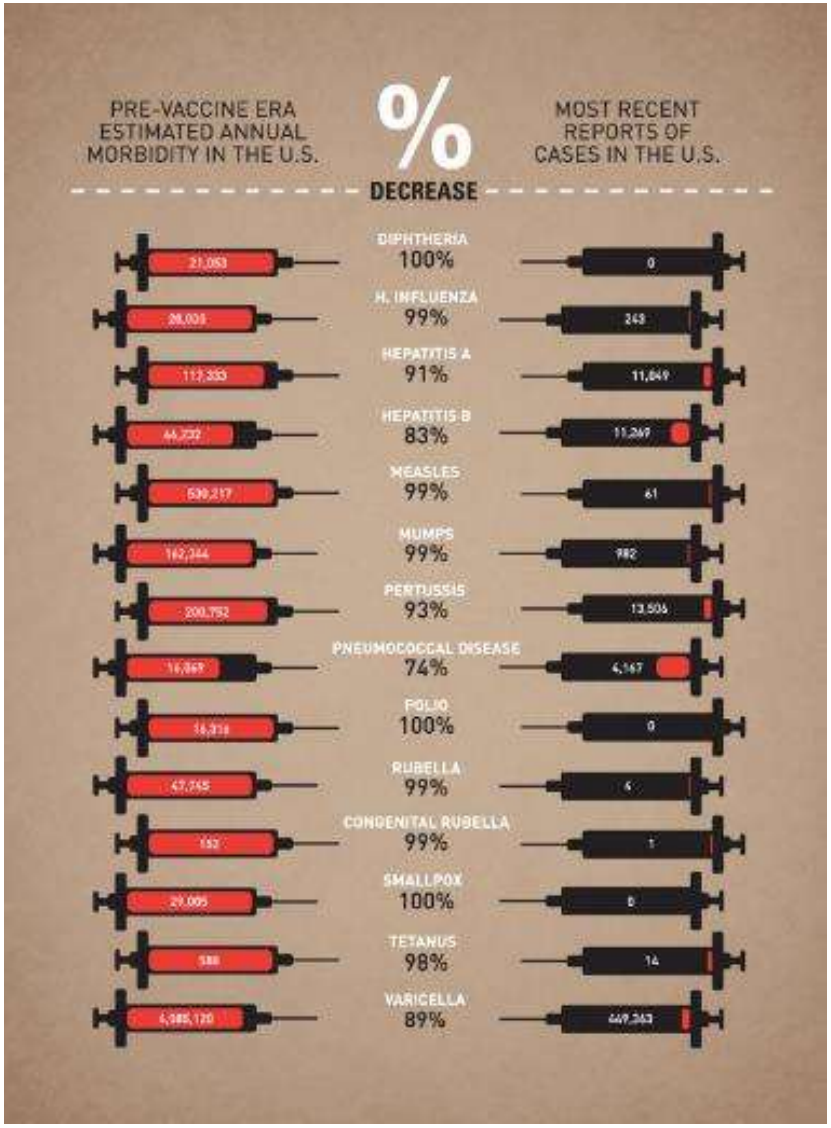
UNIVERCELLS

# Innovative Cell culture and purification approaches applied to cost-effective manufacturing of viral vaccines

DCVMN Seminar

October 12th, 2017 -- Gosselies, Belgium

# **Vaccines** are the most efficient tools to **prevent infectious diseases**




Immunization currently averts an estimated **2 to 3 million deaths every year (of DTP and Measles).**

An additional **1.5 million deaths could be avoided**, however, if global vaccination coverage improves.

An estimated **19.4 million infants** worldwide are still missing out on basic vaccines.

In addition :

**Insufficient supply and late availability** (i.e.)

Prevnar in 2011, USA

BCG in 2015, France

Meningitis C in 2015, Africa

DPTP in 2015, India

**Crisis examples**

Zika Virus spread

Ebola epidemic

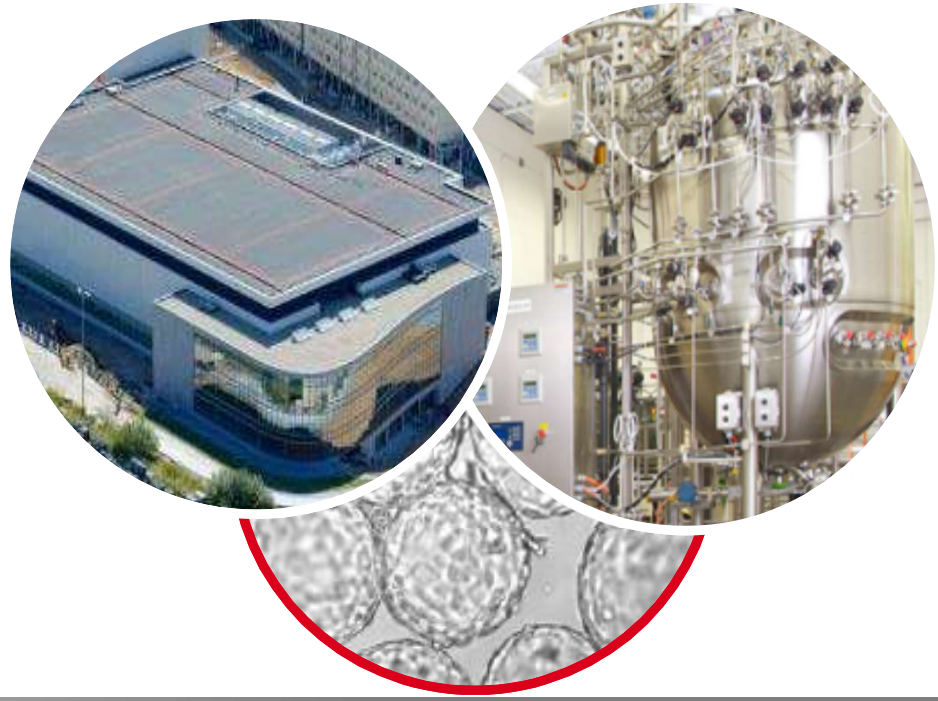
**Increased capacity** of production and **cheaper vaccines** are urgently needed

The global vaccine market will reach **48Bn$ in 2021**, and 90% in the developed countries.

**Emerging countries** must become able to **manufacture their own vaccines**

# Vaccine Manufacturing Today… Limited Innovation

> Over 80% of viral vaccines are still manufactured by the scaling out of lab-scale systems
> **Barrier**: Very high CAPEX
> **Risk**: High number of asceptic manual operations
> **Production** capacity ↓↓, cost ↑



> Some vaccines are manufactured in bioreactors – scaling up
> **Barrier**: Extremely high CAPEX
> **Reduced risk**: Limited aseptic manual operations
> **Production** capacity ↑↑, cost ↑↑

# Problems with the current technologies… Barriers to entry

- Current manufacturing methods require large factories and high CAPEX (>100M$)
- Manufacturing are complex processes, which needs large, well-trained workforce
- Production is still based on *Batches* processes (separated steps of manufacturing)
- The production uses low-density manufacturing technology, leading to high COGS.
- Regulatory and quality-control processes are costly and complicated.

