The 3C process for extremely low COGs in biologics production

Biosana PHARMA

Advanced biopharmaceutical manufacturing

Dutch Life Sciences Conference

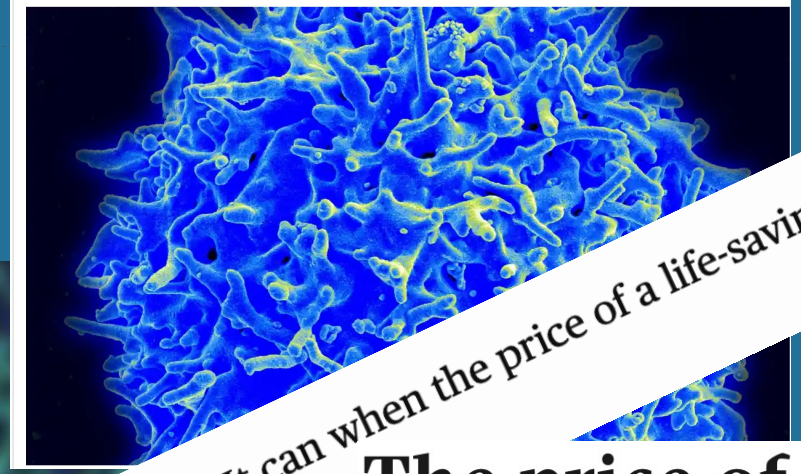
24 May 2022

Nettie Buitelaar

Biologics (mAbs, fusion proteins,…) are miracle drugs, but….

Immunotherapy: the big new hope for cancer treatment

Analysis: A combination therapy – helping the body's own defences fight cancer cells – has shown impressive results for terminally ill melanoma patients



Can a miracle drug also be a bitter pill? It can when the price of a life-saving prescription drug - is more than most people could possibly afford.

The price of being pain free: Why are life-changing biologics out of reach for so many?

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So what if…..
prices would go down to make those biologicals affordable and accessible for all?

That is the mission of BiosanaPharma:

The core purpose of BiosanaPharma is to develop the 3C process to full maturity for ultimately low Cost of Goods of biologics and biosimilars so these drugs can be made available to patients all over the world at affordable prices.

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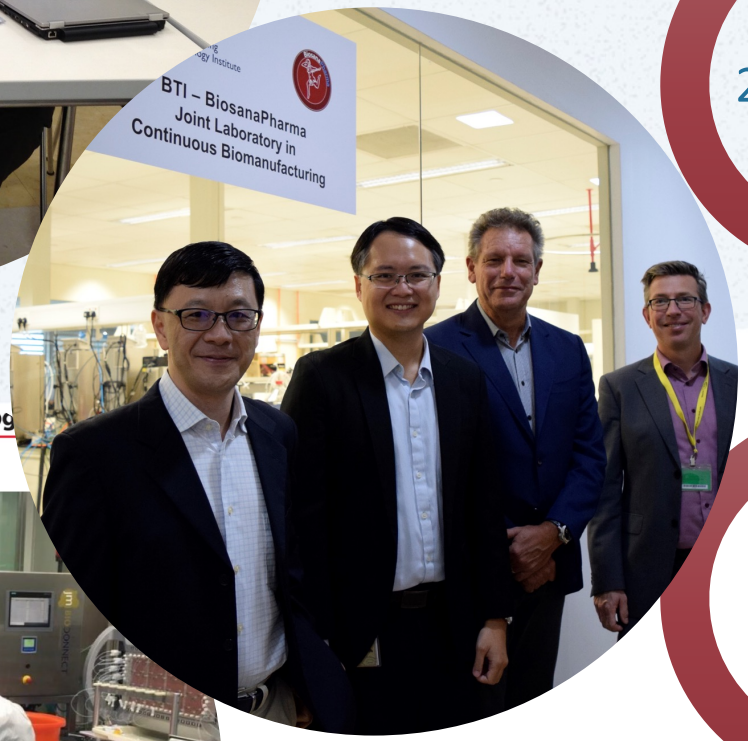
Timeline BiosanaPharma



