainty		
Resistance to doing something new	X	X
Competing cultures	X	X
Project attrition	X	X
Dose uncertaintly		X
Uncertainty in peak volume	X	
Containment level	X	X
Process validation strategies	X	X
Organizational acceptance of models	X	X
Control / Quality Assurance		
Complex control strategy	X	X
Cohesive materials. System accumulation	X	X
Start up waste	X	X
Diverting non conforming material	X	X
Analytical detection of low level impurities	X	
Traceability	X	X
Lifecycle of equipment	X	X

	DS	DP
Business Challenges		
What is the cost to go continuous?	X	X
Lack of infrastructure	X	X
Large existing batch infrastructure	X	X
Justifications for CM of low volume products	X	X
Underdeveloped external network	X	X
Lack of a powerful advocate	X	X
Multiple dev and manuf sites	X	X
Technical Challenges		
Feed rate limitations for low dose compunds		X
Lack of scale down models for development	X	X
Solids dosing for DS	X	
DS / DP interface for end to end CM	X	X
Molecular Complexity	X	
Underdeveloped external network	X	X

	DS	DP
Regulatory		
Regulatory buy in world wide	X	X
New technology in PAI	X	X
Fear of how to file what is a batch	X	X
What is sufficient verification / qualification for models	X	X

Major Discussion Themes

- Supply Chain Assurance
- CM implementation earlier in development
- Business case for CM
- Is end-to-end CM realistic?

Supply Chain Assurance

- Potential benefits include speed, flexibility, portability and inventory control.
- Barriers discussed included:
  - CMO capabilities for CM
  - Equipment lifecycle / Robustness
  - Internal capacity and equipment limitations

CM implementation earlier in development

- Benefits included reduced parallel efforts, avoid bridging concerns, consistent impurity control strategies and speed.
- Barriers
  - Lack of alignment at the interfaces. Requires education and improved interactions between disciplines.
  - Material availability. *Do more with less! Requires better scale down equipment and predictive models.*
  - Project timelines and uncertainty

Business case for CM

- Barriers:
  - Lack of detailed ROI analysis for demonstrated CM processes in pharma.
  - There are many publications on general economic advantages, but these lack the detail required to justify a real decision.
  - Sensitivity to publishing development costs.
  - Difficult to quantify many advertised CM advantages.
    - Value of improved quality assurance?

Opportunities

- Shared knowledge on defining the material properties that impact DP CM.
  - Many companies have individual efforts here.
  - Improved understanding could lead to earlier adoption, faster development and better process control.
- Push for publications on actual CM experiences.
  - True economic benefits, business cases, payback period, CapEx requirements, etc.
  - Examples of other CM advantages such as tech transfer, and improved QA.