**=> Those barriers are preventing small players and emerging countries to enter the market**

**INNOVATION in MANUFACTURING**

**Densification and Chaining of operations**

**Disruptive innovation in the manufacturing technology could reduce the footprint of factories, simplify and automate the Process, which will simplify the QC and be run in a continuous fashion.**

# Univercells' Vaccine Manufacturing Proposal

## Concept:

Single-Use, very **high-density bioreactor** (reduction of size)

- Cells grow in fibers in bioreactor, medium perfused through
- Bioreactor scalable from 0.5M2 to 2000M2
- Cell density up to 250M cells/mL achieved in small footprint

**Inline** filtration, **adjustment of perfusate** (pH, conductivity) and **purification** – No intermediate storage tank
Continuous process allow to **use small purification columns up to 100 cycles** during a single run

CHAINING of operations allows simple **micro-facility**, with very small footprint

**UNIVERCELLS' NEW CONCEPT**

**Intensification of unit steps**

**Integration into a continuous process**


**SINGLE-USE "CLASSICAL" PROCESS**

# Evolution of the vaccine manufacturing using Bioreactors

## Conventional reactor + Microcarriers

> Based on Microcarriers
> **1 to 10M cells/ml**
> Batch process, not integrated with DSP
> High footprint

## iCELLis bioreactor


> Microcarriers replaced by microfibers
> High cell density **- up to 100M cells/ml** (20-fold increase compared to microcarriers)
> Can be integrated with Purification (DSP)
> Reduced CAPEX & OPEX, small footprint
> sIPV in 500M$^2$ (65L) iCellis = 500,000 doses (equivalent to 750L Conventional)

## Univercells Microfacility

> Simpler/lower cost reliable design
> High cell density - **up to 250M cells/ml**
> Continuous process USP => DSP
> Housed into isolators
> Reduced CAPEX & OPEX, small footprint
> sIPV in 500M$^2$ (25L) = Up to 2M doses

# UNVC team has experience with bio-manufacturing technologies, following a first success with Artelis, subsequently sold to ATMI & Pall

## 2005


Innovation concept

## 2008


Innovation
early adoption

## 2012


Innovation
global adoption

## 2013


Innovation
complete solution

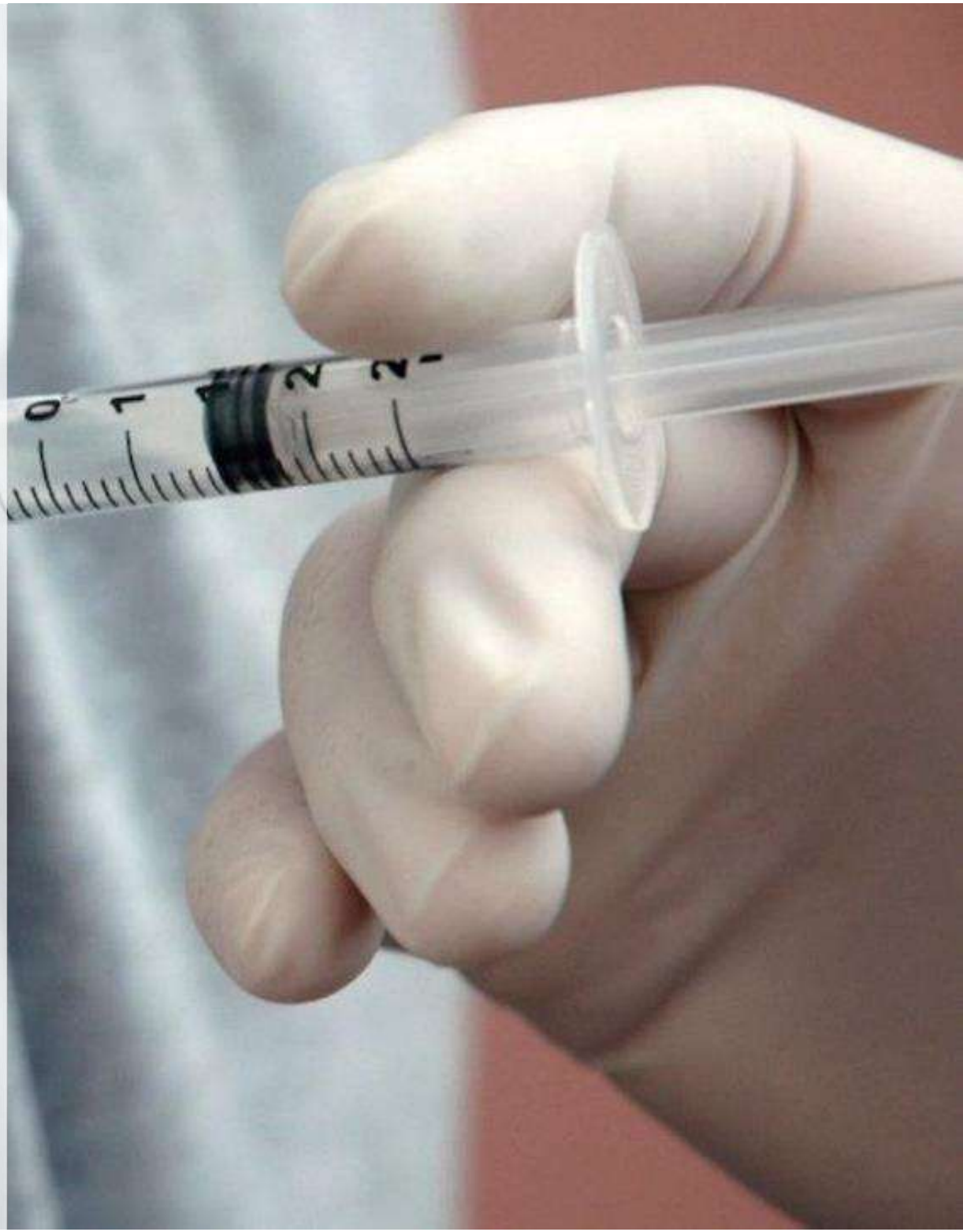
Source: Univercells

UNIVERCELLS BATAVIA biosciences Natrix

OmniVax

# Development of an Integrated Platform for the Low Cost Manufacture of Vaccines for Global Health

BILL & MELINDA GATES foundation



# The Platform goals

## Target $0.15 per dose vaccine drug product cost

> Increased process productivity, yield and robustness
> Reduced process-related operating costs (materials, labour, utilities etc)
> Simplified, smaller facility with much reduced capital costs

## Expansion of market supply - 40M doses / year with ‘micro-facilities”

> High productivity ensures global supply from multiple small facilities

## Low hurdle for implementation

> Low CAPEX
> Suitable for new facility or retrofit of existing facility
> Single-use templated platform reduces overall risk
> High safety and containment

# Representatives of the chosen consortium (out of 155 candidates)

UNIVERCELLS

> Consortium integrator, coordinator and responsible party
> Integrated continuous manufacturing technologies
> High cell density bioreactor


Natrix

> High capacity / high flow purification membranes
> High efficiency affinity ligands

