CONTINUOUS BIOPHARMACEUTICAL MANUFACTURING:

CHALLENGES & POSSIBILITIES

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ISPE Boston Chapter Presentation
March 16, 2017
Cambridge, MA

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BioPharm Mfg Consultant

Compliance
Engineering
Manufacturing
SUCCESS

Program Management
Investigations
Risk Assessments
Audit Readiness
Leadership Coaching
Etc.

Former Director, Biogen, Cambridge, MA and Hillerød, Denmark

- *Manufacturing Engineering*
- *Facilities, Maintenance, Validation*
- *Manufacturing Sciences*

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Continuous Biopharmaceutical Manufacturing:
The Promise…

further encouraged by guidance expressed in recent FDA conference presentations. The advantages of continuous manufacturing include sustained operation with consistent product quality, reduced equipment size, high volumetric productivity, streamlined process flow, low process cycle times and reduced capital and operating cost. This technology, however, poses challenges, which need to be

K.B. Konstantinov and C.L. Cooney, "White Paper on Continuous Bioprocessing," presentation at the International Symposium on Continuous Manufacturing of Pharmaceuticals: Implementation, Technology & Regulatory (Cambridge, MA, 2014).

https://iscmp2014.mit.edu/white-papers

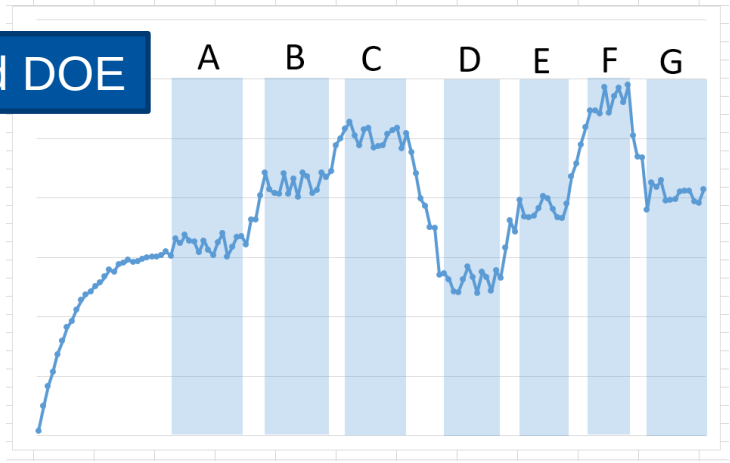
2nd International Symposium on Continuous Manufacturing of Pharmaceuticals

Implementation, Technology & Regulatory

September 26–27, 2016

Scale out (*time*), not up (*volume*)

Rapid DOE



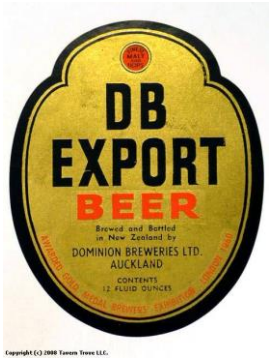
FDA U.S. Food and Drug Administration Protecting and Promoting Public Health www.fda.gov

Advantages of Continuous Manufacturing (CM)

- Integrated processing with fewer steps
  - No manual handling, increased safety
  - Shorter processing times
  - Increased efficiency
- Smaller equipment and facilities
  - More flexible operation
  - Reduced inventory
  - Lower capital costs, less work-in-progress materials
  - Smaller ecological footprint
- On-line monitoring and control for increased product quality assurance in real-time
  - Amenable to Real Time Release Testing approaches
  - Consistent quality

Potential for reduced cost

8



IFPAC Annual Meeting, Baltimore, January , 2012
Sharmista Chatterjee, Ph.D. CMC Lead for QbD, ONDQA/CDER/FDA

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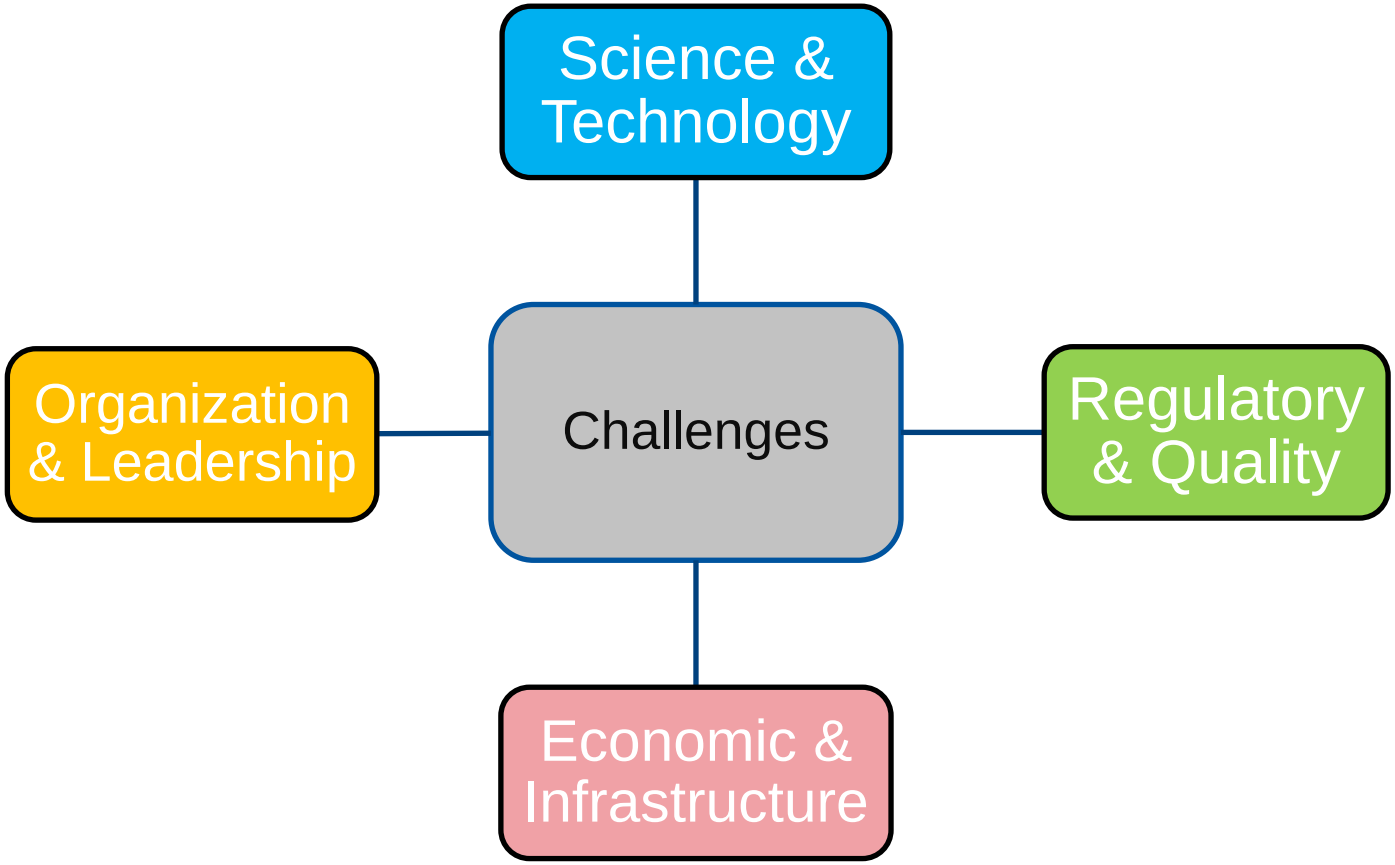
DB Breweries Ltd, Aukland, NZ