2012-2015

- Invention 3C process by Ard Tijsterman
- Start of Biosana Pty in Australia; Ard Tijsterman CEO & Jaap den Engelsman CFO
- Nettie Buitelaar joins as CBO
- Set up of BiosanaPharma BV in NL as the holding company
- Proof of concept 2L 3C process at Mycenax, Taiwan
- 3C patent filed
- Selection first product; omalizumab biosimilar
- Jaap Wieling joins as CSO

2016-2017

- Maarten Pennings appointed CTO
- Proof of concept 50L scale 3C at Mycenax

2018-2019

- Manufacturing licence Dutch authority
- Production of GMP material for phase I omalizumab
- Start phase I
- Set up of BiosanaProcess PTE LTd in Singapore

2020

- Start of joint PD lab of BiosanaProcess and A*Star/BTI in Singapore
- Positive report phase I omalizumab biosimilar
- Transfer 3C process to CDMO Halix in Leiden

2021 - today

- Menne Zaalberg joins as COO
- Global M&S deal omalizumab with Alvotech
- Fundraising for expansion

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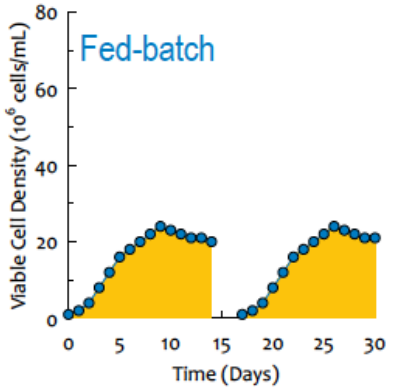
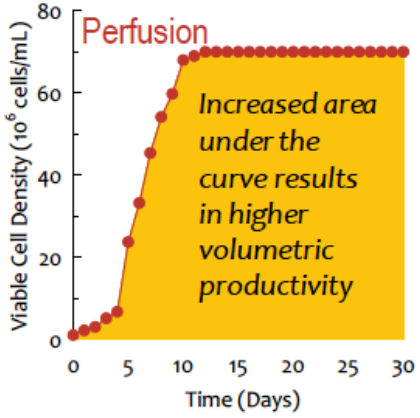
Why continuous manufacturing?