BATAVIA biosciences

> Viral vaccine process development & manufacturing
> Cell line development

# Addressing the Challenge

1 BATAVIA biosciences

Optimized cell line and production medium
Target: >2-fold increase in virus productivity

2 UNIVERCELLS

High Cell Density Bioreactor (Target: >20-fold increase in cell density and virus productivity) and

Natrix

Affinity Purification Membranes (Target: 2-fold increase in recovery, single step purification)

3 UNIVERCELLS

BATAVIA biosciences

Integrated continuous process Linked process in modular isolators – small footprint, low cost (OPEX and CAPEX), high containment manufacturing environment

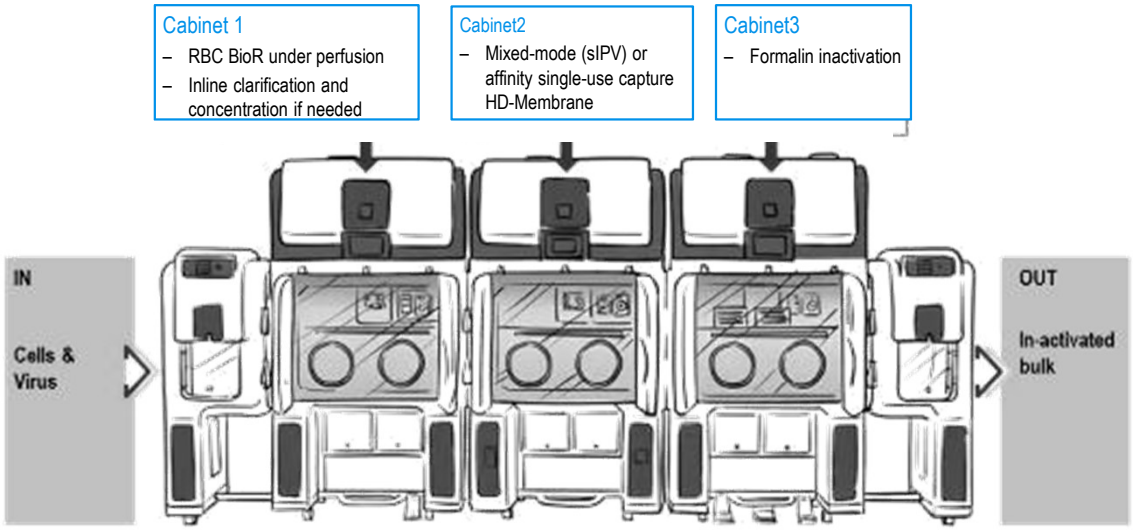
**3 pillars**
to establish an integrated manufacturing platform, applicable to multiple vaccines

# Path to sIPV at $0.15/dose – 40M doses/year from a lab-scale micro-facility

**Pillar 1**
Expression system
- Process optimized WHO Vero cell lines

**Pillar 2**
Intensification technologies
- High density bioreactor **chained** with *inline* single-step high capacity capture chromo

**Pillar 3**
Micro-facility technologies
- High containment, low footprint, low cost micro-facility utilizing isolators




## Driving down the cost

…to 15¢ per dose

> sIPV process and facility ready for manufacture in 2 yr timeframe

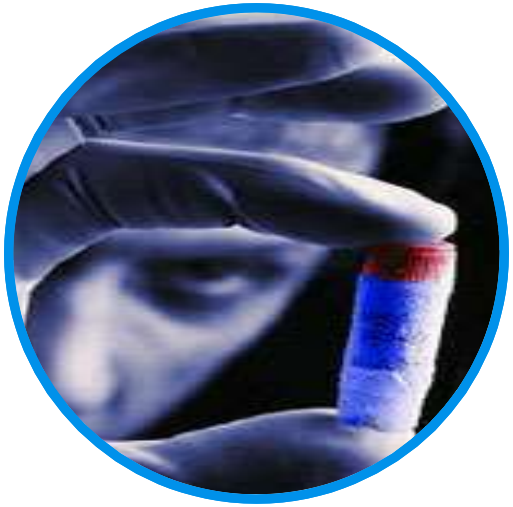
> **Chained process** with intensification technologies for fewer, smaller unit ops enables isolators to miniaturize the facility

> Industrial production at lab scale with **isolator-based micro-facility** for
  > Simplified infrastructure and dramatic decrease of CAPEX, the biggest factor driving reduction in cost/dose
  > Simplified operations for a robust platform that can be replicated and/or quickly deployed for in-region manufacturing

> 40M vaccine doses per year from **$10M investment in the facility** that delivers sIPV product at as low as $0.15/dose

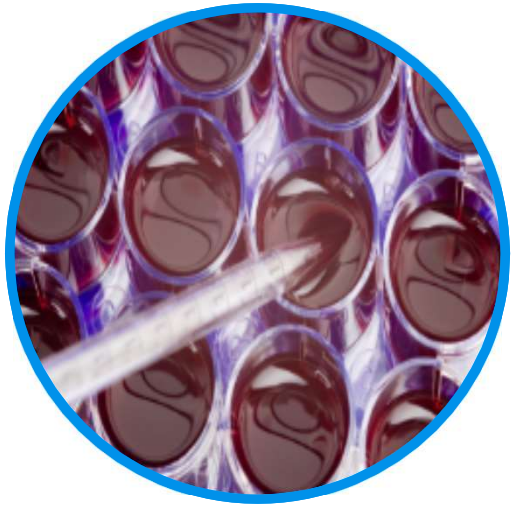
# Pillar 1: Optimized cell line & production medium

Sub-clone of
WHO 10-87 cell line



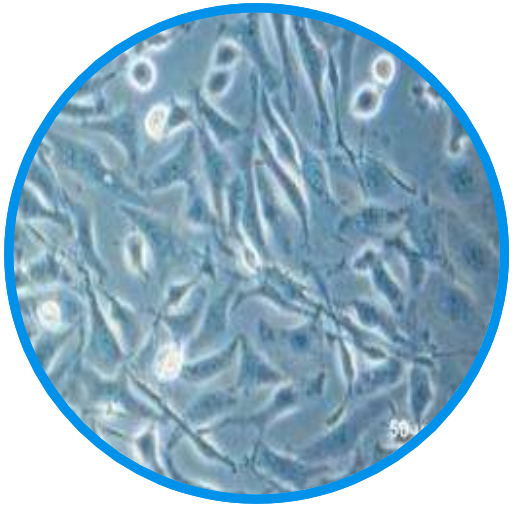
Increased virus
production capabilities

Selected viral sensitizers
and (lipid-based) viral yield
enhancers



Increased virus yields

Selected low serum or
serum-free growth media



High cell densities and low cost

# Pillar 2 (1): high cell density, small footprint, single-use bioreactor

## Conventional reactor + Microcarriers

## iCELLis


- Microcarriers replaced by microfibers
- High cell density - up to 100M cells/ml (20-fold increase compared to microcarriers)
- Reduced CAPEX & OPEX, small footprint
- sIPV in 500M$^2$ (65L) iCellis = 500,000 doses (equivalent to 750L STR)

