The Potential for Continuous Manufacturing in the Plasma Products Industry

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Plasma Product Biotechnology Conference 2015 - Sardinia

Outline:

- What is Continuous Manufacturing (CM)?
- Regulatory Acceptance
- Review of industry trends
- Change drivers
- Potential for Plasma Industry
  - Process model case example: Industrial scale IVIG
- Technology challenges
- Vision for the future

Definitions of Batch and Continuous

- Batch Processing
  - Process is in a dynamic state from start to end of a unit operation
  - Inter and intra batch unit operations are segmented
    - Discrete material transfers
    - Product testing holds
    - CIPs and manual cleaning
    - Labour intensive setup and turnaround
- Continuous processing
  - Process is in a steady state within each unit operation
  - Integrated processing (unit operations not segmented)
    - Direct and continuous material movement
    - Highly automated process with inline real time testing (PAT)

Regulatory Acceptance?

- FDA actively supporting the industry shift to CM
  - Funding CM research at the University of Washington since 2008
  - Initiated and co-chaired CM conference in-conjunction with MIT in 2013
  - CM consistent with FDA guidelines towards QbD & PAT
    - Improves assurance of homogeneity and quality
    - Real time monitoring and adjustments of quality attributes and parameters
  - Existing codes support CM
    - Lot defined by mass, volume or time (21CFR210.3 & ICH10)
    - Laboratory determination of final specifications for release (21CFR 211.165(a))
    - Documentation of Manufacturing (21CFR 211.188)
- **There are no regulatory barriers to CM, only lack of experience**

Chatterjee, S (FDA Lead for QbD). “FDA Perspective on continuous manufacturing”, IFPAC Annual Meeting, 2012
Alinaghian, L., Ates, A., Bititci, U., Harrington, T.S., Srai, J.S., Talati, R. 2012. Drivers and Barriers of Continuous Manufacturing in the Pharmaceutical Industry. 16th Annual Cambridge International Manufacturing Symposium

Change Drivers

- Relentless drive to improve quality
  - CM is the ultimate goal of QbD & PAT philosophy
  - Lot to lot variation
- Improve capabilities to meet global demand: Security of supply
  - Increase production volumes
    - Ageing existing markets, Growing clinical applications, Emerging markets
  - Pressure to decrease manufacturing costs to maintain profits while decreasing unit price to market
    - Significant unmet needs in less wealthy nations
    - Increasing R&D costs
    - Increasing energy, labour and consumable costs
    - Gov’t and patients demanding cheaper products

Occurring Pharmaceutical Industry trend

(Bio)pharmaceutical Company	Continuous (bio)manufacturing	Remark
Pfizer ☑	Continuous Processing in Pharmaceutical Manufacturing new manufacturing technology of continuous processing involving chemistry in a pipe and continuous extraction (implemented at Pfitzer, Ireland 2009)	Matthew J. Mollan Jr., Ph.D. and Mayur Lodaya, Ph.D., Pfizer Inc.
Roche/Genentech ☑	Continuous wet granulation process using QbD and PAT presented in December 2012 during PDA/EMA conference	Martin Wunderlich
GSK ☑	IChemE 2012 Award: fully integrated and closely controlled tablet production process	Cooperation with Siemens, GEA, Sagentia and academia
Novartis/Sandoz ☑	10-year study MIT-Novartis cooperation on small molecule, pilot plant in headquarter started, 5-10 years forecast to convert all Novartis production sites	Bernard Trout
Sanofi/Genzyme ☑	Continuous manufacturing will be presented during BPI europe in 2013	K. Konstantinov
Merck Serono ☑	Pilot study for conti downstream presented in BPI Europe meeting Feb 2013	Norbert Rasenack, Thomas Linden

Slide from: Daszkowski , T (Bayer Technology Services) presentation “ Continuous Processing in Biotech Production”, 2013

Bio-pharma industry already utilising CM

Current adoption in bio-pharma

Type	# of Facilities
Semi-Continuous	9
Continuous	1

Amgen opens $200M continuous purification plant in Singapore

November 20, 2014 | By Eric Palmer

Amgen CEO Robert Bradway hinted several years ago that the company was on the "cusp" of a new manufacturing process for making cell-based drugs that would upend the industry, being faster and cheaper. Today, Amgen ($AMGN) said that time has arrived, with completion in Singapore of a $200 million plant that incorporates continuous processing.