A Flexible Manufacturing Approach Readily Incorporates Continuous Technologies





Key recent advances that enable continuous manufacturing

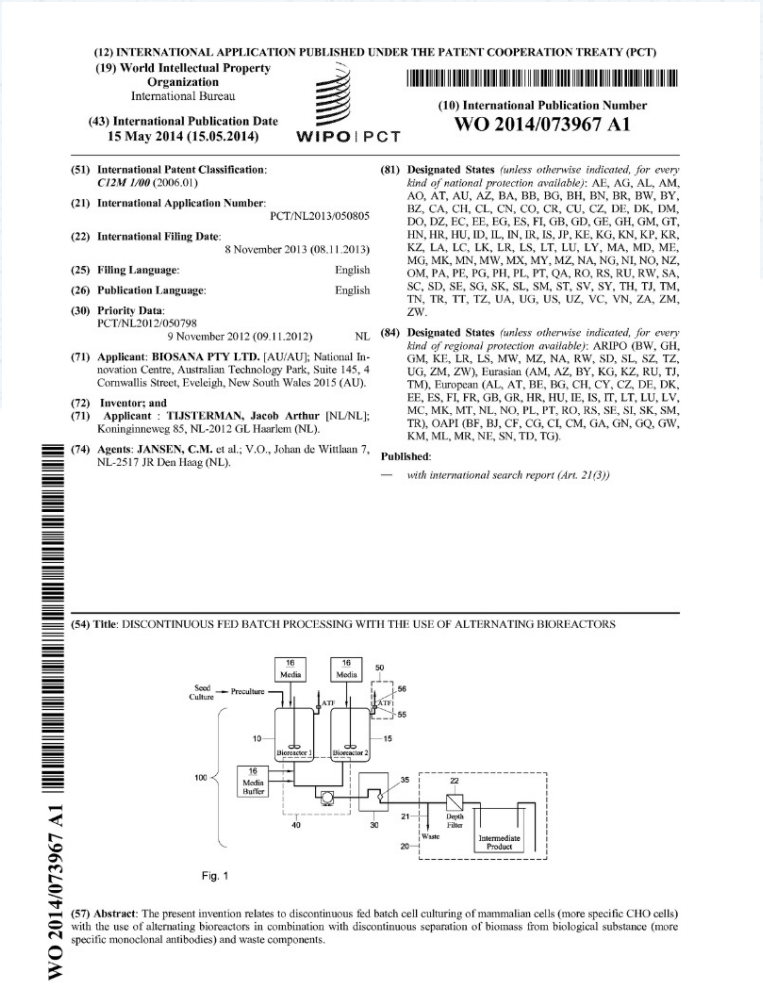
Cell Culture

- ❑ Disposable bioreactors
- ❑ Cell culture media that support high cell densities
- ❑ Robust cell retention devices
- ❑ Stable cell lines that could produce consistent product over longer durations

Purification

- ❑ Continuous chromatography systems
- ❑ Pre-packed and disposable purification columns

AMGEN



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(54) Title: DISCONTINUOUS FED BATCH PROCESSING WITH THE USE OF ALTERNATING BIOREACTORS

Fig. 1

(57) **Abstract**: The present invention relates to discontinuous fed batch cell culturing of mammalian cells (more specific CHO cells) with the use of alternating bioreactors in combination with discontinuous separation of biomass from biological substance (more specific monoclonal antibodies) and waste components.

WO 2014/073967 A1

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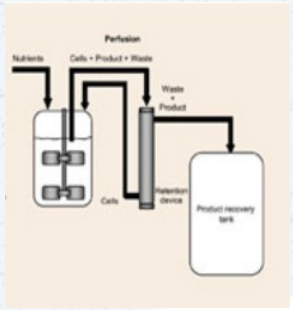
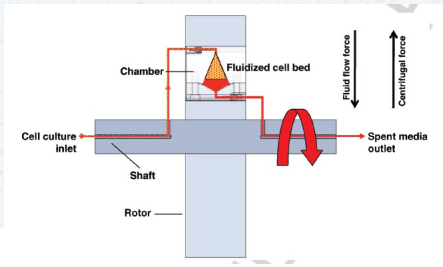
3C process: **C**ontinuous **C**ounter **C**urrent

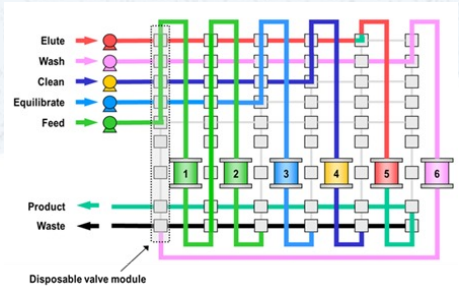
Multi cycle
High Cell
Density
Cell Culturing

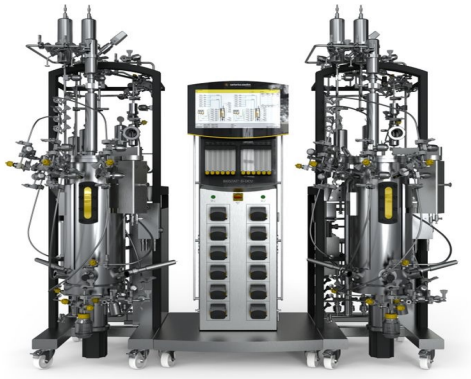


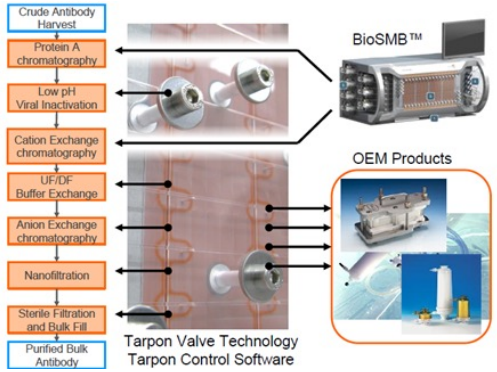
Multi cycle
Counter Current
Centrifugation



