



Flexible Facility Designs Complimenting Continuous Manufacturing

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G-CON Manufacturing Inc.

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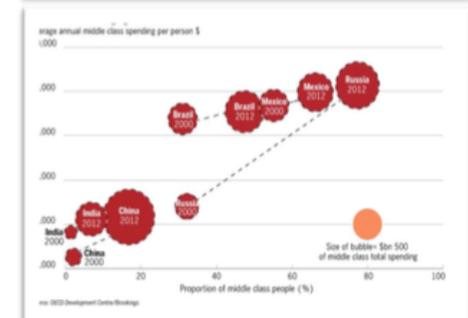
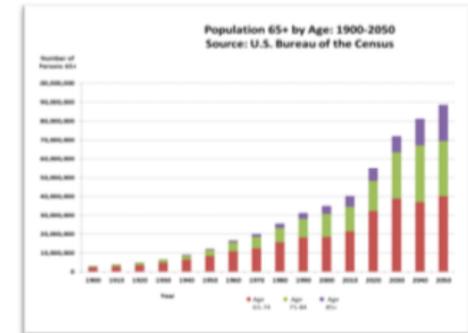
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Agenda

- The Industry Situation & Future Indicators
- The Continuous Manufacturing Paradigm
- OSD Manufacturing Advances
- Biopharm Manufacturing Advances
- Rethinking Facility Design
- Summary

Future Indicators

- Aging population on the rise with further needs for capacity to avoid stock-outs/drug shortages
- Rising middle class in different countries require in-country/for country manufacturing capabilities
- Changing viral and microbial diseases require fast response possibilities utilizing new technologies and deployment methods
- Regenerative/personalized medicines require specific processing systems in accordance with any possible logistic hurdle and robust containment needs
- Continuous processing further reduces process footprints



Past Facilities may not fit New Needs



- High CAPEX (>\$500M)
- Long time-to-run (3-4y)
- Product dedicated
- Inflexible/non-scalable
- Extensive qualification needs
- Difficult containment
- Difficult to clone

Change
is
Needed



Some New Concepts may be Lacking

“Until now, modular facilities have reproduced traditional architecture with regard to embedding utilities piping and HVAC ducts in the interspace between the physical module limits and the suspended ceiling making refurbishment, if required, extremely complicated.

The new approach is to segregate pre-assembled modules into laboratory and utility modules, which are designed such that they permit even simpler and faster construction, qualification, validation and maintenance, respectively....”

Alan Pralong (2013)



The Future requires...

✓ Speed

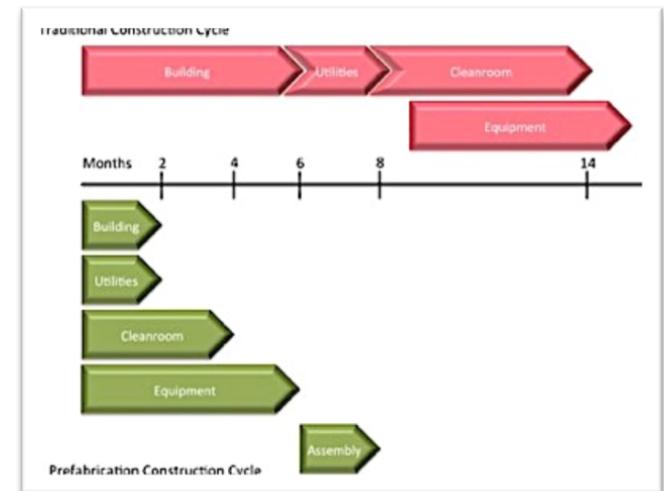
- Abbreviated design phases
- Time-to-build/Time-to-run
- Adoption of new technologies

✓ Agility

- Scaling up and down w/o interruption of existing processes
- Rapidly deployed in multiple locations (in-country/for country)