## Univercells Bioreactor

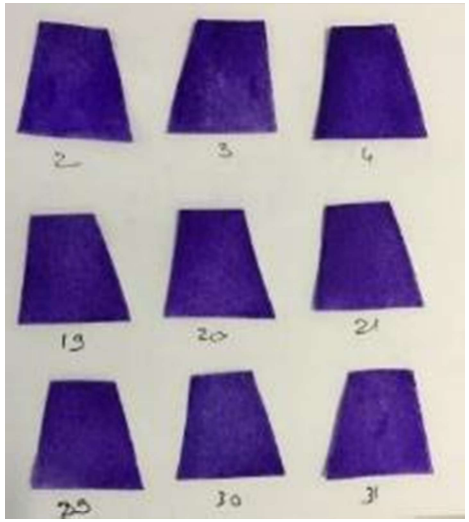
- **Simpler/lower cost reliable design**
- High cell density - up to 200M cells/ml
- **"Integratable" into isolators**
- (40-fold increase compared to microcarriers)
- Reduced CAPEX & OPEX, small footprint
- sIPV in 500M$^2$ (25L) = 500,000 doses

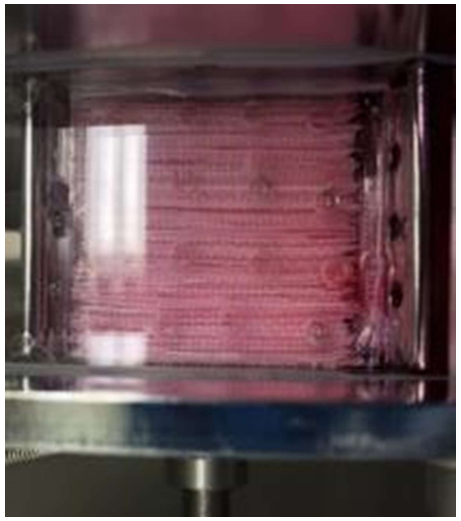
# Pillar 2 (1): high cell density, small footprint, single-use bioreactor

## Evaluation of microfiber technology – structured fixed bed with multiple embodiments

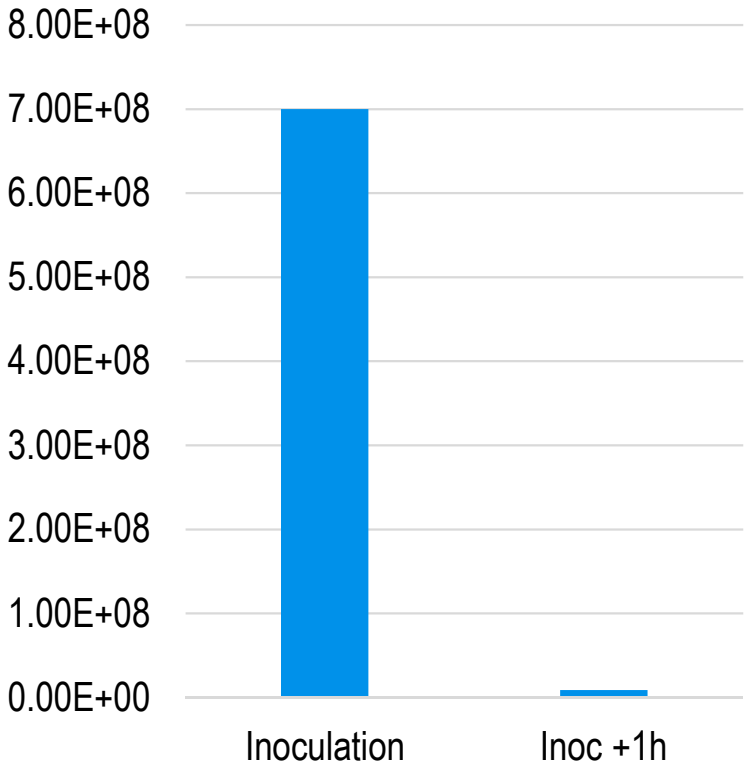
### Benefits of a structured bed

> Homogeneity – scale up virtually non limited
> Fast cells entrapment/attachment
> Easier to fabricate – cost effective
> Compatible with multiple bioreactors





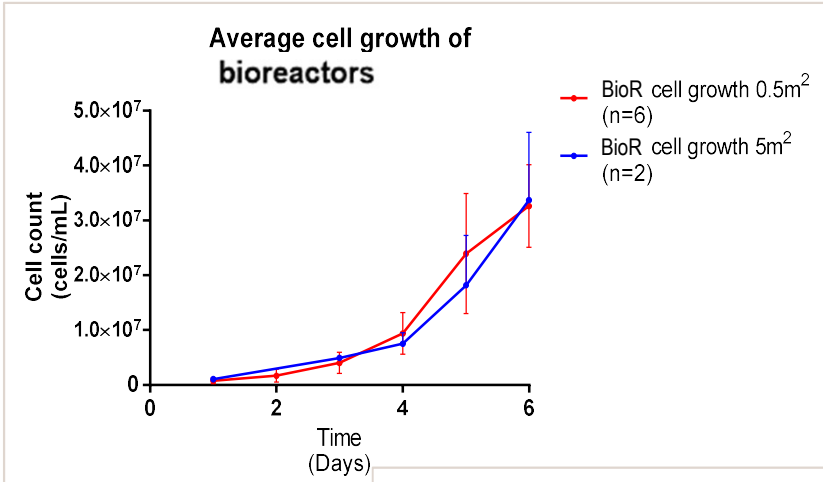
### Cell Entrapment Kinetics

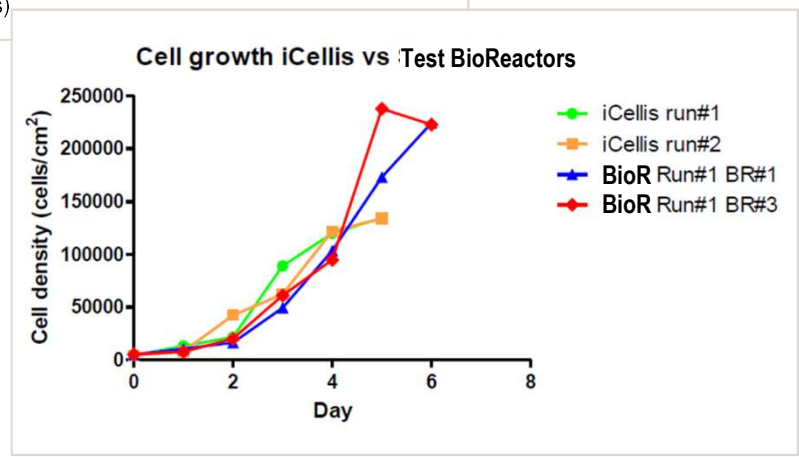


# Pillar 2 (1): high cell density, small footprint, single-use bioreactor

## Bioreactors evaluation – structured fixed bed with multiple embodiments

- **Cell culture and virus production** in **Tested bioreactors**:
  - Use of parental cell line
  - Target density at infection: 30-40M/ml
  - Reproducible growth in DMEM-Serum
- **3x 2,5m² bioreactors have undergone cell culture trials**
  - Multiple runs show similar cell growth compared to the reference run performed at Univercells and on iCellis bioreactor system
- **25m² to be tested in November**