Multi cycle
Counter Current Chromatography
And Continuous DSP







- Target yield 50 L (wv) scale process : 1 Kg mAb/week (batches of ~ 500 gr)

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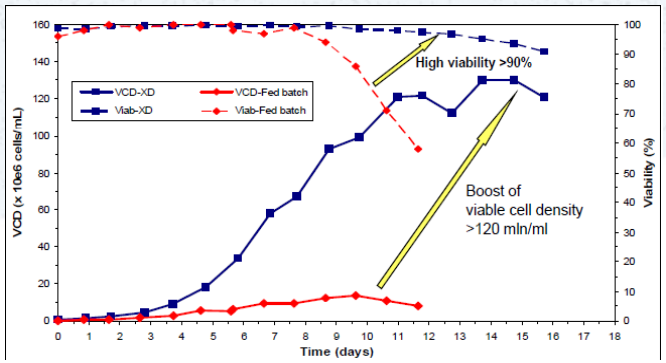
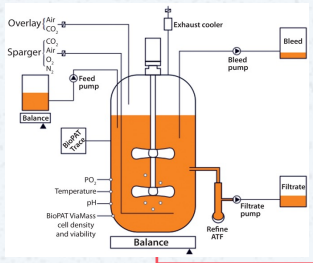
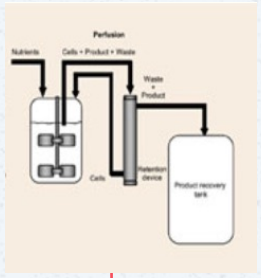
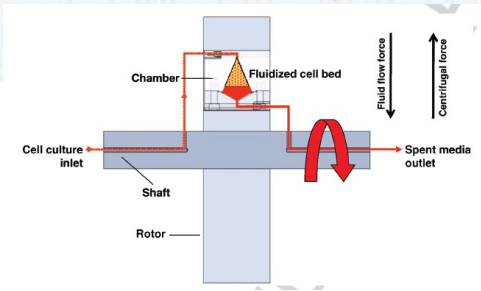
Multi Cycle HCD Perfusion & Clarification (Biosana IP)









- Continuous removal of product
- Continuous HCD culturing
- Semi continuous removal of all contamination & revitalization of the cell culture
- Overall continuous operation at cell level and production level
- Extreme high overall yield and volumetric productivity

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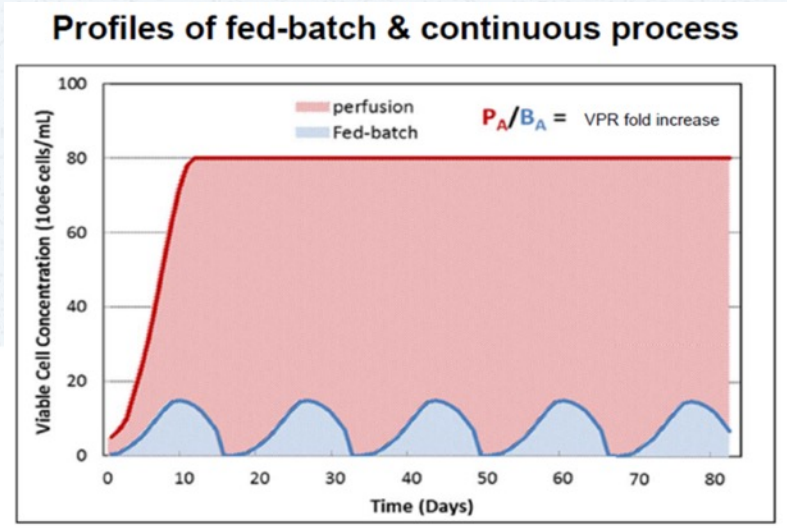
Continuous USP: very high productivities

The Promise of Continuous Biomanufacturing, Konstantin Konstantinov, ECI, ICB, Barcelona, 2013



Adapted from Presentation by Karl Rogler, PREP Conference (2015)