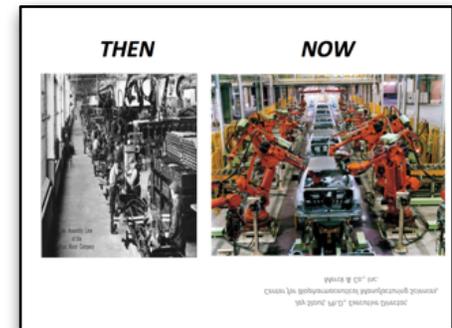
✓ Efficiency

- Higher yield per footprint
- Faster turn-around/Set-up time
- Multi-product and parallel operations
- Infrastructures for multi-purpose use



The Continuous Manufacturing Paradigm

- Continuous processing was developed as early as the late 18th century (eg. Pig iron blast furnace, Fourdrinier paper machine)
- By the early 20th century continuous manufacturing processes were common in the food, chemical, and automotive industries
- The pharma and biopharma industries have relied heavily on the traditional batch based manufacturing processes developed over 50 years ago
- In the past 5 years, significant progress has been made in the development of continuous processes in pharma



FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

Pharmaceutical Manufacturing: The Path Ahead..

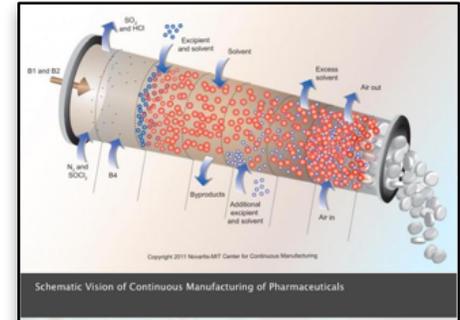
*“ Right now, manufacturing experts from the 1950s would easily recognize the pharmaceutical manufacturing processes of today. It is predicted that manufacturing will change in the next 25 years as current manufacturing practices are abandoned in favor of cleaner, flexible, more efficient **continuous manufacturing**.”*

Dr. Janet Woodcock, AAPS Annual meeting, October 2011

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OSD Manufacturing Advances

- Collaborations are driving technology advances and adoption
 - Novartis-MIT
 - Janssen-Vertex-Rutgers (C-SOPS)
 - Pfizer-GSK (PCMM)
- Companies are combining resources to effect the fastest path to success
 - Compete on products, not manufacturing technologies
 - Specialized expertise for new technologies
 - Regulatory leverage
 - Establishing guidance and standards



A purple banner with the text 'Transforming the Way the Pharmaceutical Industry Makes Tablets' and the Pfizer logo. Below the banner are four small images showing industrial manufacturing equipment. At the bottom, text reads: 'Pfizer Announces Collaboration with GSK on Next-Generation Design of Portable, Continuous, Miniature and Modular (PCMM) Oral Solid Dose Development and Manufacturing Units' and 'Further Enhances Pfizer's Collaborative Effort to Help Establish PCMM as Industry Standard in Continuous Processing'.