# Pillar 2 (1): high cell density, small footprint, single-use bioreactor

## Structured fixed bed bioreactors with multiple embodiments

**sIPV3**

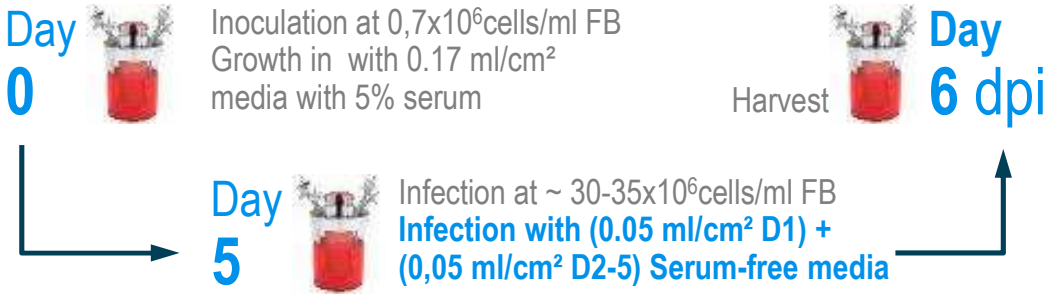
> **Cell culture and virus production** in tested bioreactors:
  – Use of parental cell line first
> **Initial optimization** leads to:
  – Doubling of D-antigen output per run
  – Concentrated DU/mL thanks to medium feeding

**Improvements**

> 90 DU/mL (n=26) vs 4560 DU/mL$_{FBed}$(n=1)
> **~40x** in BioR volumetric productivity
> With current small scale yields and parental cell line, **Univercells process would yield:**
  – @500m² / 37L FB and 2x250L medium in perfusion, ~650DU/mL in 250L
  – ~4.2M doses/run in crude harvest

| Production system | D-Ag/mL of culture media | D-Ag/cm² | D-Ag/cell at infection | D-Ag/mL of fixed-bed |
|---|---|---|---|---|
| Spin tube | 89 ± 31 (n=49) | TBD | TBD | NA |
| Fixed-bed bioreactor (Standard process) | **118** ± 18 **(n=2)** | 18.8 | 7.2 x10$^{-5}$ | 2664 |
| **Fixed-Bed bioreactor (Optimized process)** | **646 (n=1)** | **32.3** | **1.7 x10$^{-4}$** | **4560** |

**x 1,7**



# Pillar 2 (1): high cell density, small footprint, single-use bioreactor

## Univercells Bioreactor – structured fixed bed with multiple embodiments

**sIPV2**

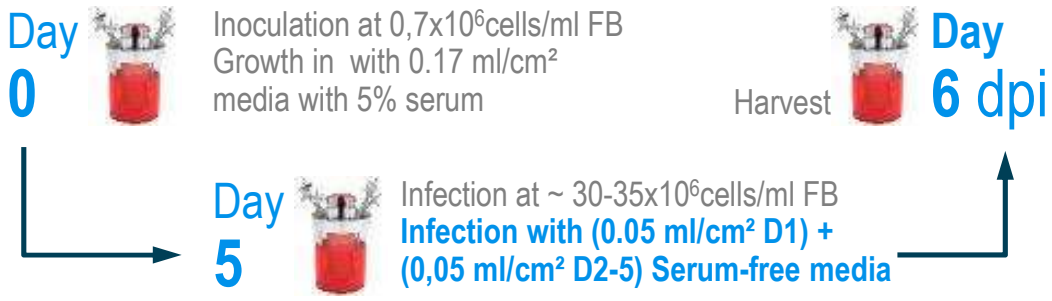
> sIPV3 improved process used for sIPV2
- Infection medium reduction (from 0.17mL/cm² to 0.1 mL/cm²) and feeding optimization
- Cell growth performed in serum-free
- sIPV2 production is feasible in UNC Bioreactors

| Production system | D-Ag/mL of culture media | D-Ag/cm² | D-Ag/cell at infection | D-Ag/mL of fixed-bed |
|---|---|---|---|---|
| Spin tube | 9.1 ± 5 (n=50) | 0.67 | 4.48x10-5 | NA |
| **Fixed-Bed bioreactor (Optimized process)** | **52 ± 2 (n=1)** | **2.6** | **1.4 x10$^{-5}$** | **364** |

**Improvements**

9.1 DU/mL (n=50) vs 364 DU/mL$_{Fbed}$ (n=1)
**~40x** in BioR volumetric productivity

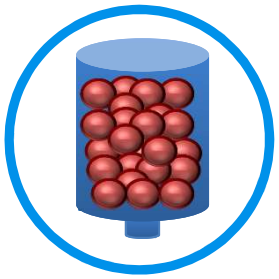
With current small scale yields and parental cell line, **Univercells process would yield:**
> @500m² / 37L FB and 2x250L medium in perfusion, 52DU/mL in 250L
> ~0.7M doses/run in crude harvest

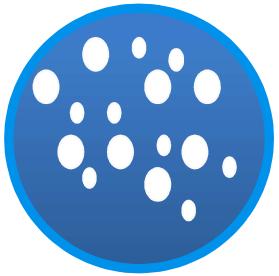


JC5

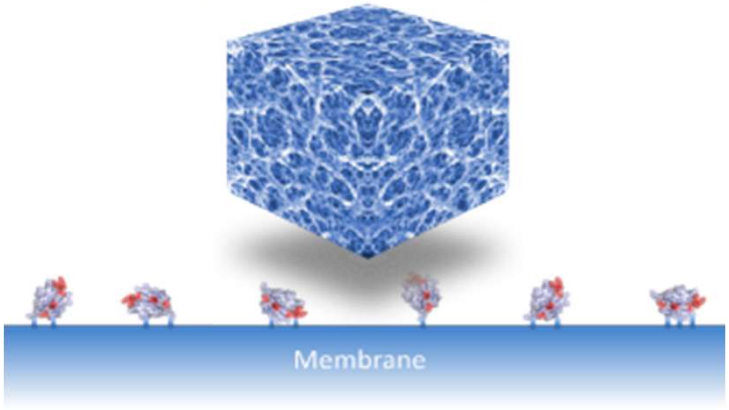
# Pillar 2 (2): High capacity purification membranes

RESINS =
+ High Capacity
- Long Residence Time





MEMBRANES =
+ Short Residence Time
- Low Capacity




+ Short Residence Time
+ Cycle times in minutes
+ High binding capacity

➔ Maximized Productivity
➔ Reduced process time
➔ Reduced cost

> Affinity membranes drive >3-fold productivity over traditional resins
> Membranes introduced in 2013, accepted for GMP manufacturing

**Slide 19**

**JC5** Thought we had a better slide than this one that shows the same evolution for chromatography as for reactors. I'll look while flying to Mumbai
John Chickosky; 27 Mar 2017