THE ADVANTAGES OF CONTINUOUS vs. BATCH FERMENTATION Continuous fermentation allows better vessel and space utilisation through faster fermentation. The fermentation proceeds more rapidly because it is stirred and higher yeast concentrations are present than in standard batch fermentations. Capital and labour costs are reduced since there is only one fermentation to control and test. The fermentation system can be tuned according to market demands; in peak periods the CF can be run at a high flow rate, during the off-peak season the flow rates are reduced so that beer is produced more slowly by the system. Because of the blending effect of the recycle from CF1 to the HUV there is excellent product consistency. A number of parameters (such as yeast concentration, wort oxygenation rate and flow rate) can be used to fine-tune the flavour and quality of the beer produced from the system. The control of the fermentation also has the advantage of being automated.

From http://nzic.org.nz/ChemProcesses/food/6A.pdf
Sarah L. Campbell (DB Breweries Ltd.).

survey

Continuous Biopharmaceutical Manufacturing:
The Challenge…



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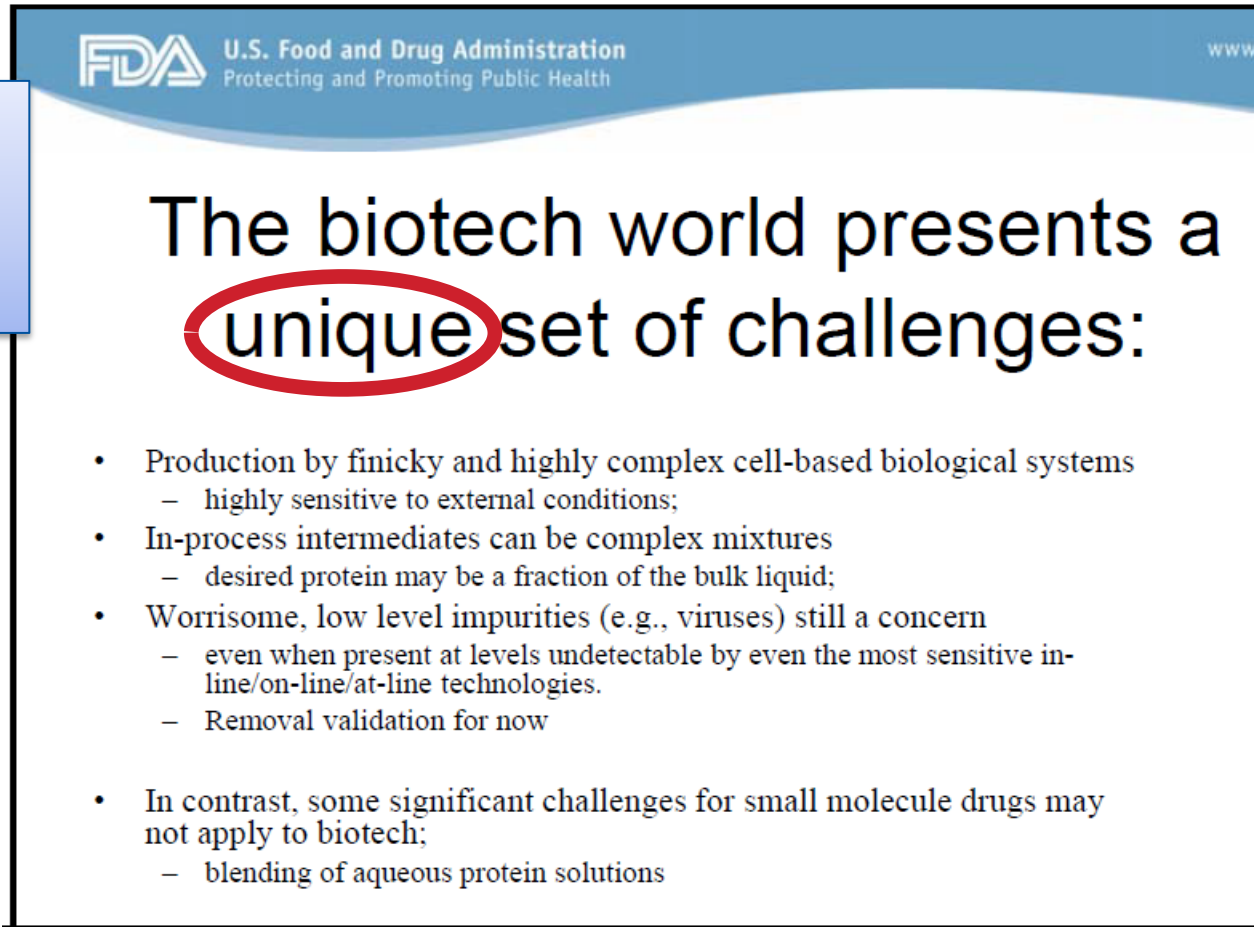
Continuous Biopharmaceutical Manufacturing:
The Challenge…