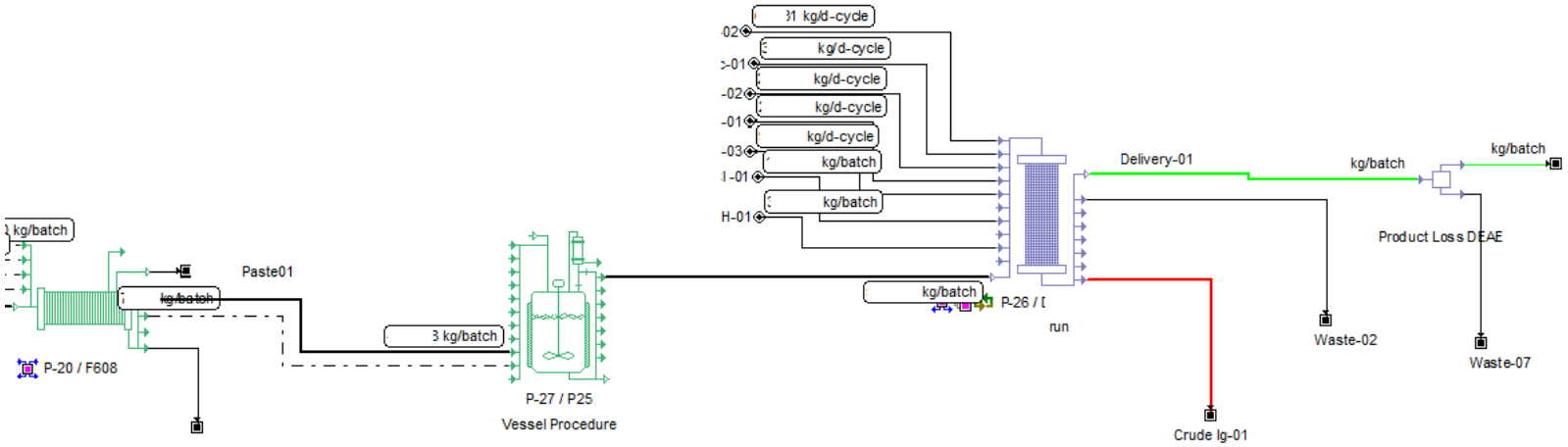
The Thousand Oaks, CA-based biotech said the plant in Tuas uses single-use bioreactors, disposable plastic containers, continuous purification processing and real-time quality analysis for monoclonal antibody manufacturing. Started in early 2013, it was built in less than two years, about half the time it would have taken to build a conventional manufacturing plant. It also will have the same capacity as a conventional plant but occupy a single building. It will use less water and less energy while producing fewer solid wastes and fewer emissions.

"At Amgen, we are reinventing what it means to manufacture biologic medicines," Bradway said today in a statement.

http://www.fiercepharmamanufacturing.com/story/amgen-opens-200m-continuous-purification-plant-singapore/2014-11-20

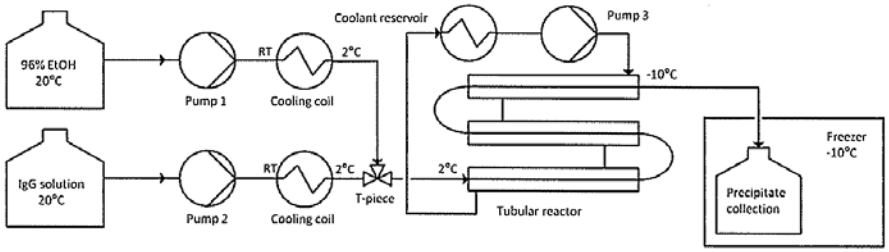
Case examples: Intragam®P Process

- Unit selection to replace established processes
- Process modelling evaluation of:
  - Batch (Base case)
  - Semi-continuous (single process step continuous)
  - Continuous process (fully integrated CM)



Process Unit selection:

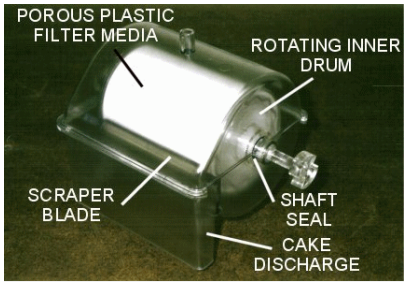
- Cold ethanol precipitation separation
  - Continuous precipitation in tubular reactors feeding either;
    - Continuous centrifugation
    - Belt filters
    - Rotating drum or disc filters
- In-line mixing of product and buffers
  - GE Healthcare: Straight-through processing (STP)

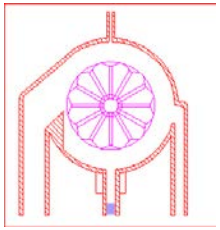


Hammerschmidt, et al. **Continuous precipitation of IgG from CHO cell culture supernatant in a tubular reactor**. *Biotechnology Journal*, 2015

http://www.gelifesciences.co.jp/products/bioprocess/pdf/29013303ab.pdf

http://www.bhs-sonthofen.de/en/products/filtration-technology/indexing-belt-filter.html





http://www.steadfastequipment.com/rotops.htm

Process Unit selection:

