Fall 11-4-2015

Transforming the present into the future with uncertainty and imprecision

Chales Cooney
Department of Chemical Engineering, MIT, ccooney@mit.edu

Transforming the Present into the Future with Uncertainty and Imprecision

Charles L. Cooney

Robert T. Haslam (1911) Professor of Chemical and Biochemical Engineering, Emeritus

MIT, Cambridge, MA

Integrated Continuous Biomanufacturing II
Berkeley, CA
November 4 2015

Massachusetts Institute of Technology

Opening Questions to ICB II

- Will ICB meet are future needs?
- How good does it need to be?
- Are we at a tipping point?
- Is ICB *game changing* in pharmaceutical manufacturing?
- **Where do we want to go, why and how?**

Integrated Continuous Bioprocessing
a starting point

- We are here as *believers* in ICB but we need to understand why we should invest
- We all have similar and different reasons to pursue ICB
- We all bring a disability to the table
- The number of symposia attests to expanding interest, BUT how will that translate to action?
- As I have listened to the presentations and discussion in the hallway, what have I heard?
- I will try to place ICB into context with the issues in the industry and the needs of the firms

The **GOAL** of pharmaceutical manufacturing is the **sustained delivery** of a **quality product** (safe and efficacious) to the **patient**

Technology provides the tools that can tactically be deployed to help us get there (cost, productivity, quality, etc.)

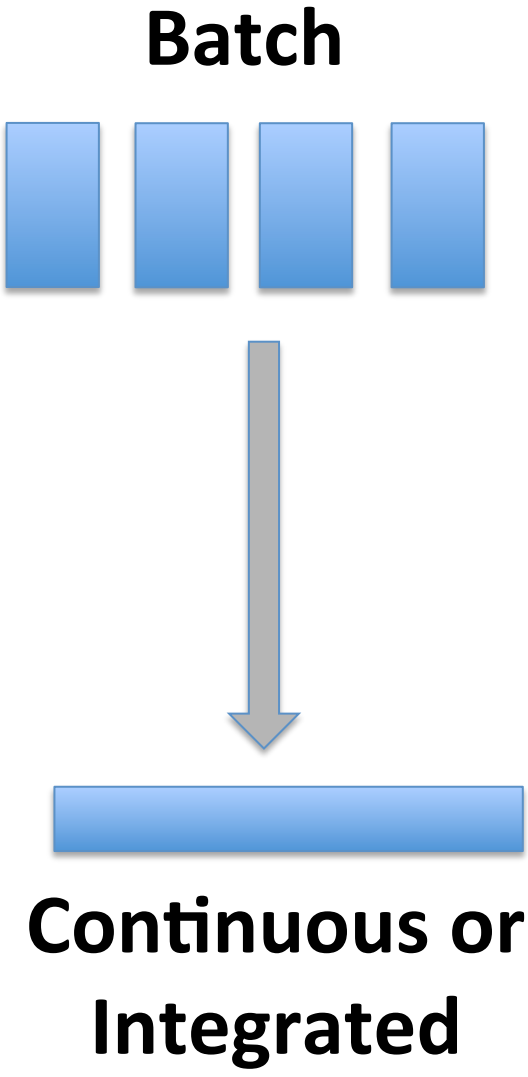
Emerging Issues in Pharmaceutical Industry

- Diverse portfolio of biological products
- Uncertain regulatory outcome on novel therapies
- Expanding markets with demand uncertainty
  - New and small indications – Precision Medicine
  - New and large indications – Access to Medicine
- Redefining the *blockbuster* drug
- Changing structure of the industry
- Tension on pricing and capital constraints