Science & Technology

Kurt Brorson, Ph.D., Division of Monocolonal Antibodies
OBP/CDER

ISPE Continuous Manufacturing Conference, April 20-21, 2016



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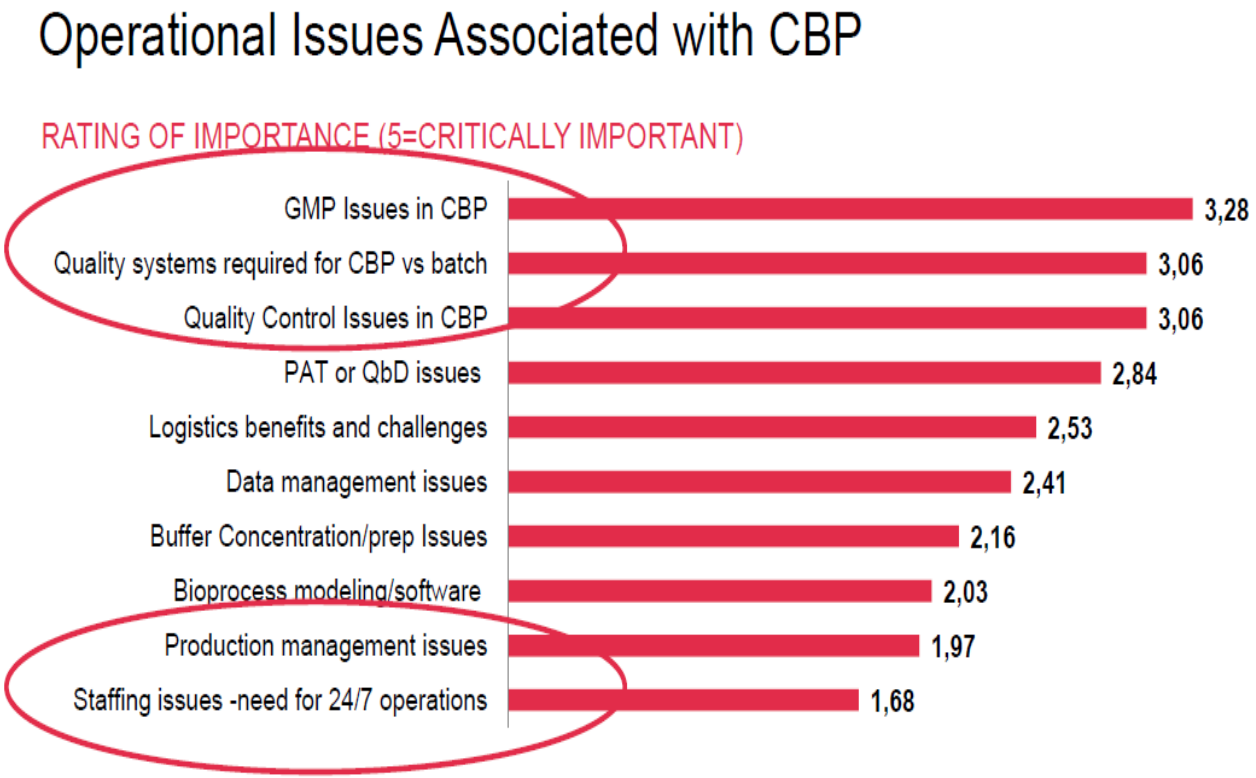
Continuous Biopharmaceutical Manufacturing:
The Challenge…



Regulatory & Quality

Survey performed by BioPlan Associates, for NNE Pharmaplan

nne pharmaplan

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Continuous Biopharmaceutical Manufacturing:
The Challenge…

Janet Woodcock, Director CDER, FDA (AAPS meeting, 2011)

"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**"

Regulatory & Quality

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Continuous Biopharmaceutical Manufacturing:
The Challenge…Regulatory & Quality

Sharmista Chatterjee, CMC Lead for Qbd ONDQA / CDER/ FDA

IFPAC Annual Meeting
Baltimore, January 2012

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Continuous Biopharmaceutical Manufacturing:
The Challenge…Regulatory & Quality

Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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Continuous Biopharmaceutical Manufacturing:
The Challenge…Regulatory & Quality

ROW?

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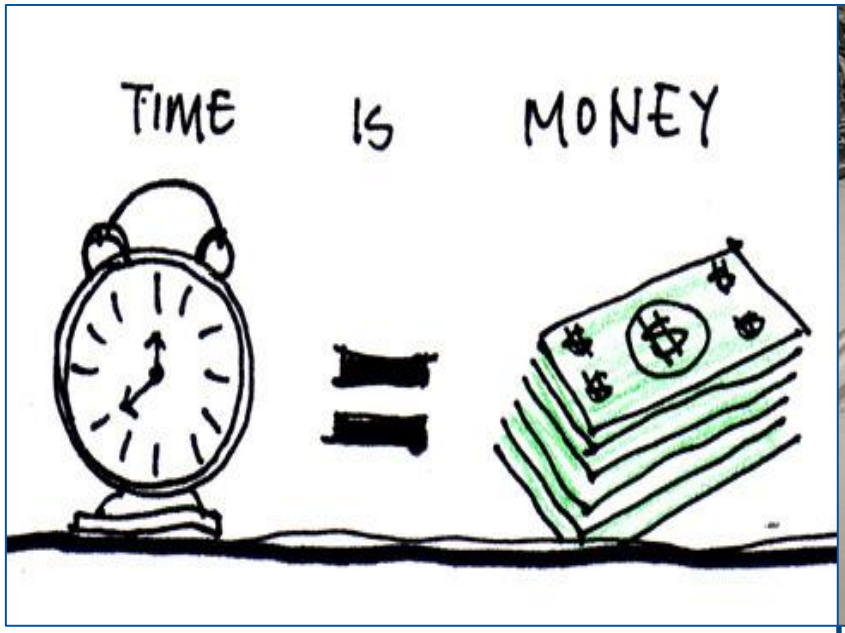
Continuous Biopharmaceutical Manufacturing:
The Challenge…



