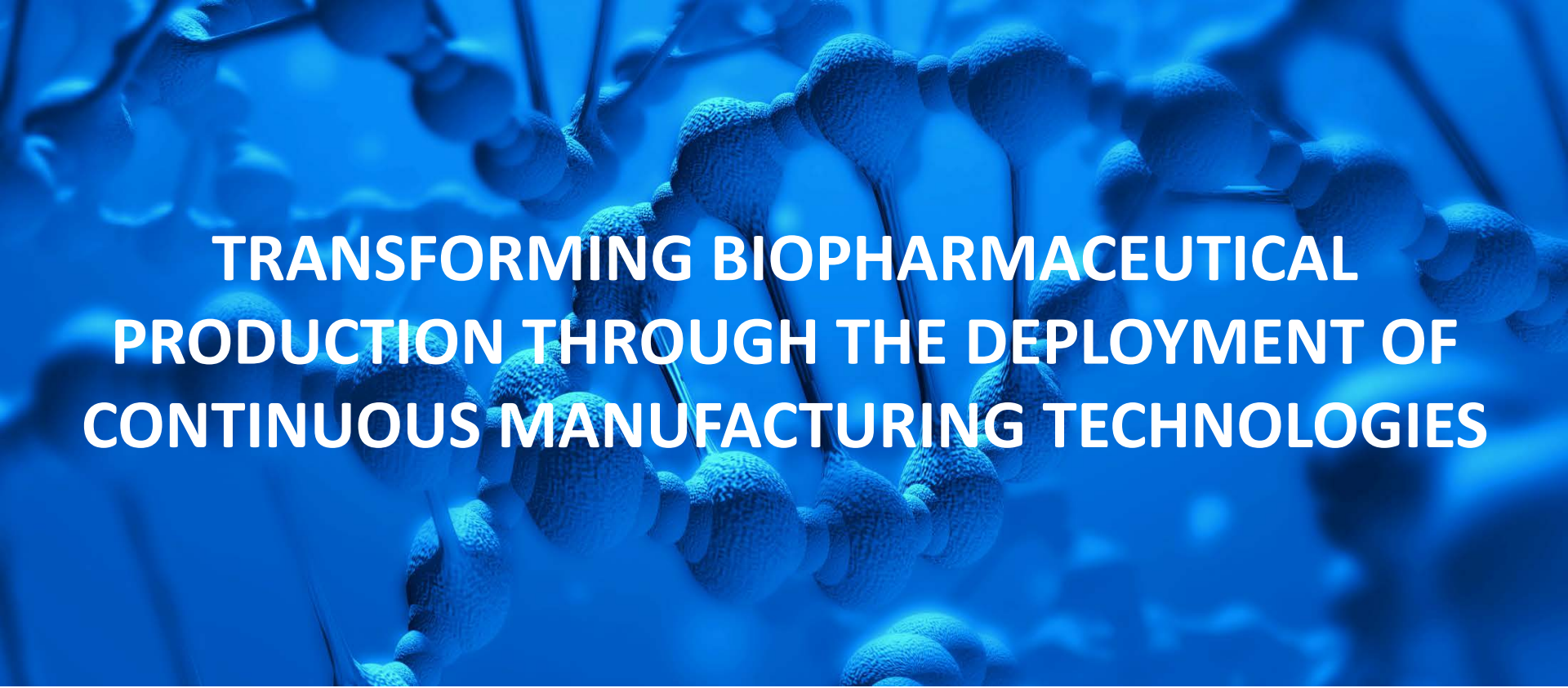


TRANSFORMING BIOPHARMACEUTICAL PRODUCTION THROUGH THE DEPLOYMENT OF CONTINUOUS MANUFACTURING TECHNOLOGIES

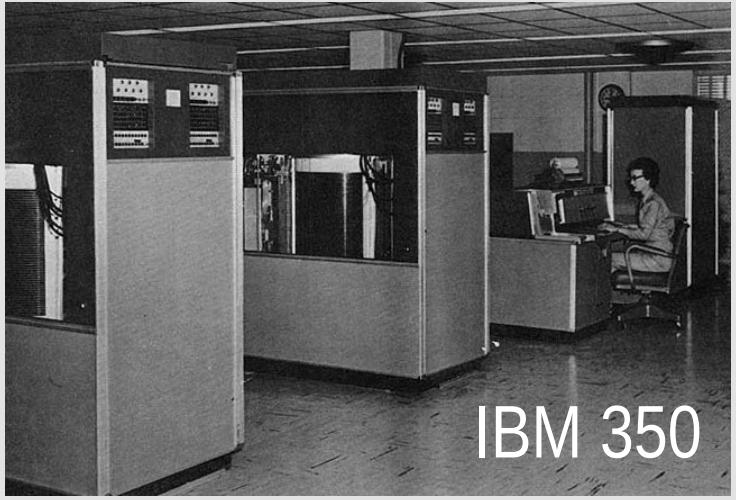
ART HEWIG AND CHETAN GOUDAR

PROCESS DEVELOPMENT, AMGEN, THOUSAND OAKS, CA

WCBP, WASHINGTON D.C., FEBRUARY 1ST 2018

AMGEN®
Pioneering science delivers vital medicines™

BIOMANUFACTURING CHANGE HAS BEEN EVOLUTIONARY IN COMPARISON TO OTHER INDUSTRIES