# Update Project progress – Technical Goal 1

## WP2: Development of DSP

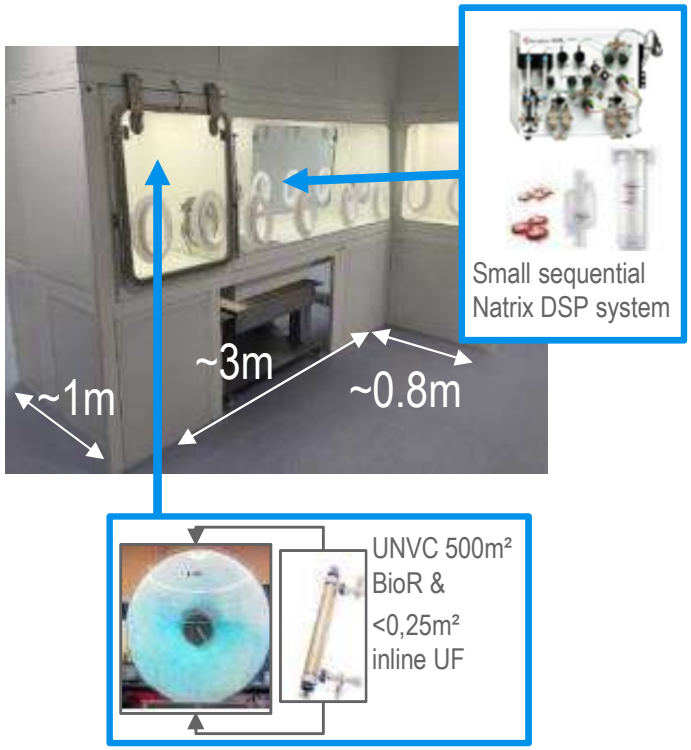
- DSP development outline and progress
  - Screening performed for S2 and S3 at small scale
- Promising results with PV3 – HD-Sb delivers expected performance
  - **High binding capacity** (>50 000DU/mL Mb)
  - **Good HCP clearance** (<0.1µg HCP/DU) – Meets WHO specs
  - **High yield**: >90% (Target for the overall DSP >70%)
- Reduction of clarification footprint and cost is underway. Footprint estimated to be less than 50% of the current depth filter-based train (data analysis ongoing)
- Similar results are expected with PV2 (data analysis ongoing)


| | | | |
|---|---|---|---|
| Recovery | 94% | ug HCP/DU | <0.04 |
| Mass Balance | 95% | DNA LRV | Pending |
| HCP LRV | 1.6 | ng DNA/DU | Pending |

# Pillar 3: Platform enabled by innovative technologies
# Streamlined, simplified & miniaturized operations enable cost savings

The **intensification** technologies, **chained** into a continuous process, allow their integration into highly flexible, low footprint, isolated micro-facilities

## Micro-Facility Isolator Units




## Key take-aways

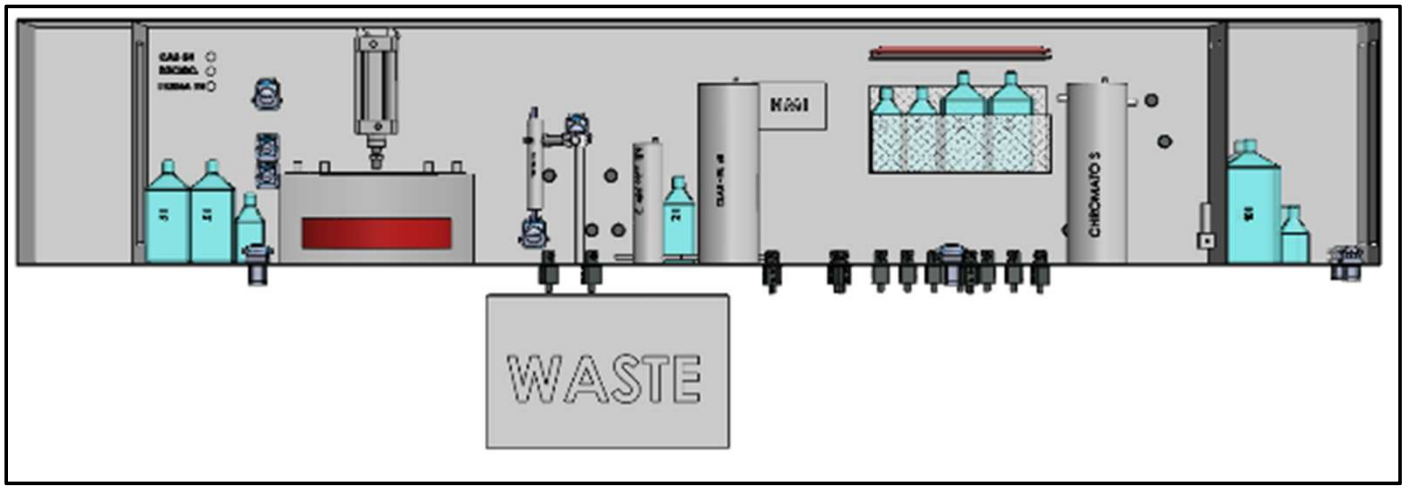
> Low cost sIPV vaccine (as low as 15 cents per dose) seems achievable
> Platform delivers commercial manufacturing at lab scale - new paradigm in vaccine manufacturing
> Platform applicability and flexible for broad range of vaccines