- Delayed Molecule to Market
- Existing Batch Infrastructure
  - Limited utilization
  - Incomplete depreciation

Economic & Infrastructure

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Continuous Biopharmaceutical Manufacturing:
The Challenge…

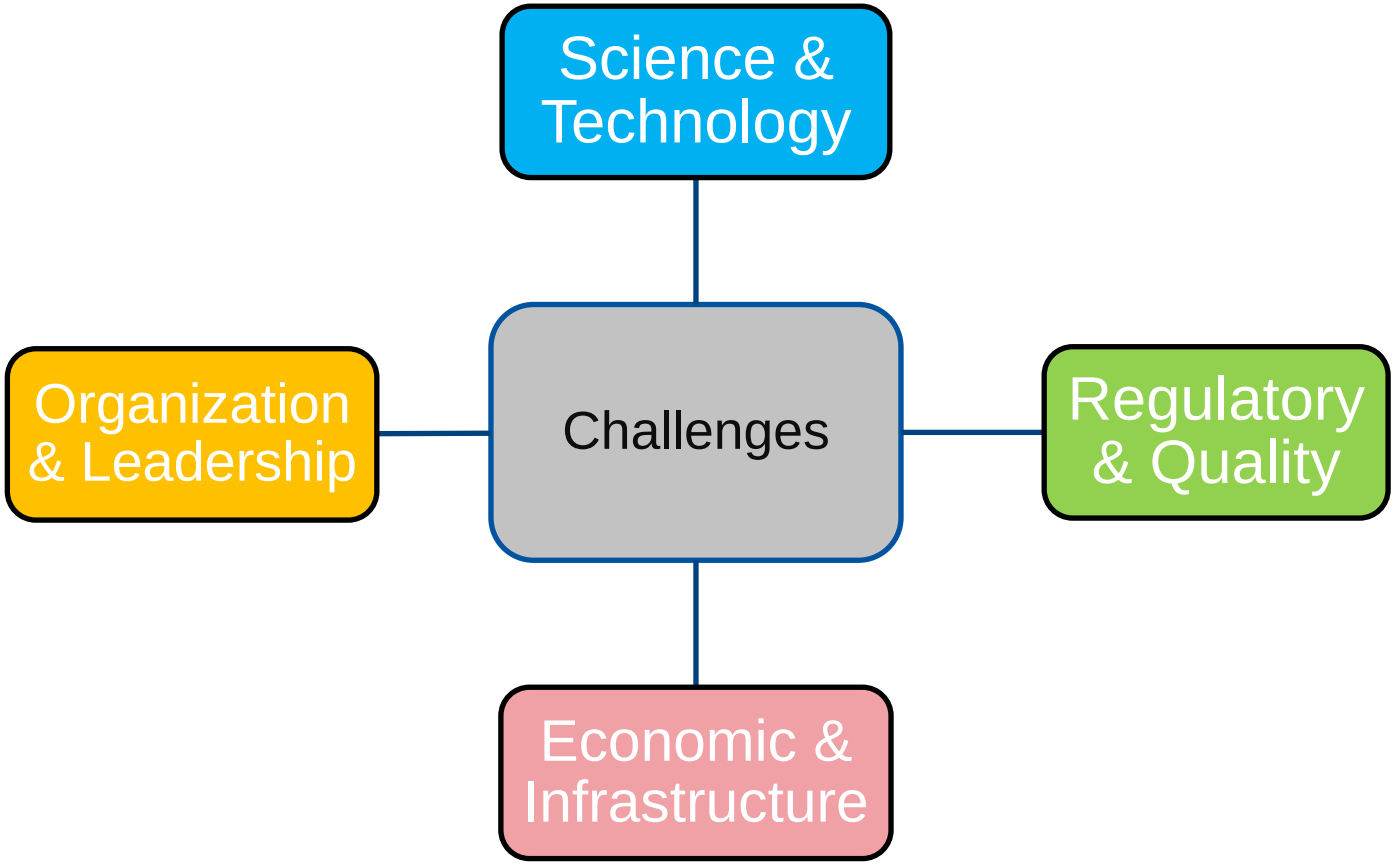
- Lack of knowledge base
- High Risk Aversion
- High integration of Development, Engineering, Manufacturing, Quality, Regulatory

Organization & Leadership

"…the success of the introduction of innovative approaches depends not only on sound technical vision, but also on broad support from the entire organization as a matter of corporate strategy."

International Symposium on Continuous Manufacturing of Pharmaceuticals (2014), Continuous Bioprocessing White Paper, Konstantin Konstantinov, Genzyme & Charles Cooney, MIT