Transforming the Way the Pharmaceutical Industry Makes Tablets

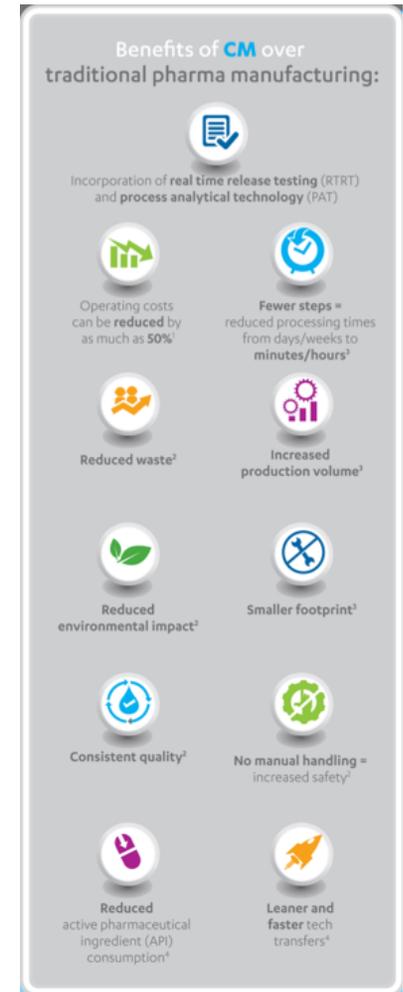
Pfizer

Pfizer Announces Collaboration with GSK on Next-Generation Design of Portable, Continuous, Miniature and Modular (PCMM) Oral Solid Dose Development and Manufacturing Units

Further Enhances Pfizer's Collaborative Effort to Help Establish PCMM as Industry Standard in Continuous Processing

OSD Manufacturing Advances

- Continuous OSD manufacturing equipment is commercially available from multiple suppliers
- Process Analytical Technology (PAT) is being implemented to provide feedback and feed forward control of processes resulting in improved product quality
- Time and costs required for process development and validation are being significantly reduced
- OSD products manufactured by continuous processes have been approved by FDA and are currently on market



Steven E Kuehn,
Pharmaceutical Manufacturing
Oct 8, 2015

OSD Manufacturing Advances

➤ FDA Approvals

- Vertex – Orkambi, Cystic Fibrosis Drug (July 2015)
- Janssen – Prezista, HIV-1 Drug (April 2016)



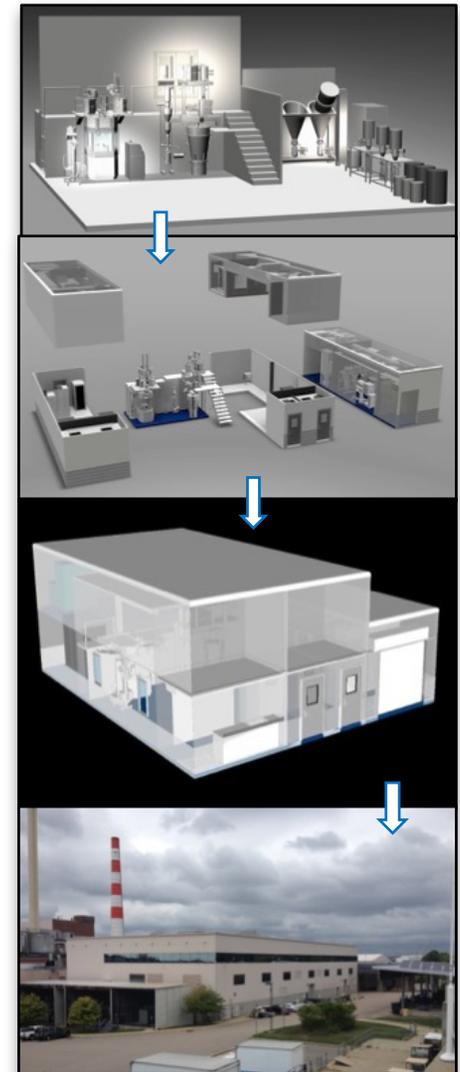
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OSD Manufacturing Advances



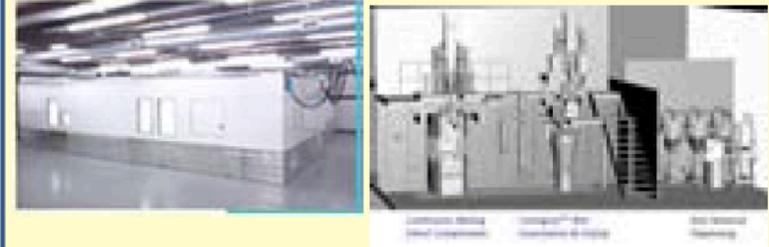
Portable Continuous Miniature & Modular

- GEA Continuous OSD Process integrated into G-CON portable cleanroom POD
- Prototype built and installed in 2015 at Pfizer Groton, CT site within existing grey space warehouse
- System designed to be used for process development, clinical manufacturing, and/or commercial production
- System can be redeployed to different location in future if required