Volumetric Productivity = VCD x qP (/ 1000)
= 80 x 40 (/ 1000)
= 3.2 g/L/Day

Productivity 500 L = 1600 g/Day
= 67 g/hr

Annual production 500 L SUB:
500 L x 280 Days → 500 x 280 x 3.2 = 448 kg

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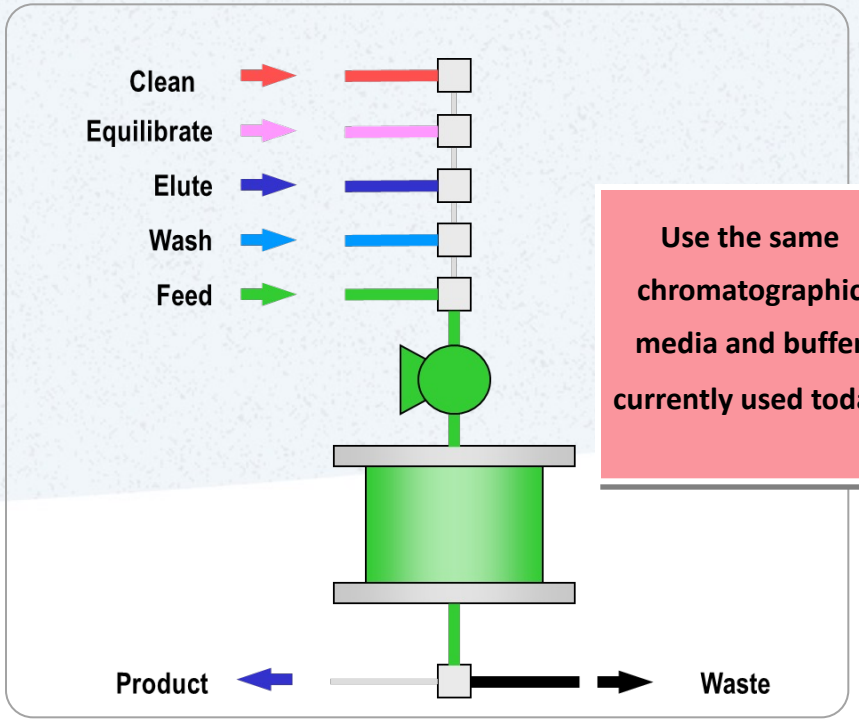
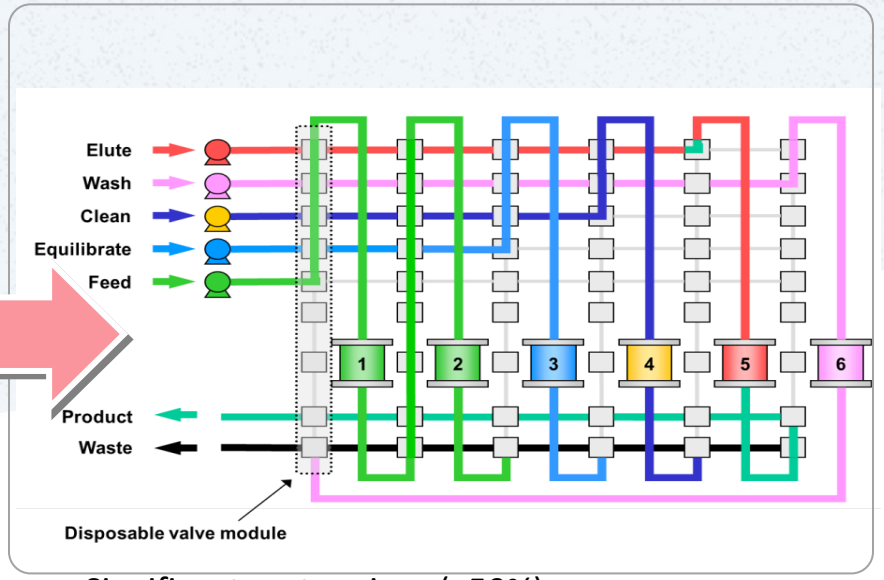
SMB: work horse of continuous DSP

Same batch steps carried out multiple times (50-400) on small columns



Use the same chromatographic media and buffer currently used today



- Expensive
- No economically viable disposable option
- Rigid process, time is not a variable
- Mass driven