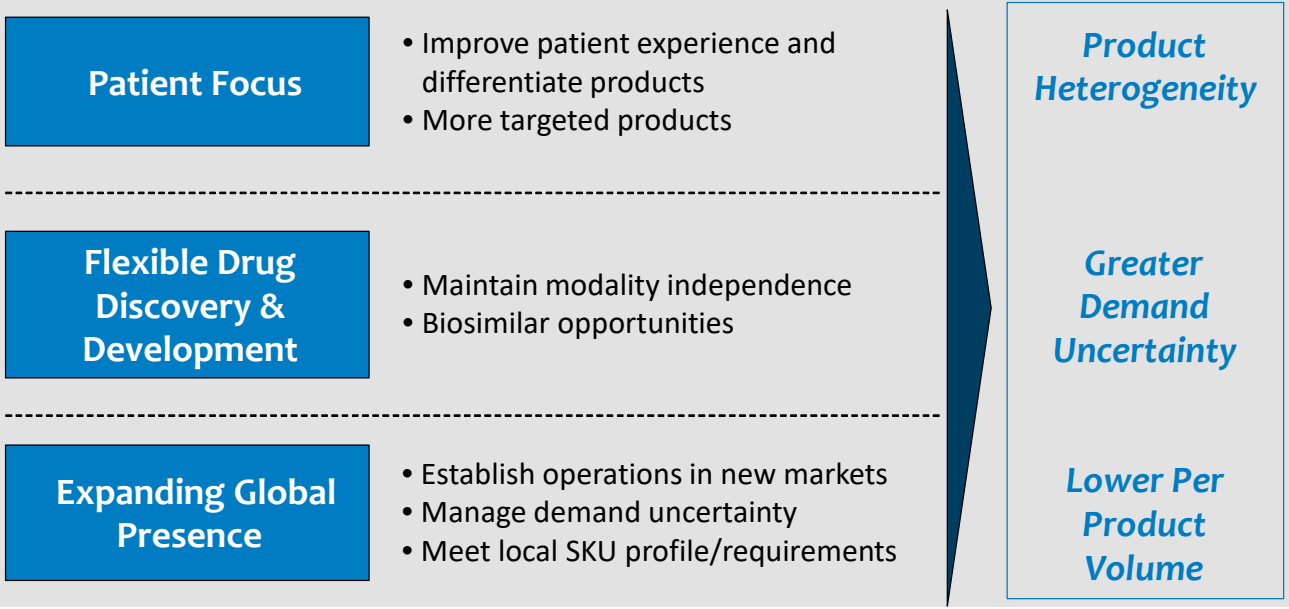


1956 (first disk drive)
3.75MB storage capacity
Weighed >1 Ton and was delivered in cargo airplanes

2017 (Largest solid state disk drive)
60TB storage capacity (can store >50,000 2-hour movies)
Weighs <1 kg and ships free

A changing business landscape is requiring agility, flexibility, modularity, and dematerialization of biomanufacturing networks. Continuous manufacturing can help support this transformation.