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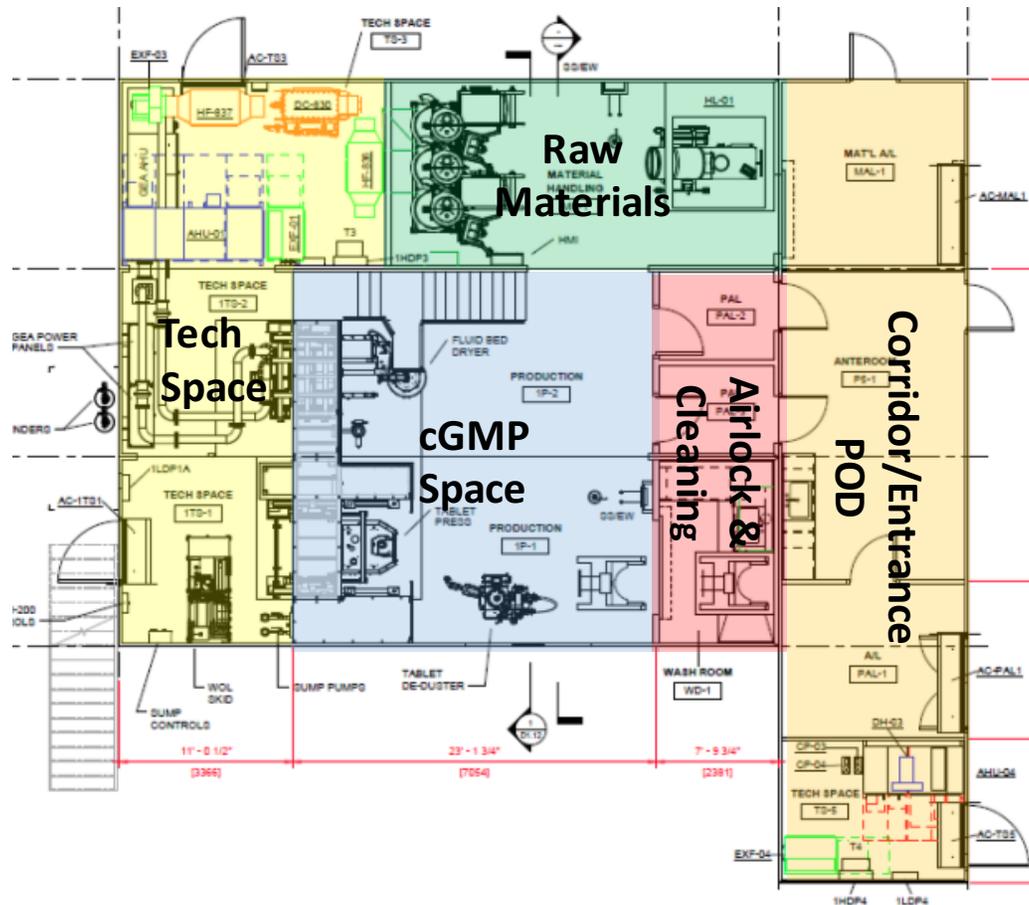
OSD Manufacturing Advances

Traditional Facility	PCM&M
	
70,000 ft ³ per process train	30,000 ft ³ per process train

Responding to a new product launch or Emerging Market tender with uncertain forecast

