The Promise of Continuous Biomanufacturing

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Agenda

- Integrated continuous bioprocessing
- Opportunities
  - Upstream
  - Downstream
- Current results with non-MAb and MAb
- Considerations about
  - Quality
  - Facilities
  - Culture
- Where are we going?
What to expect in the next 25 years?
Janet Woodcock, Director CDER, FDA (AAPS meeting, 2011)

Formative trend #1 (out of 5):
“Right now, manufacturing experts from the 1950s would easily recognize the manufacturing processes of today ... That will change in the next 25 years as current manufacturing practices are abandoned in favor of cleaner, flexible, more efficient continuous manufacturing”

“The biopharmaceutical industry is ready for dramatic innovations, said Barry Buckland, former head of bioprocessing at Merck”

“With Continuous Operations, Can Drug Manufacturing Become a Rock Star? Pharma QbD
23 November 2010. By Paul Thomas, Senior Editor
Note: This is the fourth of four posts related to a continuous manufacturing symposium held at AAPS 2010 last week.”
What is continuous?

Continuous unit operation

- Defined in respect to its downstream unit operation
- N supplies N+1 so that N+1 can work uninterrupted 24/7
- Zero or minimal buffer capacity between N and N+1
- Runs at steady state over extended periods of time

*Note: Continuous liquid flow is not required*

A continuous process is composed of only continuous unit operations
From Traditional to Integrated Continuous Bioprocessing

Current technology: fed-batch or perfusion

New platform

- Efficiency
- Simplicity
- Flexibility
- Quality
- Cost
- Facility
- Mobility
- Standardization

Small footprint

Multi-product facility
From different platforms …

to standardized biomanufacturing solutions
The evolution to continuous processing

- **Photo film**: Batch to Continuous, 1890s
- **Petrol**: Batch to Continuous, 1920-40s
- **Steel casting**: Batch to Continuous, 1950-60s
- **Plate glass**: Batch to Continuous, 1950-60s
- **Food**: Batch to Continuous, 1950-80s
- **Wood pulp**: Batch to Continuous, 1970s
- **Chemical**: Batch to Continuous, ongoing
- **Pharmaceutical**: Batch to Continuous, ongoing

“Non-assembled” product industries

Emergence of the “dominant” design
How does the transition usually happen?

Initial batch process composed of multiple batch unit operations

Some unit operations converted into continuous

Several batch unit operations integrated into a single continuous unit operation

The entire process may be converted into a single continuous unit operation

“Dominant” process architecture attributes
- Stepwise performance improvement
- Lower complexity and number of unit ops

Business impact

Time

Steel Industry

Actual data

[Graph showing time vs. business impact for the Steel Industry]
Think continuous, think small

Batch technology

Equipment / facility Size

10kL  2kL  500L  SUB  <2L Disposable

10kL  2kL  500L SUB <2L Disposable
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Progress in fed-batch process titer over the years

Fed-batch titer increase over the years

Profiles of fed-batch & continuous process

- Fed-batch titers improving over >30 years
- Continuous MAb technology less mature
- Batch and perfusion measure success differently - titer and VPR. Need both

Kindly provided by Prof. Matt Croughan, Keck Graduate Institute
High density perfusion cell culture

Suspended perfusion process with cell density control

Steady state

Steady state = Constant cell density + Constant perfusion rate

Xv

bleed

keep

Xv set point

time

Steady state = Constant cell density + Constant perfusion rate
Very high cell densities are achievable using perfusion technology

- 60-80e6 cells/mL
- No cell density control

Recent results with CHO cells

- Long-term operation at 100-200e6 cells/mL
- Theoretical maximum of 250e6 cells/mL

Monitoring and Control of the Physiological State of Cell Cultures, K. Konstantinov, B&B, 1996

Véronique Chotteau, et al. KTH, Royal Institute of Technology, School of Biotechnology, Stockholm, Sweden, IBC, Boston, Sep 16-19, 2013
Key process variables driving OPEX

*Directional comparison of fed-batch & continuous for MAb*

**BioSolve modeling of CAPEX and OPEX for enzyme and MAb**

- Major CAPEX advantages for enzyme and MAb
- Major OPEX advantages for enzyme
- Current OPEX for Mab slightly better for fed-batch (MAb perfusion still immature)
- Major intangibles not included in modeling (standardization, scale up, transfer)

**Strategic OPEX reduction directions for MAb**

- High cell density, low perfusion rate (≥50% of fed-batch titer)
- Further decrease in medium cost
Achieving long-term stable process at ultra low CSPR: History captured in T-shirts

1998

... and a few years later

... and a few more years later

... and there is no END, as the upward potential is tremendous

CSPR unit change: from $nL$ to $pL$

Next T-shirt:
Long-term stable process at $12.5pL/c-d$
The rate of evolution is highest in the interfacial areas

*Disruptive innovation happens most often at the areas of intersection of different disciplines*

*Clayton Christensen*
Continuous chromatography capture step (Periodic Countercurrent Chromatography – PCC)

Benefits over batch chromatography

- Facility footprint
- No harvest & clarification tanks
- Buffer & resin usage

- Increase productivity (g/L resin-day)
- Dramatically smaller columns (up to 100 fold)
- Fully automatic operation (ΔUV PAT)
Other compatible purification technologies

Annular chromatography

Stationary

Column Rotation Direction

Eluent & Feed Distribution system

Separated Products

Lab system

Continuous Countercurrent Tangential Chromatography system, Chromatan, Inc.