- Single pass tangential flow filtration (SPTFF) systems for continuous ultrafiltration and diafiltration

- Continuous chromatography
  - Novasep: BioSC®
  - Tarpon: BioSMB™
  - GE Healthcare: Periodic Counter-Current chromatography (PCC) system
  - Continuous counter-current tangential chromatography (CCTC)

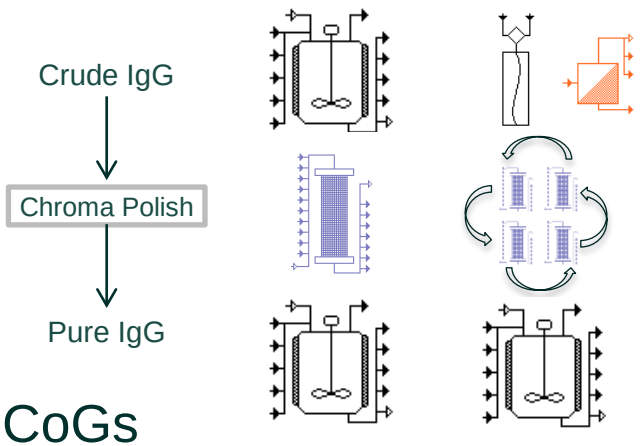
- Virus inactivation
  - Nano-filtration
  - UV radiation (eg: UVivatec®)
  - Low pH in-line conditioning
  - Single pass high temp pasteurisation

http://microsite.sartorius.com/en/uvivatec/models-features.html

Potential of Single process unit replacement: Semi-Continuous

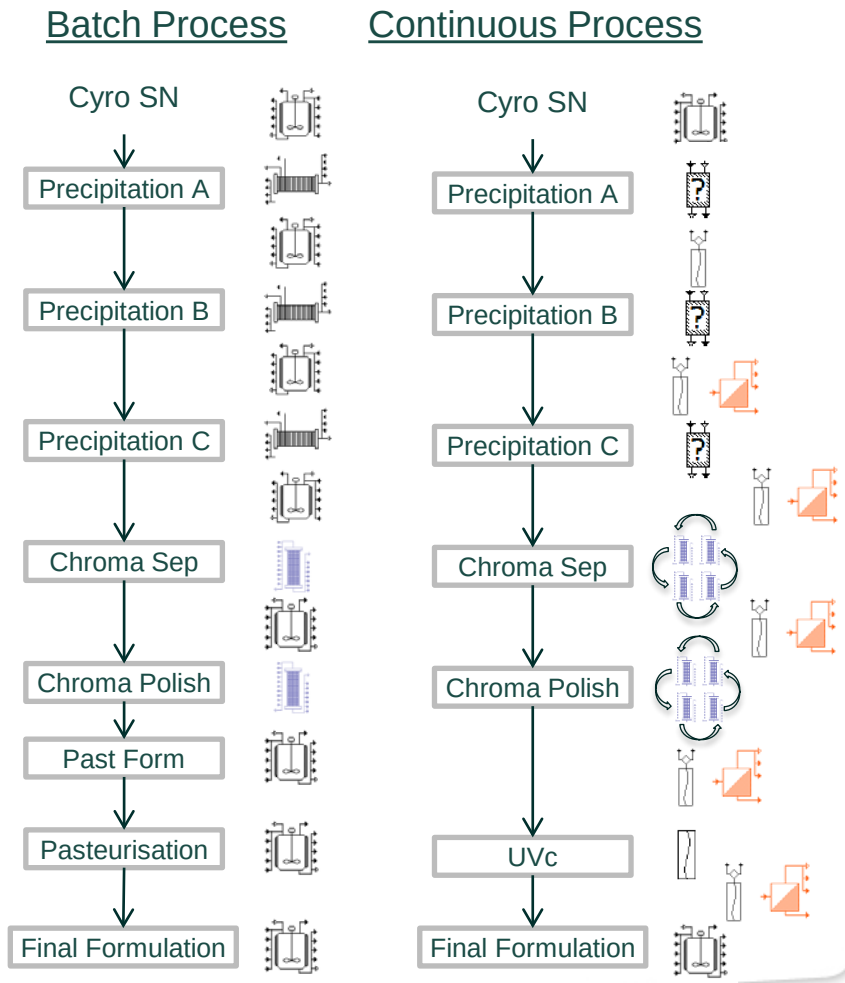
- Process model comparison of current IgG polishing chromatography step
- Reduction of one vessel
  - Replaced by small surge vessel
- Large vs medium scale columns
  - 4 columns replacing one
  - Packing risks with larger columns
- Development risks not outweighed by gains
  - Only worth while if resin cost is large % of CoGs