	Traditional Facility	PCM&M
Investment	<ul style="list-style-type: none"> Facility constructed for best case forecast. Modules and equipment are fitted out as required High up front investment (~\$40MM) 	<ul style="list-style-type: none"> Purchase new PCM&M POD & equipment or redeploy existing system Lower up front investment (~\$15MM)
Timeline	<ul style="list-style-type: none"> 24 – 36 months for facility 12-18 months for modules / equipment 	<ul style="list-style-type: none"> 12 -18 months for new POD and equipment 3 - 6 months to relocate existing PCM&M
Agility	<ul style="list-style-type: none"> Facility and batch equipment oversized or undersized A change in business case can result in stranded assets in targeted market 	<ul style="list-style-type: none"> Continuous system output is scalable PCM&M systems can be relocated if market conditions change

OSD Manufacturing Advances



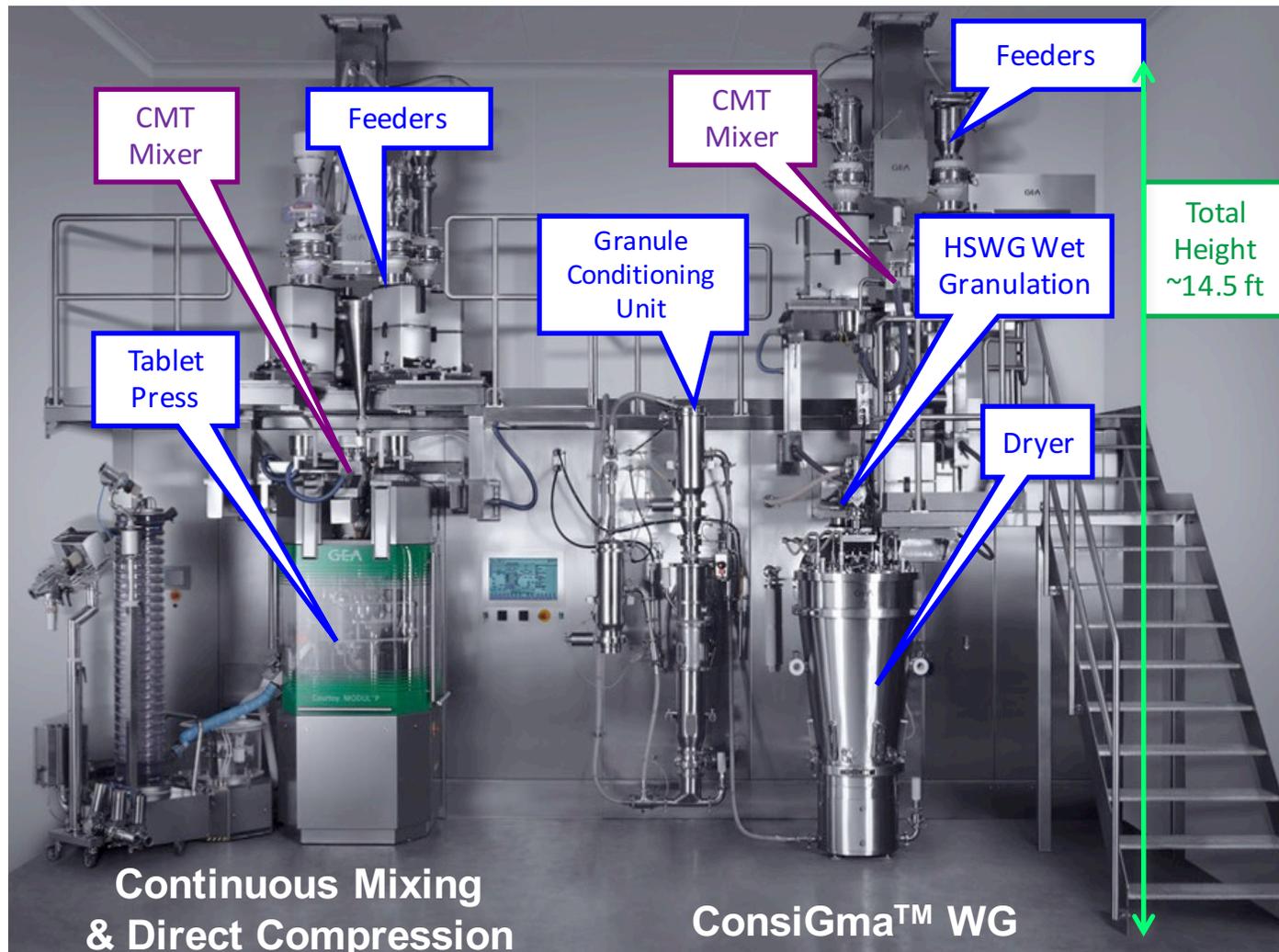
Courtesy: G-CON Manufacturing



Courtesy: GEA

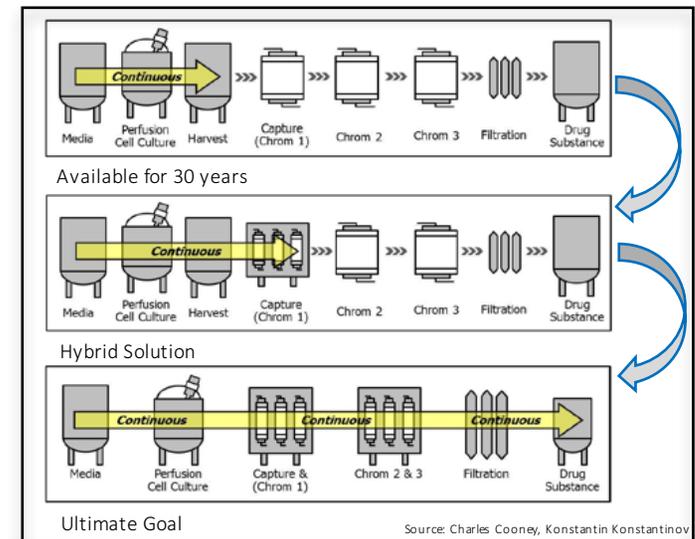
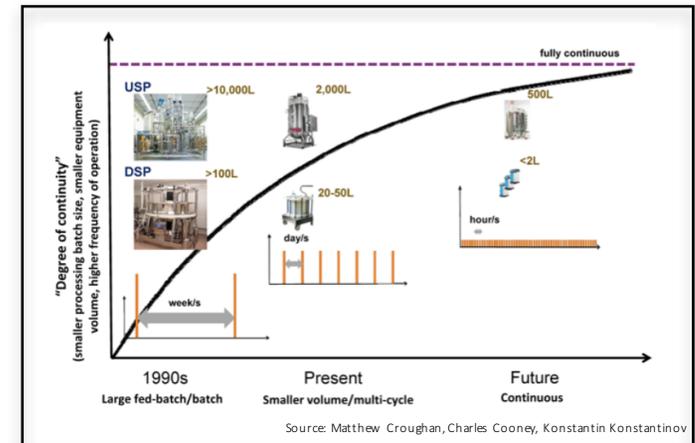
PCMM Prototype Design

OSD Manufacturing Advances

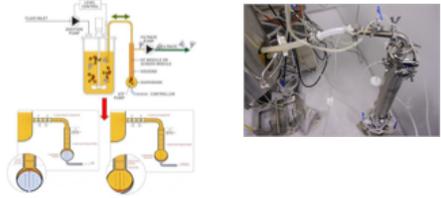
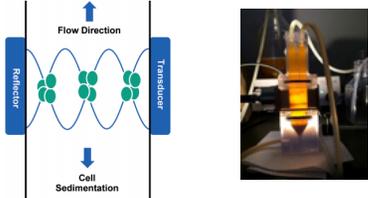
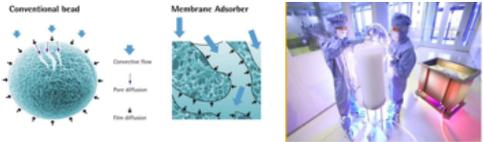
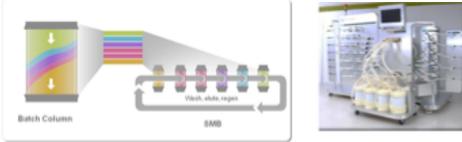