Issues drive opportunity while barriers constrain it

Historical Perspective to Meet Product Demand – *Industrial Evolution*

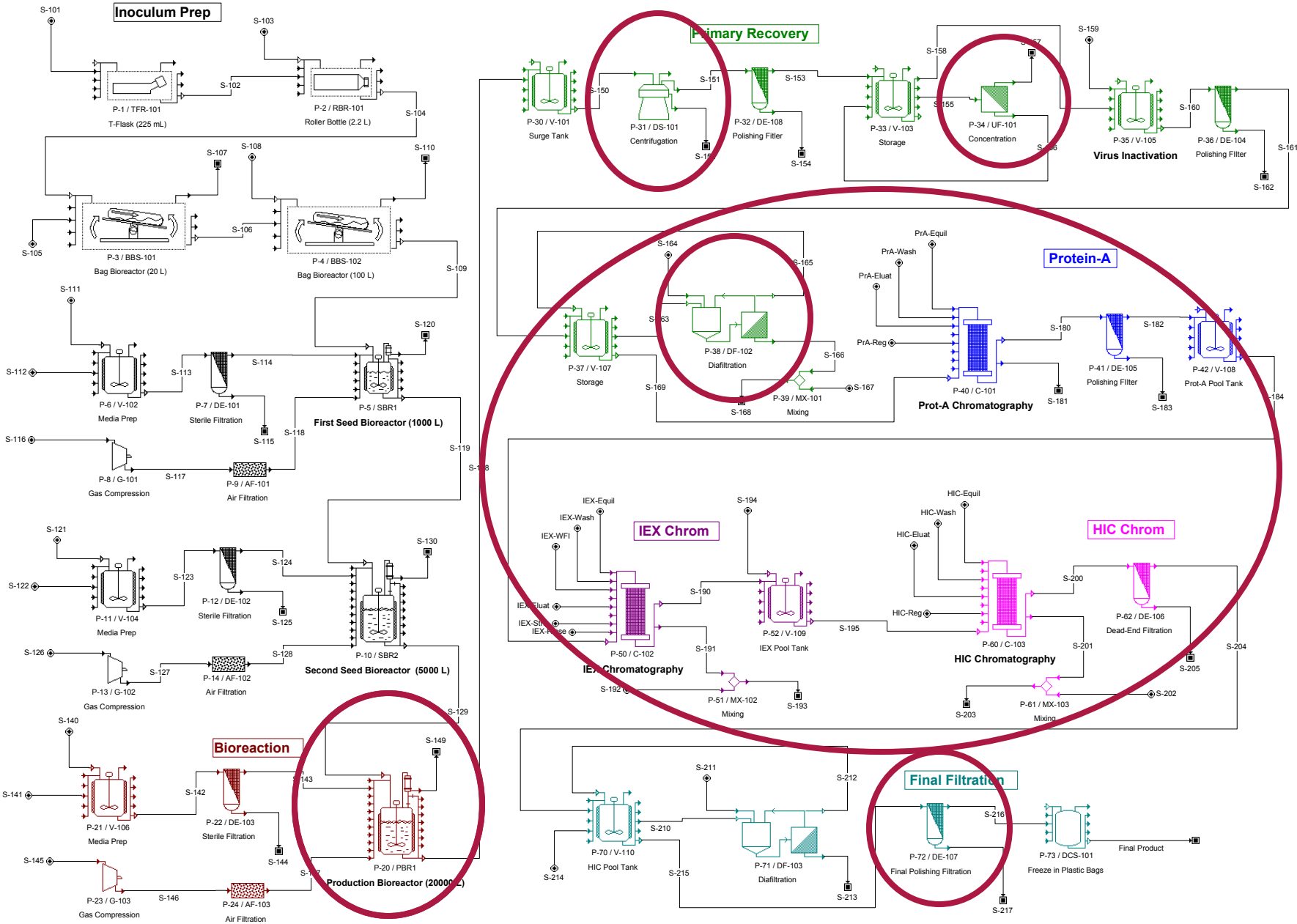
- **Industrial Intensification**
  - Steel
  - Chemicals
  - Food
  - Pharmaceuticals
- **Driven by need to**
  - Reduce cost
  - Meet market demand
  - Decentralize manufacturing
  - Assure robust quality
  - Create flexibility