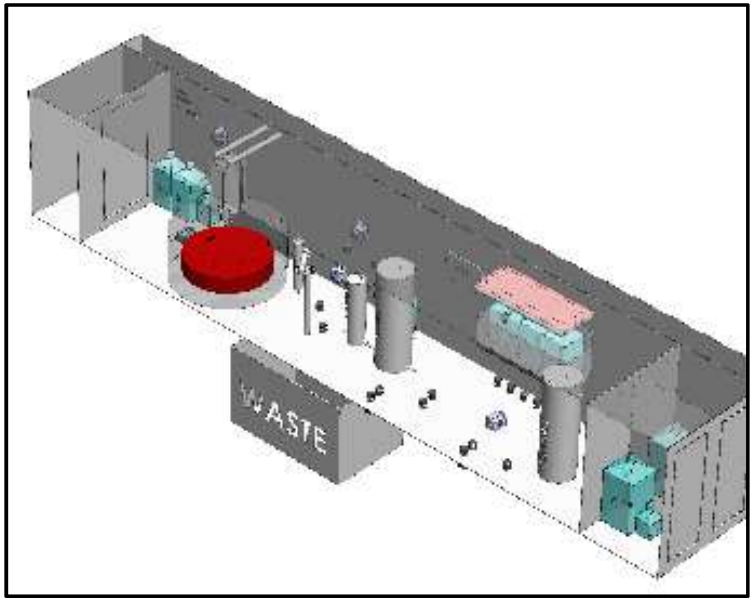
## Core innovations

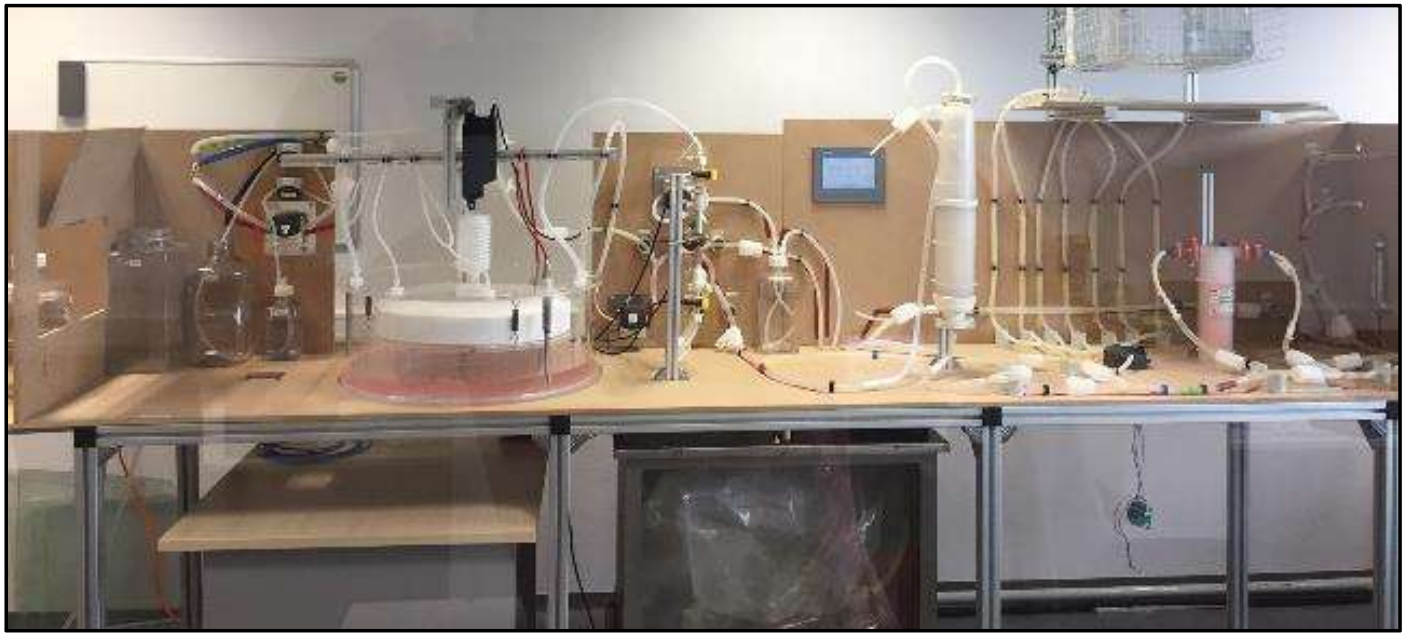
> **Chained process** (continuous operations) enabled by right-sized tools, fewer steps to pure product
> **Fixed-Bed bioreactors** operating in perfusion mode enable optimized productivity in the smallest footprint
> **Inline, single-pass high capacity HD-Membranes**– mixed-mode for sIPV, **affinity for other vaccines** – enable single-step capture and purification of targets and maximum productivity