THE CHANGING BIOPHARMACEUTICAL LANDSCAPE HAS COMPANIES RETHINKING HOW DRUGS SHOULD BE MANUFACTURED IN THE FUTURE



Balance use of *existing footprint* with addition of *new capabilities* to lower costs, and increase flexibility and speed

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FED-BATCH CULTURE IN LARGE BIOREACTORS FOLLOWED BY BATCH PURIFICATION IS THE DOMINANT MANUFACTURING PARDIGM

Stainless Steel Bioreactor and related utilities

Batch Purification with large skids and columns

A 15,000L fed-batch bioreactor with a final product concentration of 5 g/L → 50 kg Drug Substance in 15 days

HISTORICAL VIEW OF CONTINUOUS PROCESSING IN BIOMANUFACTURING (FIRST GENERATION CONTINUOUS)

Application of continuous processing to biomanufacturing is not 'new' to our industry

- Historically has been used for unstable molecules such as blood factors and enzymes
  - Minimize residence time in bioreactor
  - Kogenate-FS – approved in 1993, first product approved using continuous process

- Typical application of continuous processing has been a continuous perfusion cell culture process followed by batch purification

Biopharmaceuticals produced by continuous perfusion manufacturing

Year Approved	Tradename	Generic Description	Type of Biomolecule	Indication	Company
1993	Kogenate-FS	Factor VIII	Blood factor	Haemophilia A	Bayer
1994	Cerezyme	b-glucocerebrosidase	Enzyme	Gaucher's disease	Genzyme
1997	Benefix	Factor IX	Blood factor	Haemophilia A	Pfizer
1997	ReoPro	Abciximab	Antibody	Percutaneous coronary intervention angioplasty	Janssen
1997	Gonal-f	Follicle-stimulating hormone	Blood factor	Infertility	Merck
1998	Remicade	Infliximab	Antibody	Autoimmune diseases	Janssen
1998	Simulect	Basiliximab	Antibody	Organ transplantation	Novartis
1999	NovoSeven	Factor VIIa	Blood factor	Haemophilia A	Novo Nordisk
2000	ReFacto	Factor VIII	Blood factor	Haemophilia A	Pfizer
2001	Campath/Lemtrada	Alemtuzumab	Antibody	Lymphoma and multiple sclerosis	Genzyme
2001	Xigris	Drotrecogin alfa	Blood factor	Sepsis	Eli Lilly
2002	Rebif	Interferon beta-1a	Blood factor	Multiple sclerosis	Merck
2003	Fabrazyme	Agalsidase beta	Enzyme	Fabry's disease	Genzyme
2003	Aldurazyme	Laronidase	Enzyme	Mucopolysaccharidosis I	Biomarin
2005	Naglazyme	Galsufase	Enzyme	Mucopolysaccharidosis VI	Biomarin
2006	Myozyme	Alglucosidase alfa	Enzyme	Pompe disease	Genzyme
2008	Xyntha	Factor VIII	Blood factor	Haemophilia A	Pfizer
2009	Simponi	Golimumab	Antibody	Autoimmune diseases	Janssen
2009	Stelara	Ustekinumab	Antibody	Psoriatic arthritis	Janssen
2010	VPRIV	Velaglucerase alfa	Enzyme	Gaucher's disease	Shire
2013	NovoEight	Factor VIII	Blood factor	Haemophilia A	Novo Nordisk
2014	Vimizim	Elosufase alfa	Enzyme	Morquio syndrome	Biomarin