Biopharm Manufacturing Advances

- Single-use systems now being utilized in commercial processes after being used in clinical manufacturing for over 20 years
- Process understanding, technology advances, and improved controls have resulted in process intensification of USP
- Perfusion upstream processes were developed over 25 years ago and are currently used in manufacturing of commercial products (< 10%)
- Continuous downstream processing has been limited by the technologies available



Biopharm Manufacturing Advances

	Existing	Developing
USP	<p>Alternating Tangential Flow (Xcell™ ATF)</p>  <p>REPLIGEN</p> <p><small>Repligen has acquired the business of Radice Technology effective June 2, 2014.</small></p>	<p>Acoustic Wave Separation Cell Clarification</p>  <p>FloDesign Sonics</p> <p><small>*On June 16, 2015, Pall announced the exclusive licensing agreement with FloDesign Sonics FDS for acoustic wave separation (AWSS) in Bioprocessing.</small></p>
DSP	<p>Membrane Chromatography</p>  <p>sartorius stedim</p>	<p>SMB Chromatography</p>  <p>PALL Life Sciences</p> <p><small>* Pall Announced the acquisition the BioSMB technology platform from Tarpon Biosystems on March 31, 2015.</small></p>

“About five years ago, as the industry matured, the manufacturers were focusing on flexibility, cost, and capital efficiency in manufacturing,” he says. “It was at that point that **continuous technology** was considered **for downstream processing**, so we are really **at the early stage of a normal technology adoption cycle.**”

Andrew Sinclair, President and Founder of Biopharm Services

Biopharm Manufacturing Advances

➤ Challenges ahead but industry investing

- Immaturity of technologies for continuous downstream processing
- Significant upfront investment in process understanding is required
- Need for effective PAT including on-line instrumentation and real time monitoring of processes
- How to perform quality assurance/quality control with products manufactured through a continuous system as well as defining lots and batches
- New facility concepts and layouts needed to support end to end continuous processes

Market Alert

Will your site Expand, Introduce or Not Pursue Continuous Processing this year?

Expand	31%
Introduce	27%
Not Pursue	42%

Aspen Survey of the Bioprocessing Market

Market Alert

Which of these best describes your sites interest in continuous chromatography?

We presently have a funded or ongoing program	25%
We plan on starting a program in the near future	29%
We have no interest at this time	46%