- Significant cost savings (>50%)
  - Less buffer
  - Less chromatographic media
- Flexible and scalable
- Practical disposable parts
- Smaller footprint for same productivity
- Volume driven
- Idle mass transport zones (*i.e.*, dead space) are eliminated by cycling smaller columns

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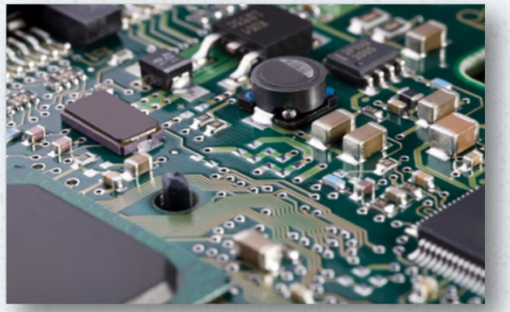
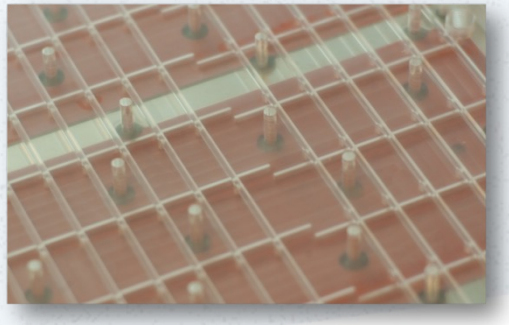
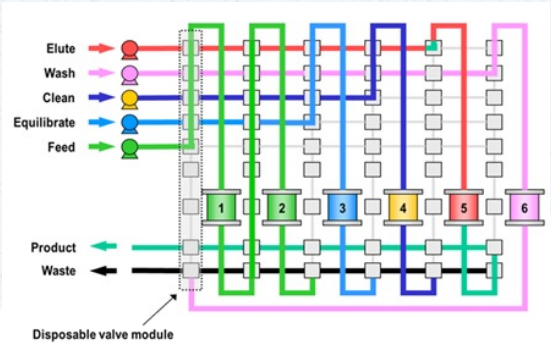
DSP made continuous with SMB technology

- SMB system valve block used as integrated circuit

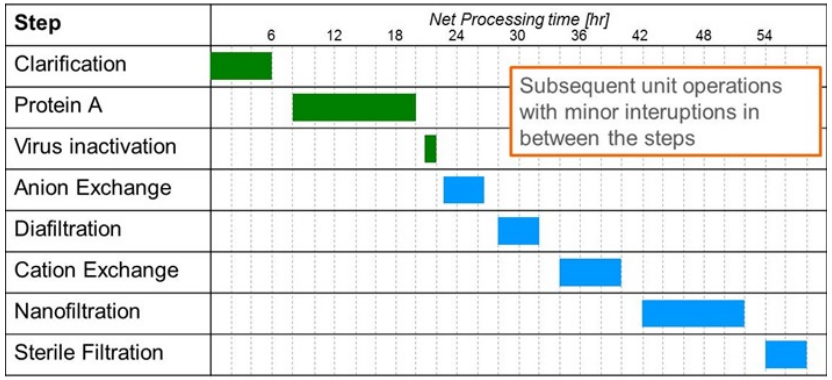




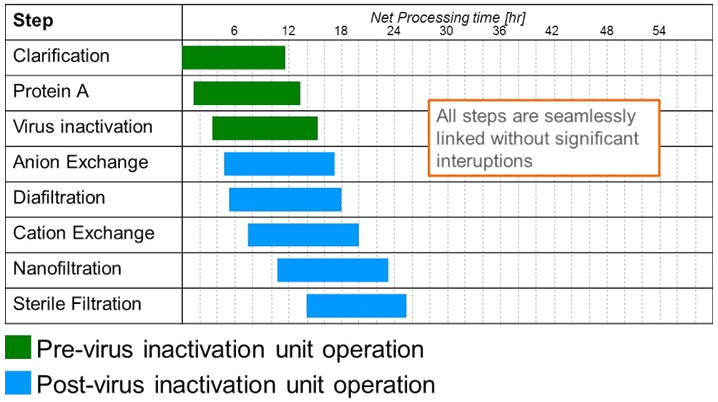


- Makes efficient continuous DSP possible (50% cost reduction)