Le et al., (2015) *CEP.* **Dec**, 132 - 37

Paradigms can be changed

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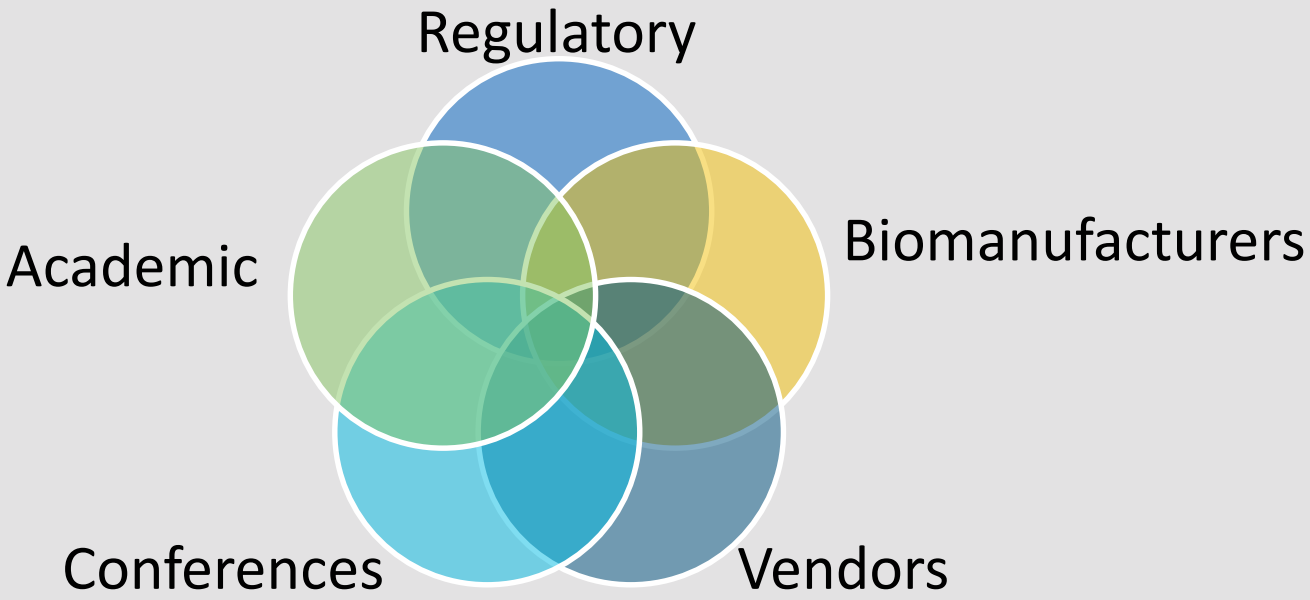
OVER THE LAST 5 TO 10 YEARS THE INTEREST, EFFORT, AND FOCUS ON CONTINUOUS BIOPROCESSING HAS SIGNIFICANTLY INCREASED