Continuous Biopharmaceutical Manufacturing:
The Challenge…



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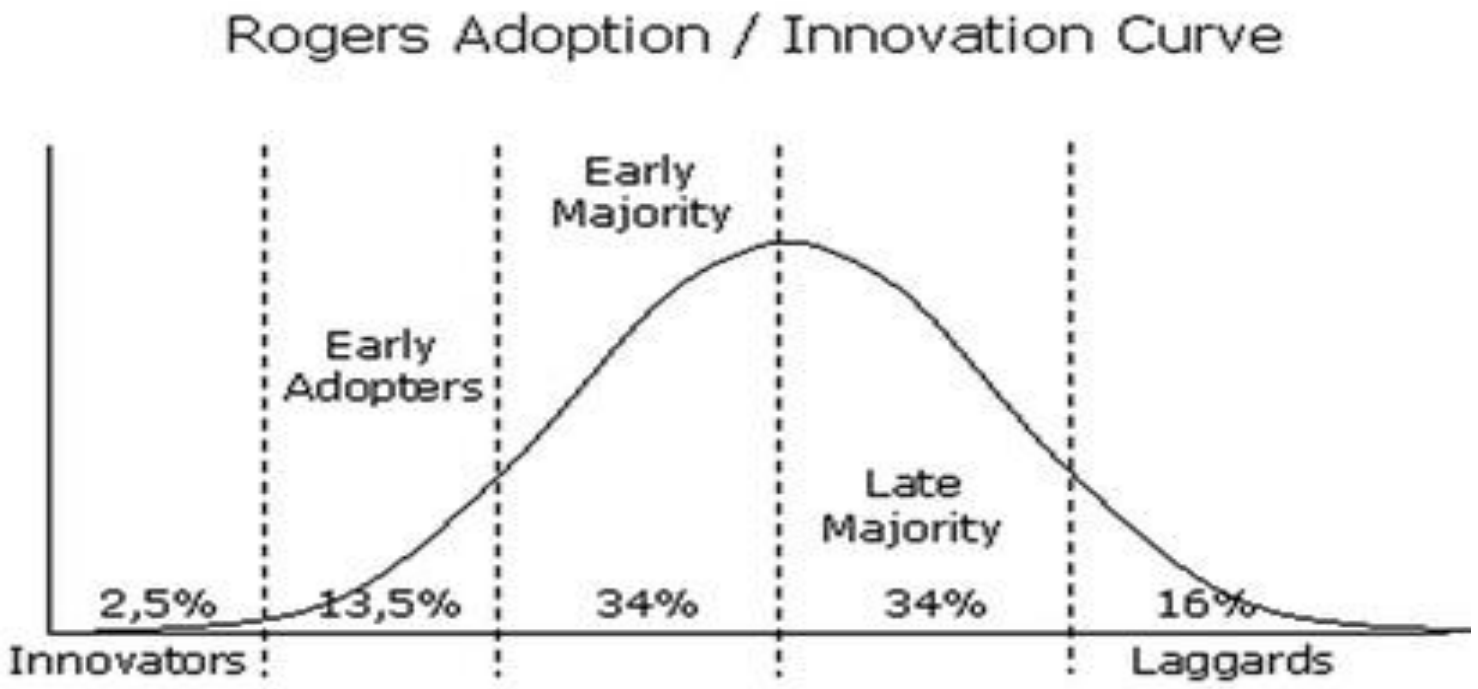
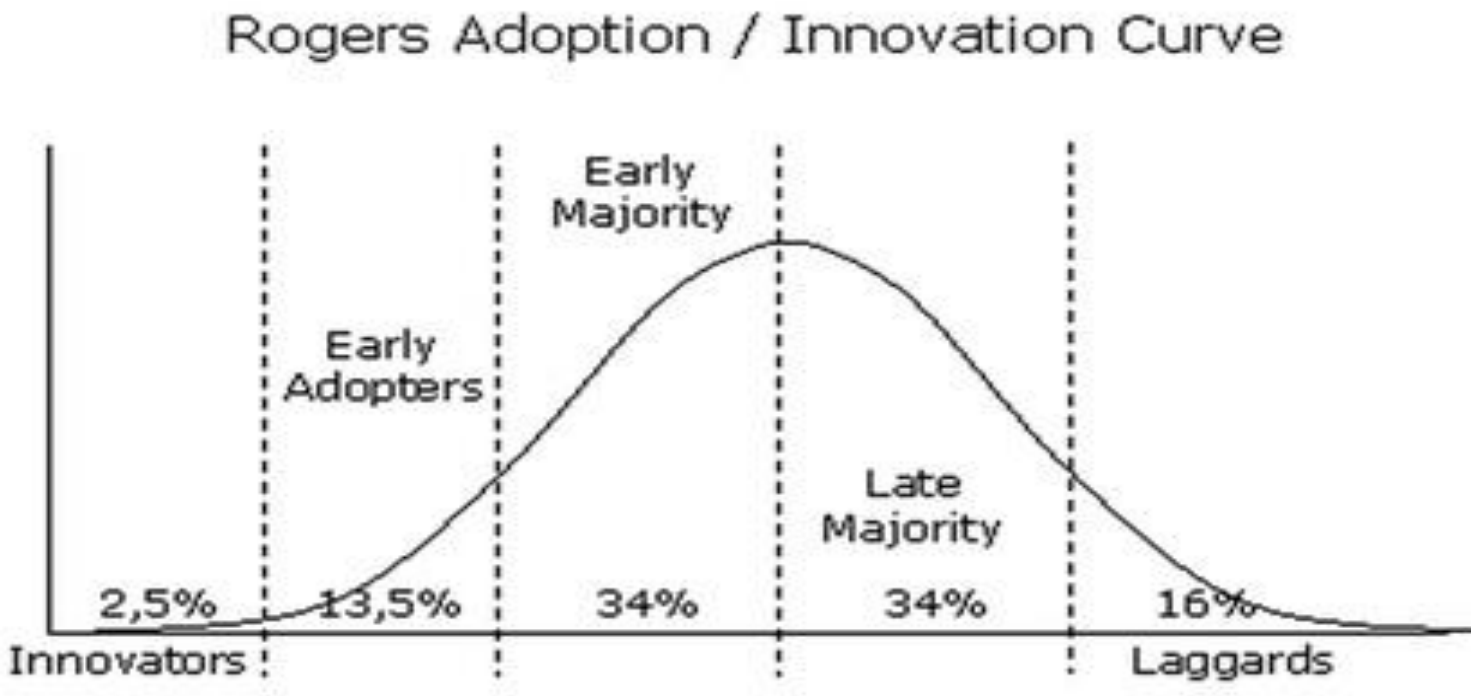
Under What Conditions Could CBM Take Root



Under What Conditions Could CBM Take Root



Science&Tech	Vendor
Reg/Qual	
$/Infrastructure	**Cash**
Org/Leadership	**Compelling Vision**