Batch processing



Continuous processing



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The continuous 3C process has 4 operational sections

- **Upstream Processing, Biosana IP**
  - Culturing at HCD (TFF/ATF) with alternating use of bioreactors
- **Downstream Processing (1), many trade secrets**
  - Initial crude purification & VI
- **Downstream Processing (2), many trade secrets**
  - Polishing steps (>99.5% pure)
- **Formulation**
  - CD until final concentration reached then final formulation in batch

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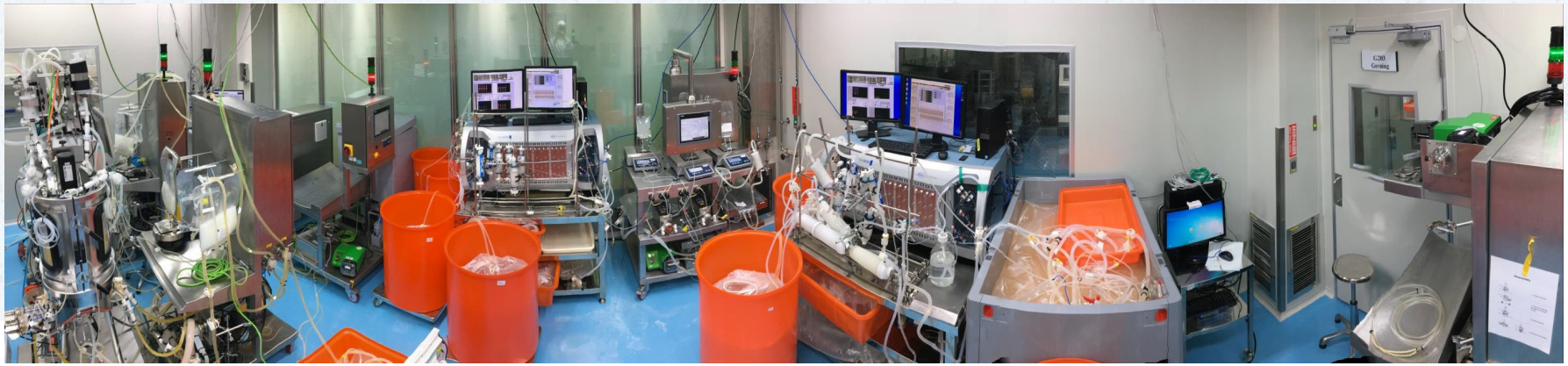
3C process in practice at 50L scale (under GMP) (room of 50m2)



- Continuous USP (Multi Cycle-HCD)
- Continuous DSP (Multi Cycle Chromatography & flow through filtration)
- Batch Formulation of Drug Substance (Concentration/Diafiltration)

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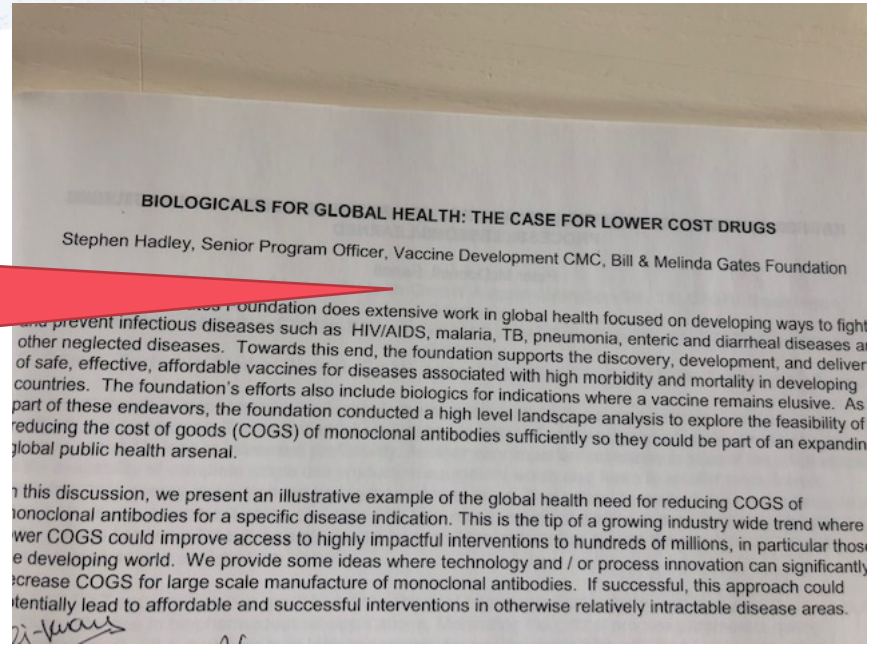
3C continuous process unique selling points