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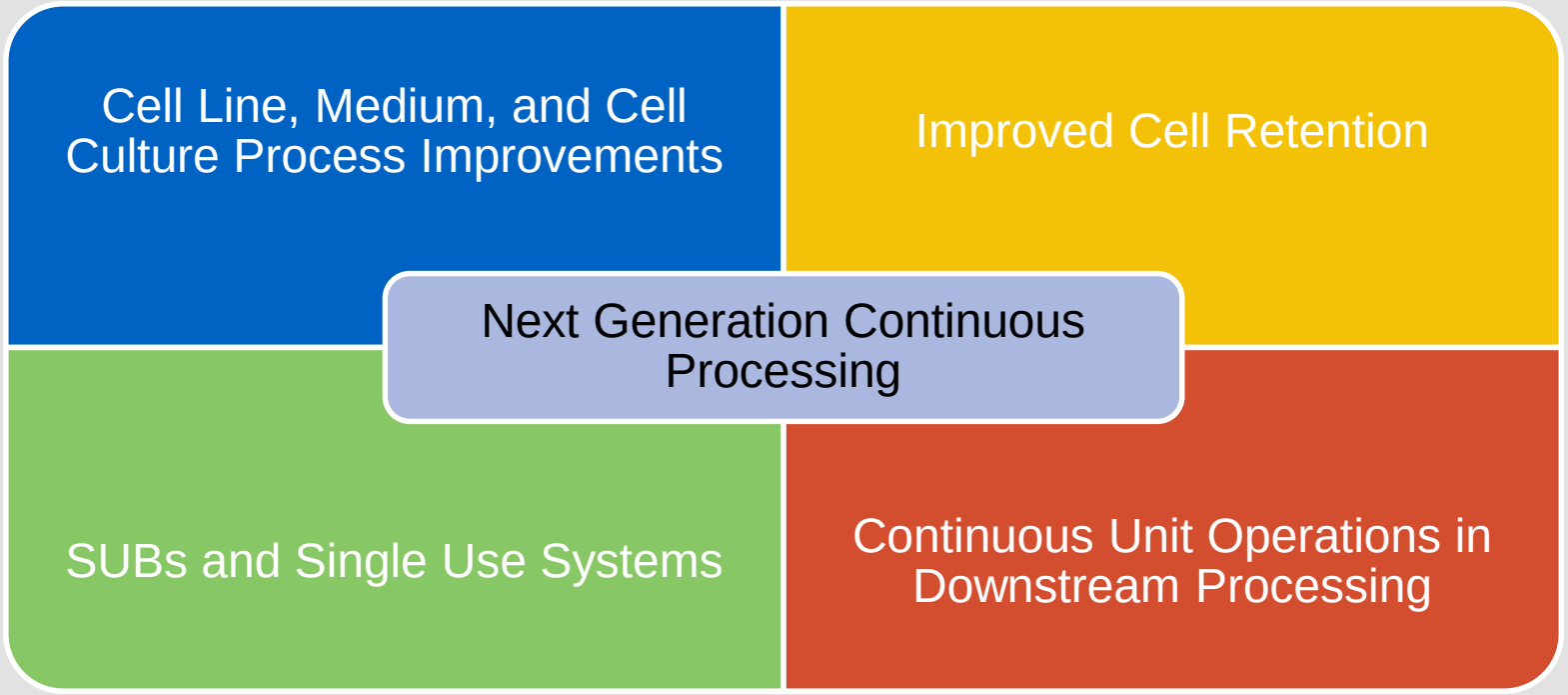
NEW TECHNOLOGIES ARE ENABLING NEXT GENERATION CONTINUOUS PROCESSING