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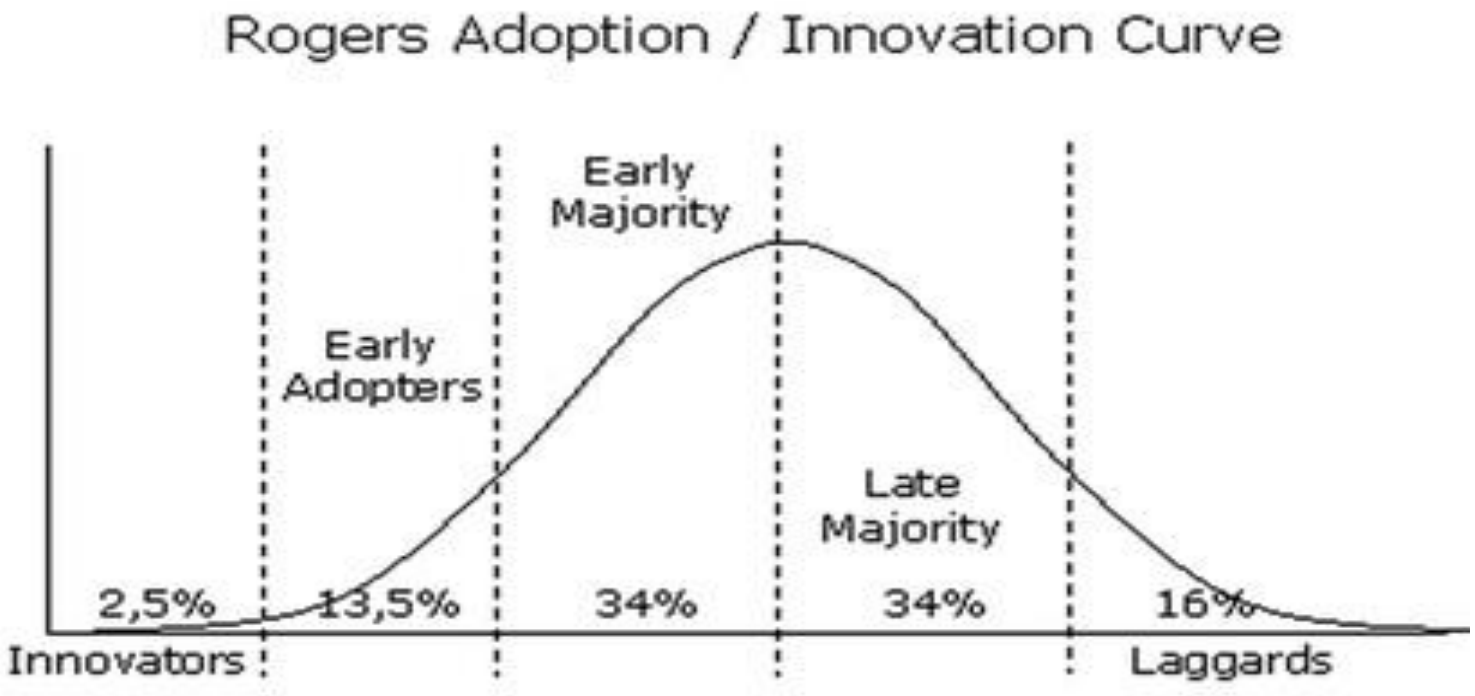
Under What Conditions Could CBM Take Root



Science&Tech	Vendor	Labile
Reg/Qual		Biosimilar
$/Infrastructure	Cash	Uncertain Demand
Org/Leadership	Compelling Vision	Bold Strategy

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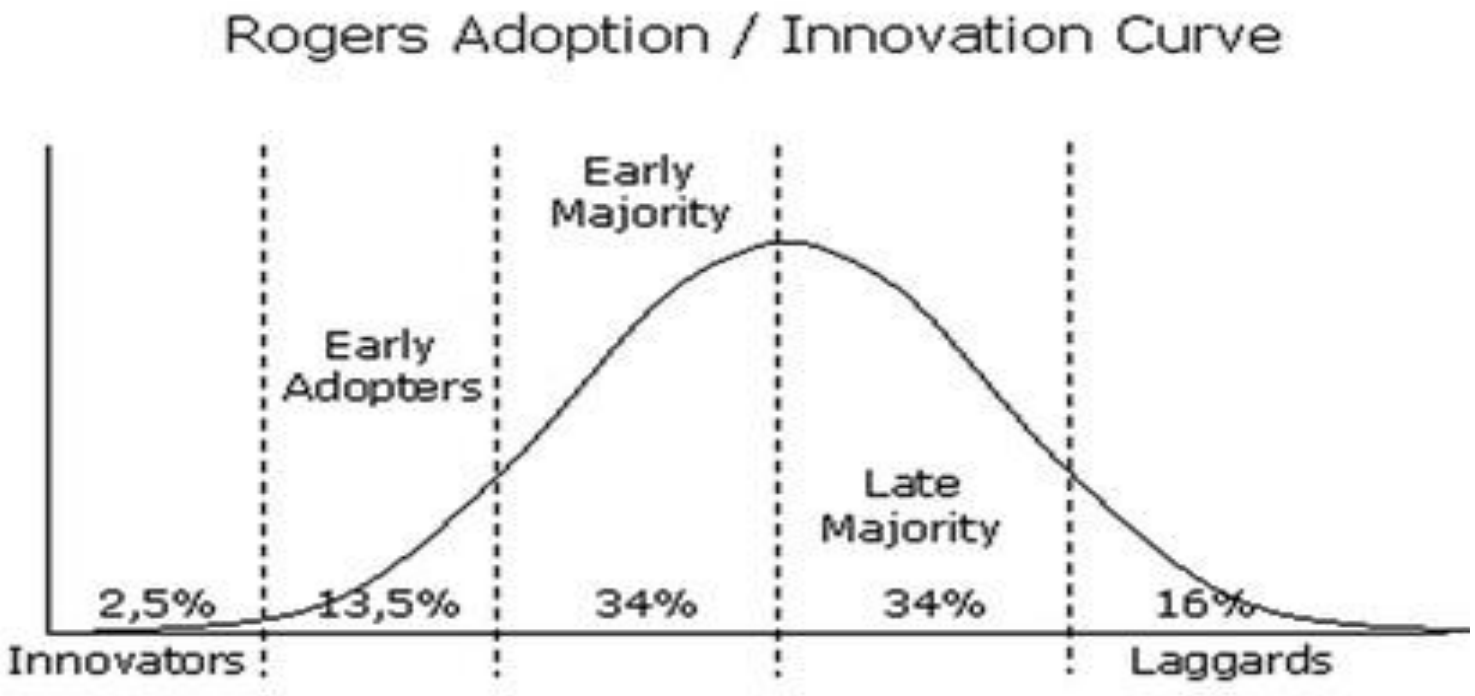
Under What Conditions Could CBM Take Root