	Batch	Semi-Continuous
Process	11t lot	11t batches
Polishing Chromatography step for IgG	2 x 7kL tanks + 1 x Large scale column [1.2m diameter]	Inline mixing + SPTFF con/diaf + 4 x Medium size columns [38 cm] + 1 x 7kL tanks



Potential of fully continuous production: Broadmeadows Case example – Intragam®P IVIG

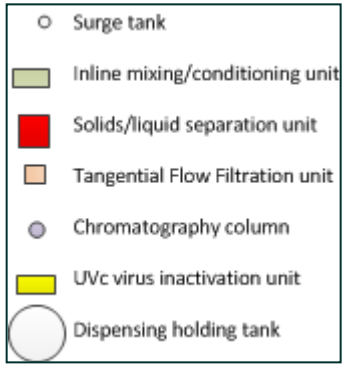
	Batch	Continuous
Process	11t lot	2 kg/min flow
Precipitation	3 x 10kL Tanks + 2 x Filter press	Tubular reactor with static mixer + Undefined S/L Sep [drum, cfg or r.disc]
Chromatography	4 x Large scale columns [1.2 to 1.6m diam] + 5 x 7kL tanks	Inline mixing + SPTFF con/diaf + 8 x medium size columns [38 to 44 cm]
Pasteurisation	2 x 4kL tanks	Inline mixing + Single pass TFF con/diaf + Pass through [UV or High Temp Past]
Formulation	3 x 2kL tanks [1 active, 2 holding]	2 x 2kL tanks [holding to decouple from filling]
Operator Labour	Base Case	70-80% reduction
CoGs	Base Case	15-40% reduction
Footprint	Base Case	60-70% reduction



Biotherapies for Life™ CSL Behring

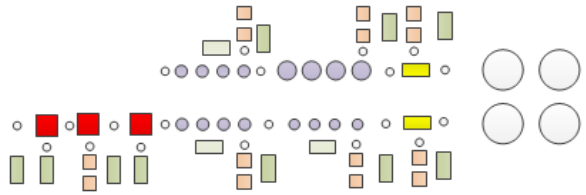
Foot Print Reduction

Existing Footprint



- Elimination of intermediate hold tanks
- Smaller columns required
- Lower flowrates required reduces size of support equipment

Estimated CM Footprint



Benefits of Continuous Processing

- Quality improvements
  - Integration of Quality decision making within the process
  - Reduces batch to batch variation
- Increased product yields: Road to >80-90% recovery
- Smaller footprint required for manufacturing facility
  - Reduction of CAPEX
    - Size and number of equipment
  - Reduction of CoGs
    - Less operational and supporting staff required
    - Consumables fully utilised
- Reduce time to market and held inventories
- Improved strategic agility
  - De-centralising manufacturing for local production
  - Manufacturing scale out not scale up

- Daszkowski , T (Bayer Technology Services) " Continuous Processing in Biotech Production ", 2013
- Cooney, C (MIT), "Transforming Pharmaceutical Manufacturing Through Continuous Manufacturing", 2014
- Raghuwanshi, A. (Gennova), "Continous Bio-Manufacturing", 2014

Challenges and Technology Gaps

- Unknowns
  - PAT: Inline Real time monitoring of target (IgG, Alb) proteins or impurity
  - Large scale continuous precipitation process units
  - Interfaces between continuous process units (eg surge vessels)
    - Control strategies , Cleaning standards
- Semi-known
  - Virus inactivation
  - Inline mixing and formulation
- Known
  - Continuous chromatography processes (SMB, PPC)
  - SPTFF Ultrafiltration and Diafiltation
  - Continuous centrifugation separations

Challenge to industry

- Vision for first CM Plasma production plant in 2025: Road Map
  1. Develop strategic business plan and company fit
     - Single or multi product approach?
     - Future supply chain
     - Risk based milestones to stage gate funding by R&D outcomes
  2. Build broad R&D knowledge base of isolated continuous units
     - Cooperative Research Centres (CRC)
       - Company, equipment vendor, university and regulatory collaborations
  3. Consolidate findings to inform process development work
     - Focus increased efforts on fewer process units

Challenge to industry

- Road map continued
  4. Bring together operational units in lab scale to develop CM interface and PAT control experience
     - Continuous process interface research (surge tanks, inline conditioning)
     - Tracer studies (vial, impurities) to show lot/batch segregation
     - PAT control of multiple process steps in continuous operation
       - Multivariate process control for non-homogeneous feed stock
  5. GMP pilot plant for clinical material
  6. Scale out pilot plant to manufacture product to market

Closing Remarks

The potential benefits of continuous manufacturing on the quality, accessibility and availability of our products to our current and future **patients** should overcome the initial perceived business and technical risks of the unknown.

Redefine your flagship product from billion of dollars to number of patients