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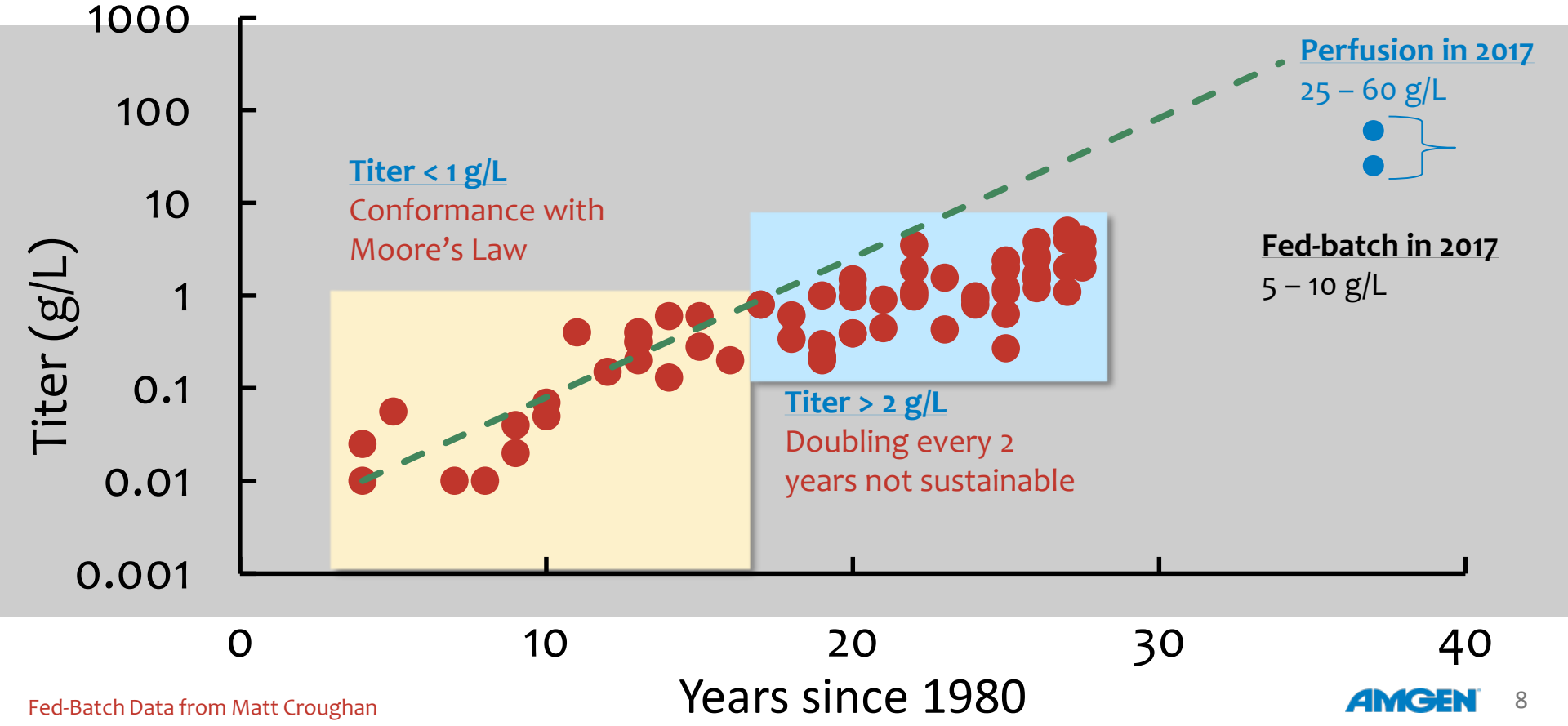
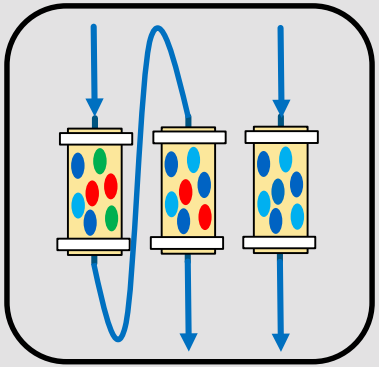
PRODUCTIVITY IMPROVEMENTS IN THE FED-BATCH PARADIGM HAVE PLATEAUED: PERFUSION CAN HELP MAINTAIN THE MOMENTUM



Fed-Batch Data from Matt Croughan

SIGNIFICANT ADVANCES ARE BEING MADE IN CONTINUOUS PURIFICATION THAT WILL FURTHER INTENSIFY PROCESSES AND DRIVE FOOTPRINT REDUCTION