More DSP options
- Crystallization
- Precipitation
- Membrane adsorption
- Single-pass filtration
- ATPS
- Continuous viral reduction
- Others

G. Jagschies, IBC, Boston, Sept 16-19, 2013

High performance counter current chromatography (HPCCC). Liquid-liquid separation
Purification opportunities for non-MAB & MAb

Likely to include novel continuous unit operations

- Platform non-MAb process
- 3 chromatography steps
- Affinity capture step
- Fully continuous, no hold tanks
- Closed system

- Disposable components, incl. columns
- Ultra low cycle times (hours to DS)
- Small footprint
- Automated, PAT
- Steady state, overall yield ≥80%
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Integrated continuous bioprocessing architecture: Applications with a MAb & an enzyme
Non-MAb production in 12L bioreactors & integrated PCC
Long-term continuous CHO cell culture

- Dramatic improvement achieved with non-MAb protein
- Robust performance of the integrated continuous system
- Results beyond our most enthusiastic expectation
Mab production in 12L bioreactors & integrated PCC
High cell density results in increased productivity

Cell density (Aber capacitance probe)

MAb volumetric production rate

Increased MAb Productivity at Higher Cell Density
Is fully continuous biomanufacturing achievable?

“End to end” Fully Continuous PoC with Mab

From media to purified drug in 22hrs (12hrs Upstream + 10hrs Downstream)
Process and CQA’s in 30-day of Continuous Operation

- Chromatographic profile of Protein A column
- Chromatographic profile of Capto S column
- Chromatographic profile of Q membrane

Reducing SDS-PAGE of the DS lots produced at various time points

- No time based decline in the chromatographic profiles
- CQA’s meet specifications over run period

Critical Quality Attributes over the time course of the run

- Protein Concentration (mg/mL)
- Aggregation (%)
- Potency (comparable to control)
- Residual Protein A (ng/mg)
- HCP (ng/mg)
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Continuous processing guidance: Listening to FDA feedback

- No major regulatory hurdles for implementing continuous manufacturing
- Supportive to the implementation of continuous manufacturing using a science and risk-based approaches
  - Steady state operation – a key advantage (consistent quality, reduced heterogeneity)
  - Lessons learned by small molecule/Pharma to be applied by Biotech
Batch production of complex, less-stable proteins is often impossible.

Changes in MAb product quality over the course of fed-batch culture is reported in the literature.

In most cases, clinical impact of is considered insignificant, while others are not well understood.
AA-Labeled Oligosaccharide Profiling in non-MAb Production
Vision of Future Biomanufacturing Facility

Benefits

- Flexibility (protein, demand)
- Multi product/purpose
- Disposables
- Cost efficient
- Footprint
- Transportable
- Tech transfer
- Scale up
A few thoughts on the issue of simplicity & complexity

COMPLEX
A few thoughts on the issue of simplicity & complexity
• “The continuous process will only interest a very limited part of steel industry”

• “Continuous casting would remain a wild dream”

• “This is very interesting academically, but do not waste your time”

• As soon as the first complications cropped up, skeptics never had any trouble reciting reasons why the new process was doomed to failure

• A pioneer supporter: “Stick to your guns, continuous casting will become a world business”. That was during those weeks of 1957 when the majority of our board of directors got cold feet and resigned in panic

• It is amazing to think how long it took to accept this important technological revolution

• 20 years later a previously resistant steelmaker was producing millions tons of steel, relying 100% on continuous technology

• When we succeeded, lots of specialists were quick to declare “I told you so!”

• Even the “doubting Thomases” were forced to admit that the traditional “safe route” no longer had any chance to survive in international competition

• … the record speaks for itself: Though in 1958 only 1 million tons was cast … by 1995 the figure was 620 million tons, or 80% of the worldwide production!
The Promise of Continuous Biomanufacturing: Goals and technology (what & how)

**Goals (what)**
- Cell density: 150e6 c/mL
- CSPR: 10pL/c-d
- Titer: ≥2g/L
- VPR: ≥4g/L-d
- Affinity capture
- 3-step purification platform (any protein)
- Yields: ≥80%

**Enabling technology (how)**
- Closed
- Steady state
- High product consistency
- Disposable
- Portable
- Ultra low cycle times (hours to DS)
- Low footprint
- Standardized, platformized
- Automated, PAT
- Low OPEX/CAPEX

Left to your creativity, vision and courage to change the industry.