- ✓ Small equipment foot print (5x lower than batch and fed batch)
- ✓ Linear scale-up from 50L scale to 2000L scale under GMP
- ✓ Low COGs being realized (10x lower than traditional batch processing): CoGs 200L scale: $70/gr DS, 500L scale $40/gr DS
- ✓ Extreme low CoGs possible with high titer cell lines (6-10 gr/l in batch) and optimized 3C operation: 2000L scale $8/gr DS

"COGs mAbs must be <$10/g for low income countries"



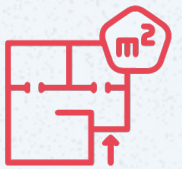
BIOLOGICALS FOR GLOBAL HEALTH: THE CASE FOR LOWER COST DRUGS

Stephen Hadley, Senior Program Officer, Vaccine Development CMC, Bill & Melinda Gates Foundation

...oundation does extensive work in global health focused on developing ways to fight ...d prevent infectious diseases such as HIV/AIDS, malaria, TB, pneumonia, enteric and diarrheal diseases a... other neglected diseases. Towards this end, the foundation supports the discovery, development, and deliver... of safe, effective, affordable vaccines for diseases associated with high morbidity and mortality in developing countries. The foundation's efforts also include biologics for indications where a vaccine remains elusive. As part of these endeavors, the foundation conducted a high level landscape analysis to explore the feasibility of reducing the cost of goods (COGS) of monoclonal antibodies sufficiently so they could be part of an expandin... global public health arsenal.

...n this discussion, we present an illustrative example of the global health need for reducing COGS of ...onoclonal antibodies for a specific disease indication. This is the tip of a growing industry wide trend where ...wer COGS could improve access to highly impactful interventions to hundreds of millions, in particular thos... e developing world. We provide some ideas where technology and / or process innovation can significantly ...crease COGS for large scale manufacture of monoclonal antibodies. If successful, this approach could ...tentially lead to affordable and successful interventions in otherwise relatively intractable disease areas.

Surface

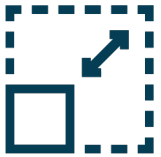


500 m2 -> 50-100m2

Footprint

5x lower

Scaling



From 50L tot 2.000L

Costs

COGs

$70/gr -> $40/gr -> $8/gr

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3C Development

- ✓ BiosanaProcess PTE in Singapore was set-up for specialized continuous process & product development, both based on the 3C process.
- ✓ In 2020 a 3-year collaboration agreement was signed with A*Star-BTI:
  - ✓ down scaled 3C process,
  - ✓ process modeling for future high throughput Process Development (PD),
  - ✓ advanced analytical (PAT) for continuous processing and
  - ✓ validation of the small-scale PD with different products.
- ✓ IP: WO2014/073967 Discontinuous Fed Batch processing with use of alternating bioreactors.
- ✓ New patent application (EPC # 22159438.5) on dual system use for continuous processing (USP & DSP) with lot traceability.
- ✓ PoC for the CoGs target of $8/gr Drug Substance : integration of high titer cell lines in the 3C process and further optimization of the USP and DSP unit operations.

Amb250 minibioreactors (12x)

2x5LPerfusion Bioreactors

Akta PCC (cont. chromatography)

Biosana PHARMA

Thank you.

We make biologics
affordable and **accessible**
for all patients.

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