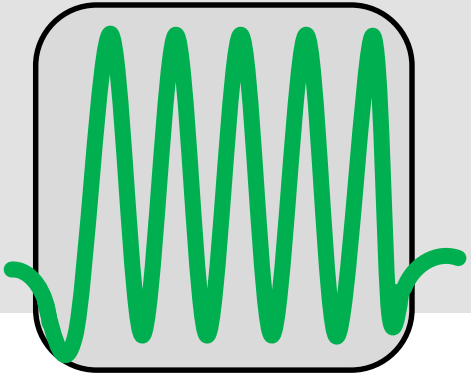


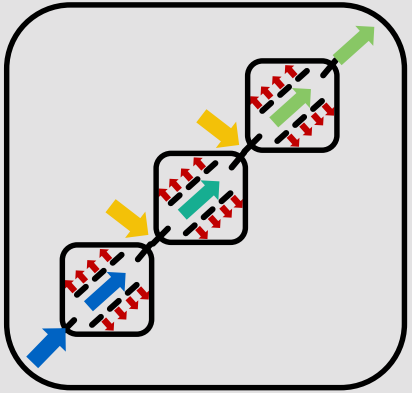
Continuous Chromatography

- PCC and Twin column

Continuous Viral Inactivation

- Inline continuous low pH hold





Continuous Formulation

- Inline continuous diafiltration

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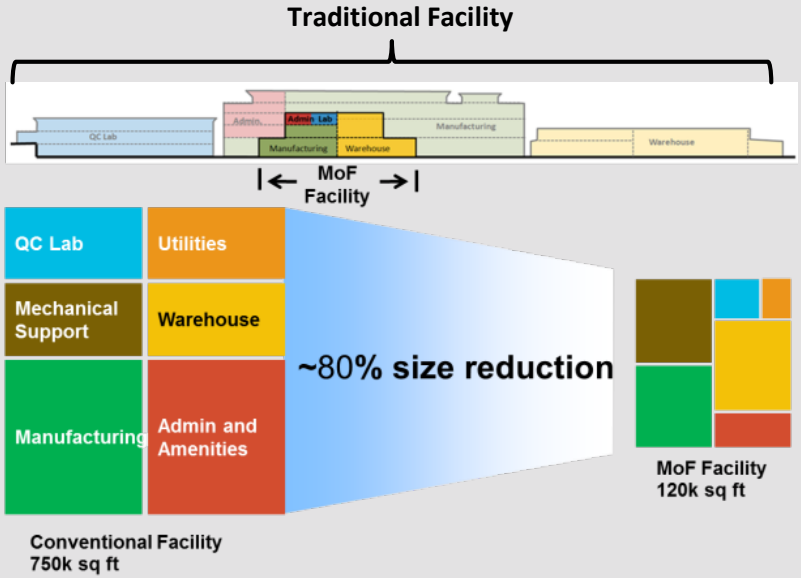
SINGLE USE SOLUTIONS ARE EXTENDING BEYOND THE BIOREACTOR, ENABLING FURTHER FOOTPRINT REDUCTION AND PROCESS SIMPLIFICATION

15 mL to 2000L single-use bioreactors
Source: Sartorius

Single-use mixing systems
Source: Millipore Sigma

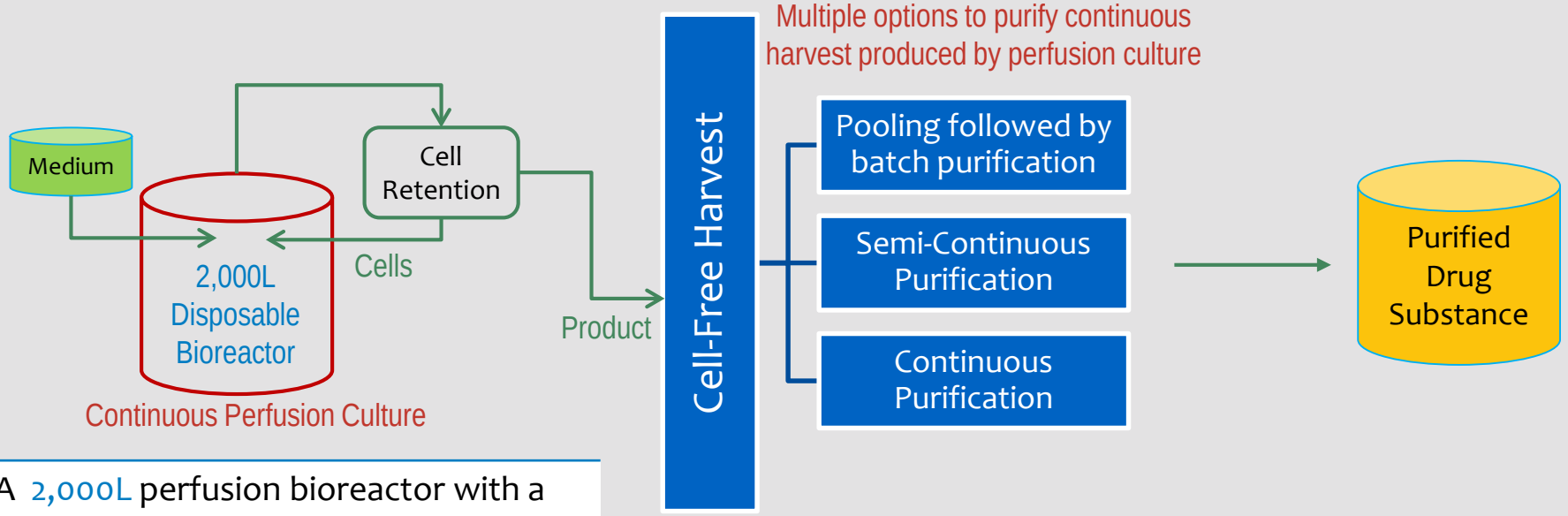
Chromatography skids with single-use flow paths and pre-packed disposable columns
Source: GE HealthCare and PALL