Science&Tech	Vendor	Labile	Proven Tech
Reg/Qual		Biosimilar	NME
$/Infrastructure	Cash	Uncertain Demand	Needed Capacity
Org/Leadership	Compelling Vision	Bold Strategy	Risk Balanced Plan

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Dave Marks, DME

How Disruptive Innovations are Changing the Way we Think about GMP Manufacturing

ISPE Facilities of the Future Conference, Nov 2016

Single-Use Technology

Enabling Both Sustaining & Disruptive Innovation

Incremental improvement to existing manufacturing methods

Big Pharma

SUT Sustaining Innovation:

Hybrid systems, sampling

Inoculum/buffer/media prep

Clinical manufacturing

Small Biotech

SUT Disruptive Innovation:

100% SUT Manufacturing

Elimination of CIP/SIP

Leveraged Process Closure

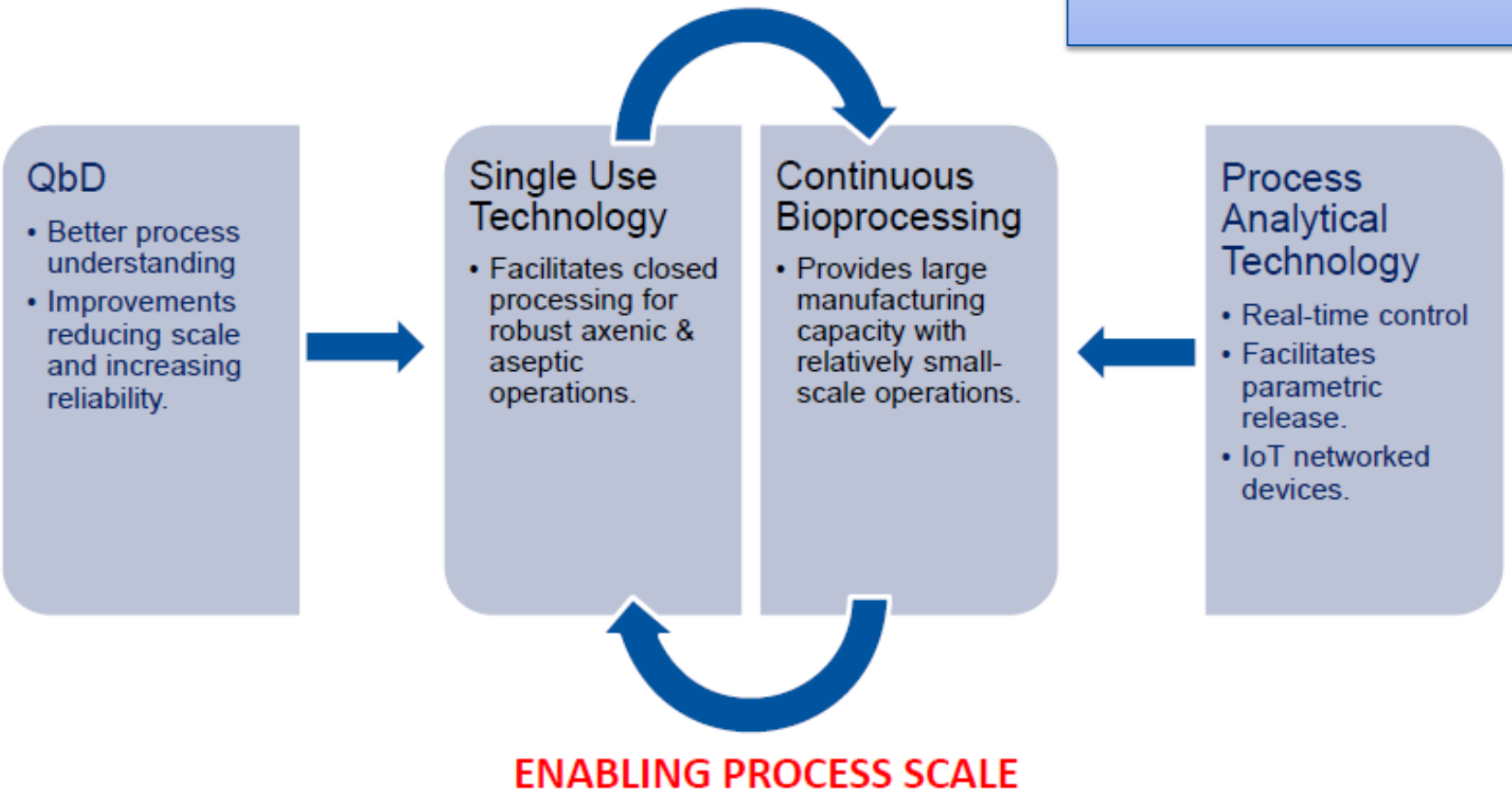
New business model disrupts market & removes barriers to entry

A Synergy of Technologies

Dave Marks, DME

How Disruptive Innovations are Changing the Way we Think about GMP Manufacturing

ISPE Facilities of the Future Conference, Nov 2016



Continuous Biopharmaceutical Manufacturing:
The Challenge…Organization and Leadership

*"The introduction of **continuous slab casting** in the late 1960s had*

*the **potential to transform** the production of steel,*

*but American producers were slow to adopt the technology, partly because of the **substantial investment involved** and partly because*

***the technology cut across the jurisdiction of departments …**within companies.*

American Metal Market
http://www.amm.com/HOF-Profile/IrvingRossi.html

survey

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Does Your Organization Have Activity in These Areas?