Continuous Biomanufacturing is Not New

- Continuous culture – 1950's
- Continuous extraction of penicillin 1950's
- Continuous chromatography 1950-60's
- Fed-batch & repeated withdrawal for penicillin production (aka Perfusion) 1960's
- Tangential flow filtration 1960's
- Continuous crystallization for AA's – 1960's
- Continuous brewing from the 1890's

Batch Manufacturing is by Choice



What I heard this week

Through an Upstream Process Lens

- **Upstream Process**
  - Robust product quality thru tighter control of chemistry and time in perfusion culture
  - High cell density and productivity = lower CapX & OpX
  - Single use technology
  - Low cost media ←→ Perfusion Culture
  - Pipeline (expanded, diverse, uncertain) requires flexibility in technology and facility
  - The Biogen Challenge: get 4X capacity from platform

What I heard this week

Through a Downstream Process Lens

- **Downstream Process**
  - Retention system is the interface - flexibility
  - Retain the DSP architecture and convert to flow through and no pooling
    - Multicolumn chromatography opens up capacity
    - SPTFF
    - Continuous viral inactivation
  - Consider alternatives: Precipitation, Extraction, Crystallization
  - *Functionally* closed systems
  - Single use technology
  - Control of fluid management
  - In-line and at-line sensors and automation

What I heard this week

Through a business lens

- Flexibility/Agility to meet uncertain demand
  - New diverse products
  - New markets
- Cost effective ability to meet future needs
- Optimize present & future capability and capacity
- Improving Speed to Clinic and Market
- Real time assurance of Product Quality
- Regulatory clarity
- Dominant design & standards in the ICB toolkit

What I heard this week
Through a Regulatory Lens

- First approval of product by continuous manufacturing
- ICB as an "evolution not a revolution"
- 15 years of Initiatives to improve & clarify approval
  - QbD and PAT enable and support transition to ICB
- Goal to align field operations with the Center
- Seek international collaboration on harmonization
- Establishment of the Office of Product Quality
- Recognition of enabling new technology
  - Emerging Technology Team
  - Encouragement of precompetitive collaboration
  - Challenges to traditional regulation by RTR, QMS, automation, scaling in time, etc.

What I heard this week

Why is ICB emerging now?

Evolution in Technology

- Cell retention
- Cellular productivity
- Media development
- MAB platform
- Multicolumn Chrom.
- SPTFF
- Single Use Technology
- Analytics and Automation
- Closed systems

Emerging Business Case

- Enabling
- Specialized & Potent molecules
- Reduce cost
- Enhance supply
- Improve productivity
- Assure quality
- Increase flexibility
- Addressing the Pharma Industry issues

What I heard this week

Barriers & Challenges

- Regulatory uncertainty
  - Little experience with innovative technologies
  - Perception of regulatory constraints (self inflicted wounds)
- Market uncertainty for new products
- Complex product and thus process portfolios
- Geographically diverse markets
- Lack of experience with new technologies
- Managing breakthrough and orphan designation
- Organization – development, operation and quality

How are we doing?

Implications of ICB
Are we ready?

- Operating in a new ecosystem
  - New dependencies on materials, suppliers and collaborators
  - Closer relationship with regulators
- Flexibility to address uncertainty in markets, products, technology – are the physical and human assets in place?
- Is your QMS appropriate and enabled?
- Do you have a culture receptive to innovation and change with an appetite for risk?
- Can you translate continuous units to processes?
- Utilization of legacy assets?

Call to Action!

- The goal is about Supply and Quality
  - Central to dispersed supply chains
  - Analytical support of quality
- Process intensification is a strategy and tactics are technology
- Improve current (incremental), develop new (radical) and employ hybrid processes
- Collaboration to sustain innovation
- Remove USP and DSP from vocabulary - it is ICB
- Break down traditional interfaces: physical, organizational, disciplinary

How are we doing?

- Excited by what is being accomplished
- Fearful that it will take too long
- Saddened that it has taken so long