Aspen's Survey of the Bioprocessing Industry 2016

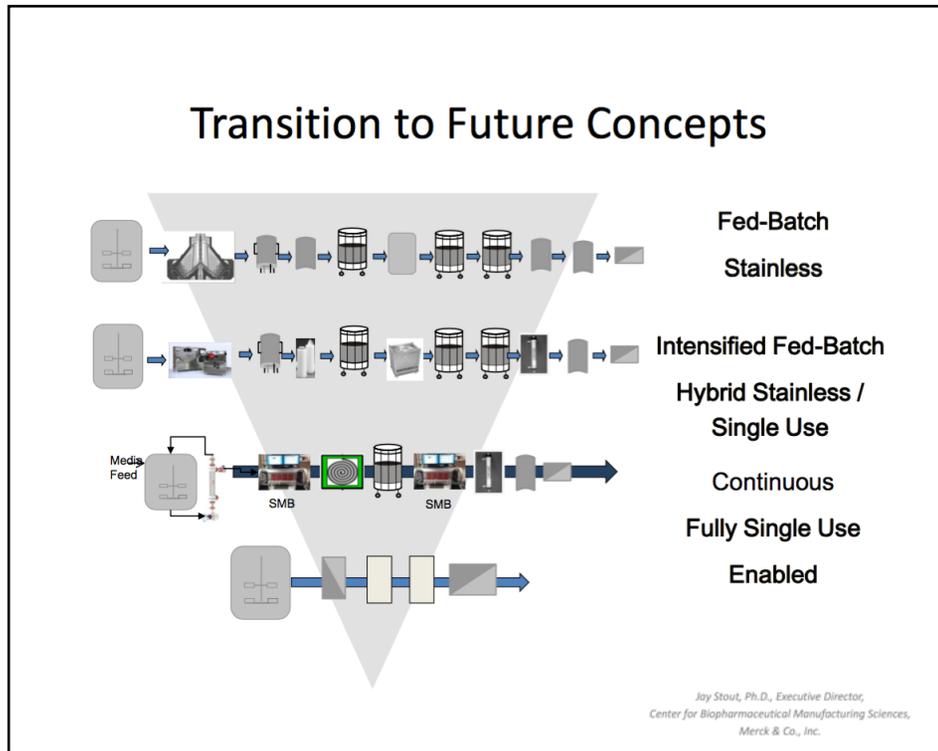
Market Alert

Which of these is most important to you?

Continuous Processing	36%
QbD	32%
PAT	15%
Other	10%
Six Sigma	7%

Aspen's 6th Annual Survey of the Year Ahead for Bioprocessing

Biopharm Manufacturing Advances

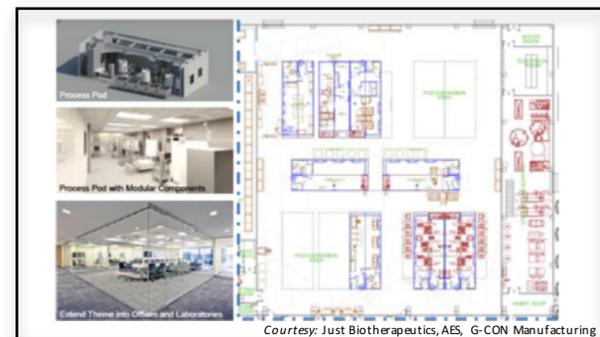
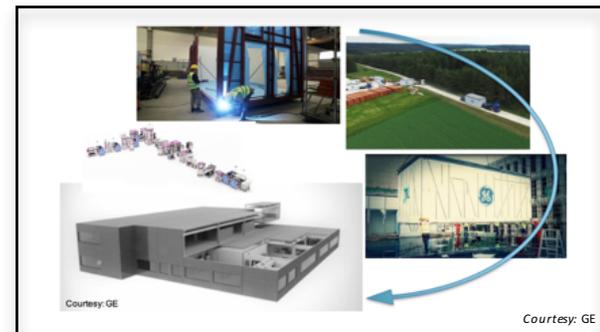


Courtesy: Fujifilm Diosynth

A continuous manufacturing facility footprint is smaller than traditional process facility for a given output

Rethinking Facility Design

- Pre-fabricated modular cleanrooms integrated into new or existing shell structure
- Build offsite and assemble onsite into facility
- Support of multi-product/tenant facilities
- Redeployed or repurposed in future as needed
- Platform facility designs allow for cloning and accelerated deployment



Rethinking Facility Design

The combination of continuous processes and single use technologies integrated within a pre-built modular cleanroom system can help meet the future need for smaller and more agile manufacturing facilities that can be cloned and rapidly deployed throughout the world.



Summary

- Traditional process and facility designs are straining to meet pressing industry requirements and application needs
- Future facilities will need to be smaller, more agile, and deployed more rapidly than in past
- Significant advances have been made in OSD continuous processing through effective collaborations and technology advances which have resulted in the recent FDA approvals
- While the biopharm industry has used continuous USP manufacturing for many years, the development and technologies for continuous DSP is still in the early stages
- New innovative facility designs have been implemented for OSD continuous manufacturing operations and are being developed for a broad range of biopharm applications

Thank you for your attention!

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“The arrogance of success is to think that what you did yesterday will be sufficient for tomorrow”

William Pollard



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