Perfusion Bioreactor

Alternating Tangential Flow

PAT

Process Analytics

Multivariate Models for Process Control or CQA prediction

On line CQA Measurement

Single Pass Tangential Flow Filtration

Periodic Counter Current Chromatography

Annular Chromatography

High Performance Counter Current Chromatography

Membrane Absorbtion

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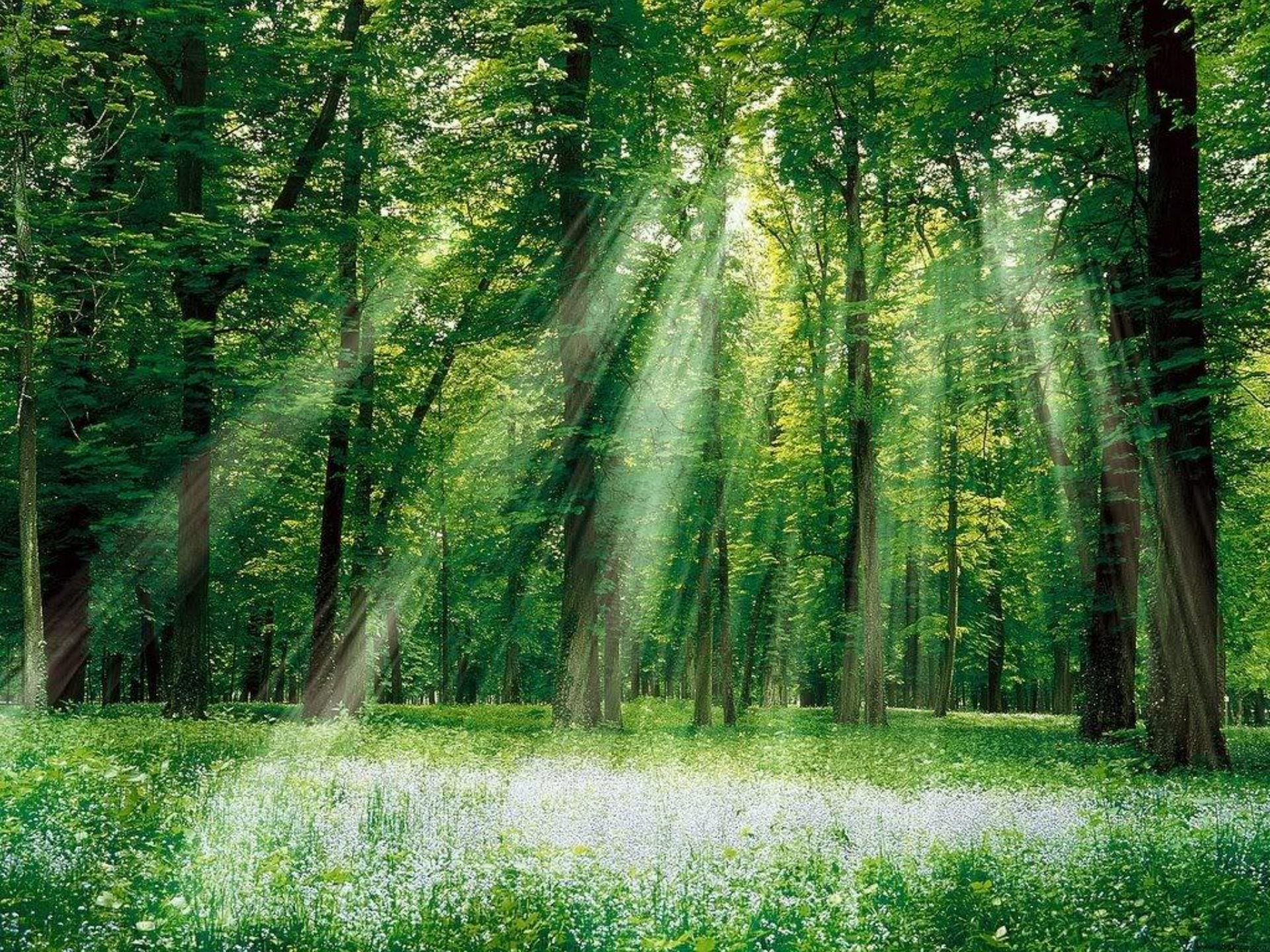

Links to Useful Content on CBM

The Promise of Continuous Biomanufacturing, Konstantin Konstantinov, VP, Late Stage Process Development, Genzyme
http://www.engconf.org/staging/wp-content/uploads/2013/12/The-Promise-of-Continuous-Biomanufacturing-Barcelona-Oct-20-2013-final.pdf

International Symposium on Continuous Manufacturing of Pharmaceuticals (2014), Continuous Bioprocessing White Paper, Konstantin Konstantinov, Genzyme & Charles Cooney, MIT
https://iscmp2014.mit.edu/white-papers/white-paper-4

Promoting Continuous Manufacturing in the Pharmaceutical Sector – Discussion Guide, Center for Health Policy at Brookings, October 19, 2015
Discussion Guide https://www.brookings.edu/wp-content/uploads/2015/10/Continuous-manufacturing-discussion-guide.pdf
Meeting Summary https://www.brookings.edu/wp-content/uploads/2015/10/meetingsummary_101915_continuousmanufacturing.pdf

Advanced Biopharmaceutical Manufacturing: An Evolution Underway, Deloitte Life Sciences
https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-advanced-biopharmaceutical-manufacturing-white-paper-051515.pdf

Continuous Manufacturing: A Changing Processing Paradigm, BioPharm International.com, Randi Hemandez, April 1, 2015
http://www.biopharminternational.com/continuous-manufacturing-changing-processing-paradigm

A Fearless Approach to Continuous Manufacturing, Drug Delivery & Formulation Summit, June 2016, San Diego http://www.ddfsummit.com/wp-content/uploads/2016/07/Steven-Dale.pdf

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