AMGEN SINGAPORE MANUFACTURING: NEXT-GENERATION FACILITY APPROVED FOR COMMERCIAL MANUFACTURING



This is version 1.0 of a flexible and intensified biomanufacturing platform

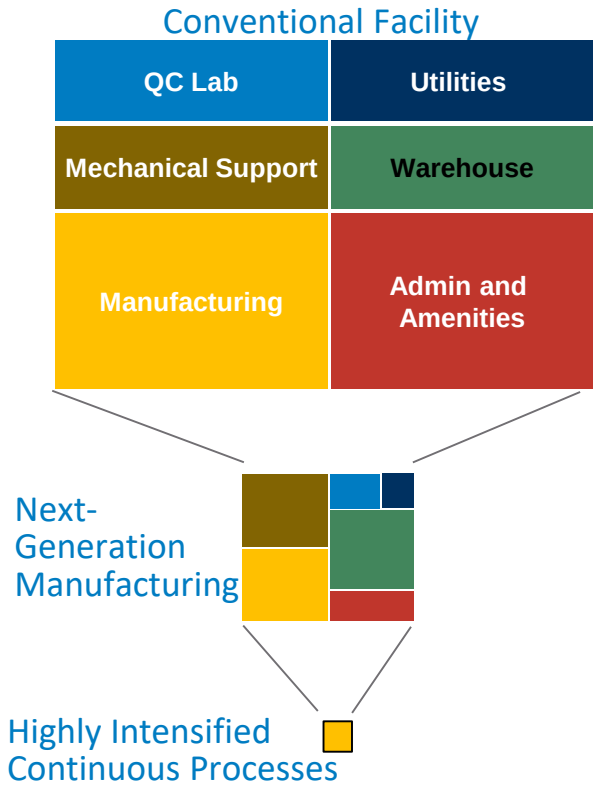
A HIGHLY PRODUCTIVE 2000L PERFUSION SYSTEM CAN ESSENTIALLY MATCH THE PRODUCTIVITY OF A 15,000L FED-BATCH BIOREACTOR



A 2,000L perfusion bioreactor with a volumetric productivity of 2.5 g/L-day
→ 50 kg Drug Substance in 15 days

This presents an opportunity to update the biomanufacturing paradigm

THE NEXT EVOLUTION OF BIOMANUFACTURING WILL INVOLVE ADDITIONAL PROCESS INTENSIFICATION AND INTEGRATION



CONTINUOUS PROCESSING CAN HELP TO TRANSFORM THE CURRENT BIOMANUFACTURING PARADIGM

Reduction in CAPEX and Footprint

- Significant reduction in capital investment
- Miniaturization and intensification of process workflows
- Shift from fixed to variable cost structure

Flexible and Scalable Capacity

- Targeted investment based on market demand/product mix

Lean Tech Transfers

- Scale out in place of scale up
- Development and training at development site

Reduction in Facility Time to Deploy

- Significant reduction in time to build
- Use of modular facilities

CONCLUSION: ‘YOUR RESULTS MAY VARY’

Considerations

- Product portfolio
- Market demands
- Existing manufacturing network
- Manufacturing business model

Opportunities (Challenges)

- Balance of Labor and Automation
- Equipment integration
- Improved Single Use systems
- Control strategies / $ for Analytical testing

THANK YOU