# Pillar 3: Platform enabled by innovative technologies

## Isolator Device Development: Full Scale Mockup

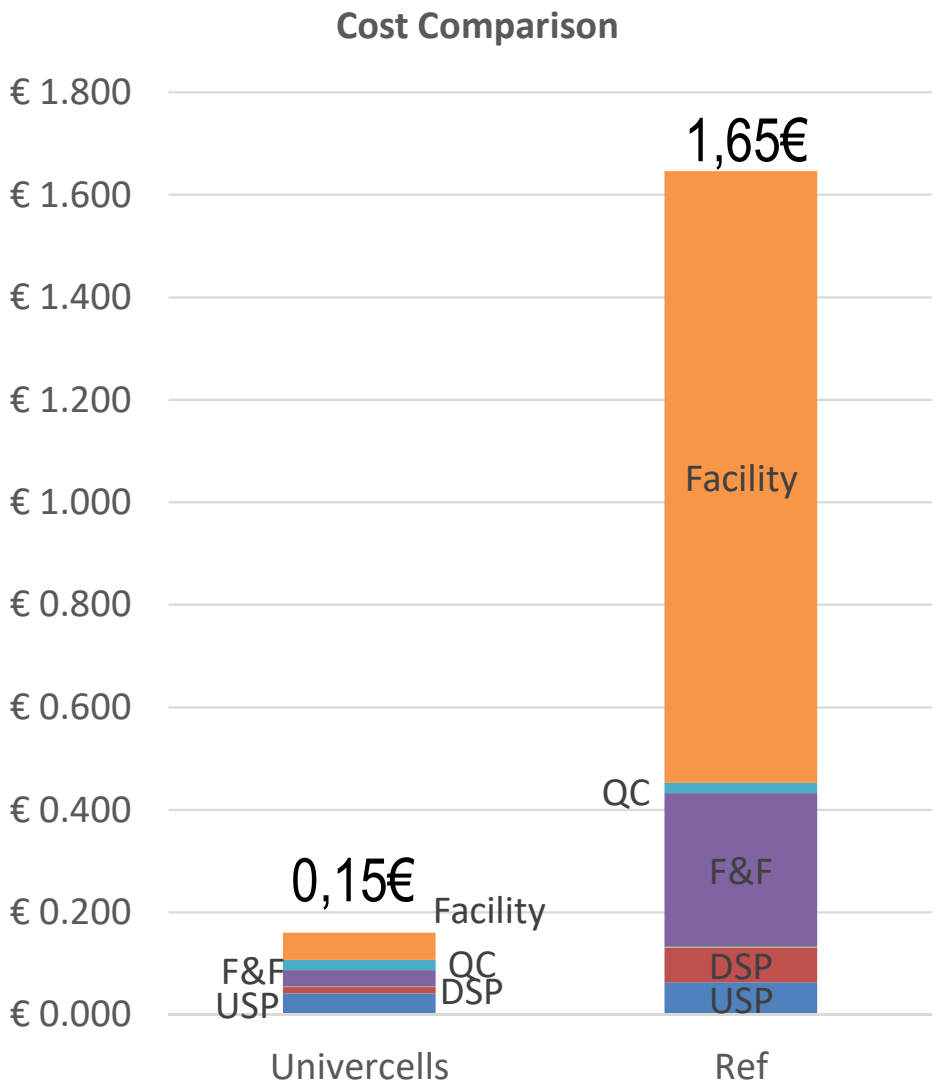


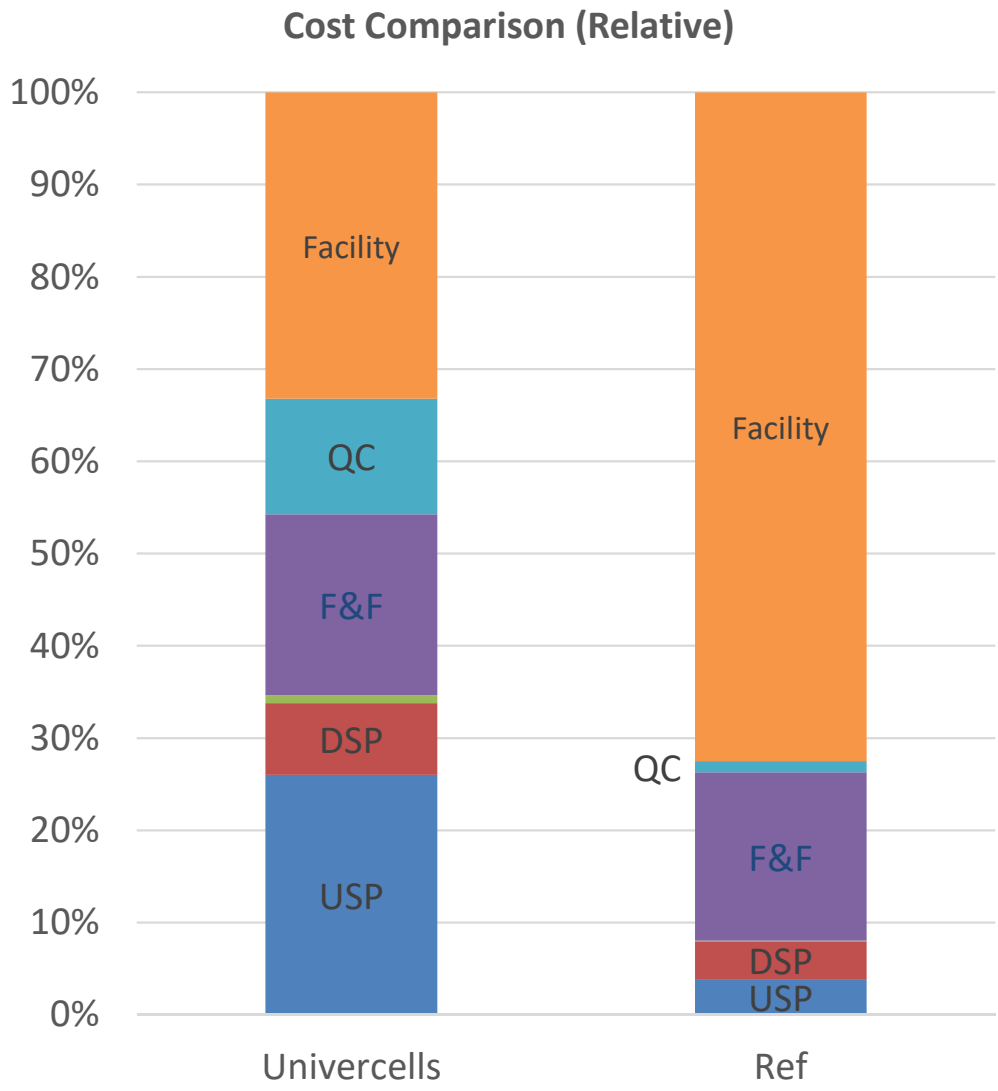



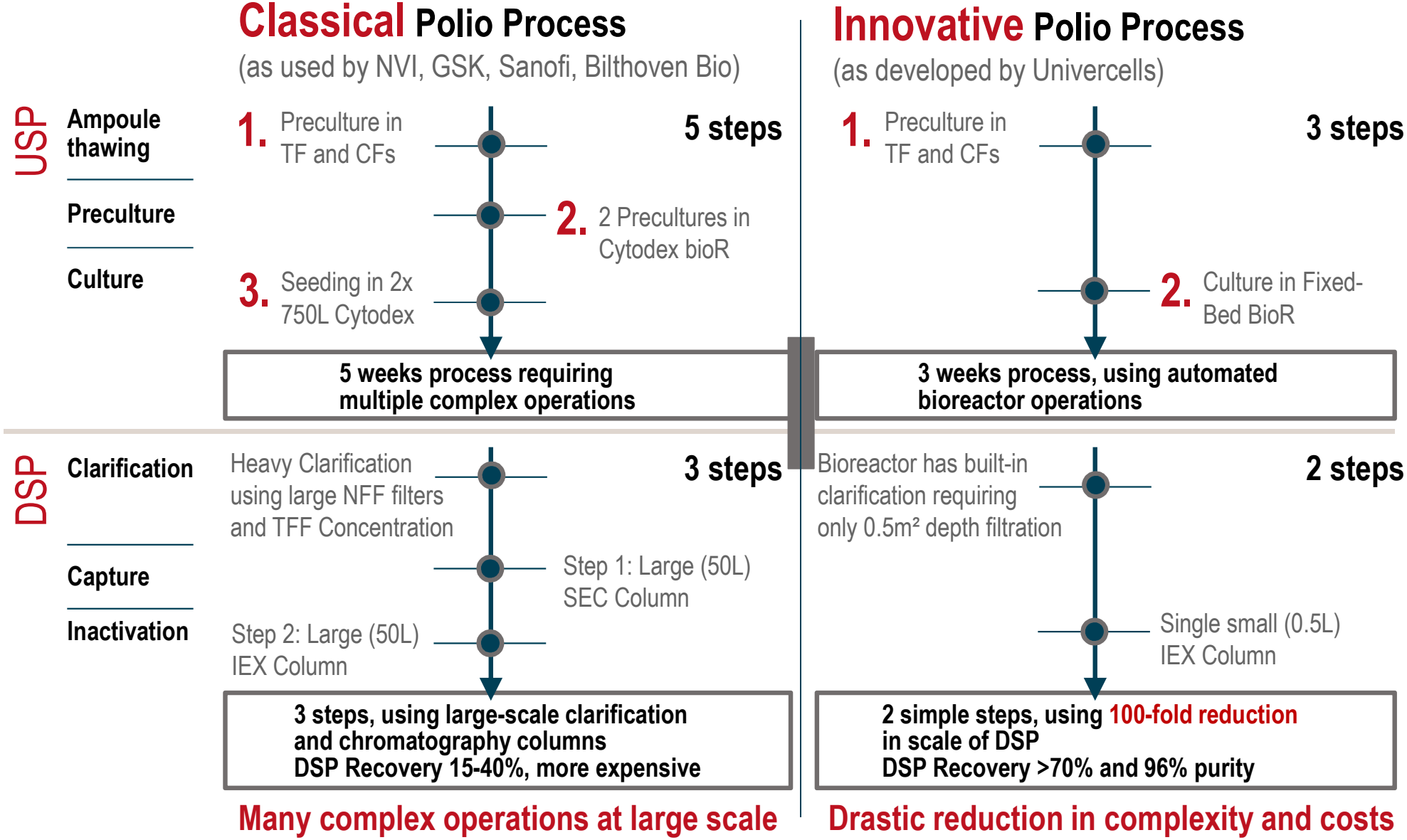
# Impact of the microfacility of the fully-loaded cost of manufacturing

## Case study on the manufacturing of a trivalent Sabin Inactivated polio vaccine (sIPV)



# Global Process Comparison (USP and DSP)




Source: Univercells

# Platform parameters (indicative) – based on Biosolve™ simulations

**Building Footprint** ($m^2$): <1000

**CAPEX**: ~€10M

**Doses/Batch** (doses): 1,000,000

**Batch/year:** 40 (2 microfacility skids)

**Doses/year** (M doses): 40

**FTE's** (Management-Logistic-QA): 15

**FTE's** (Technicians-QC): 40

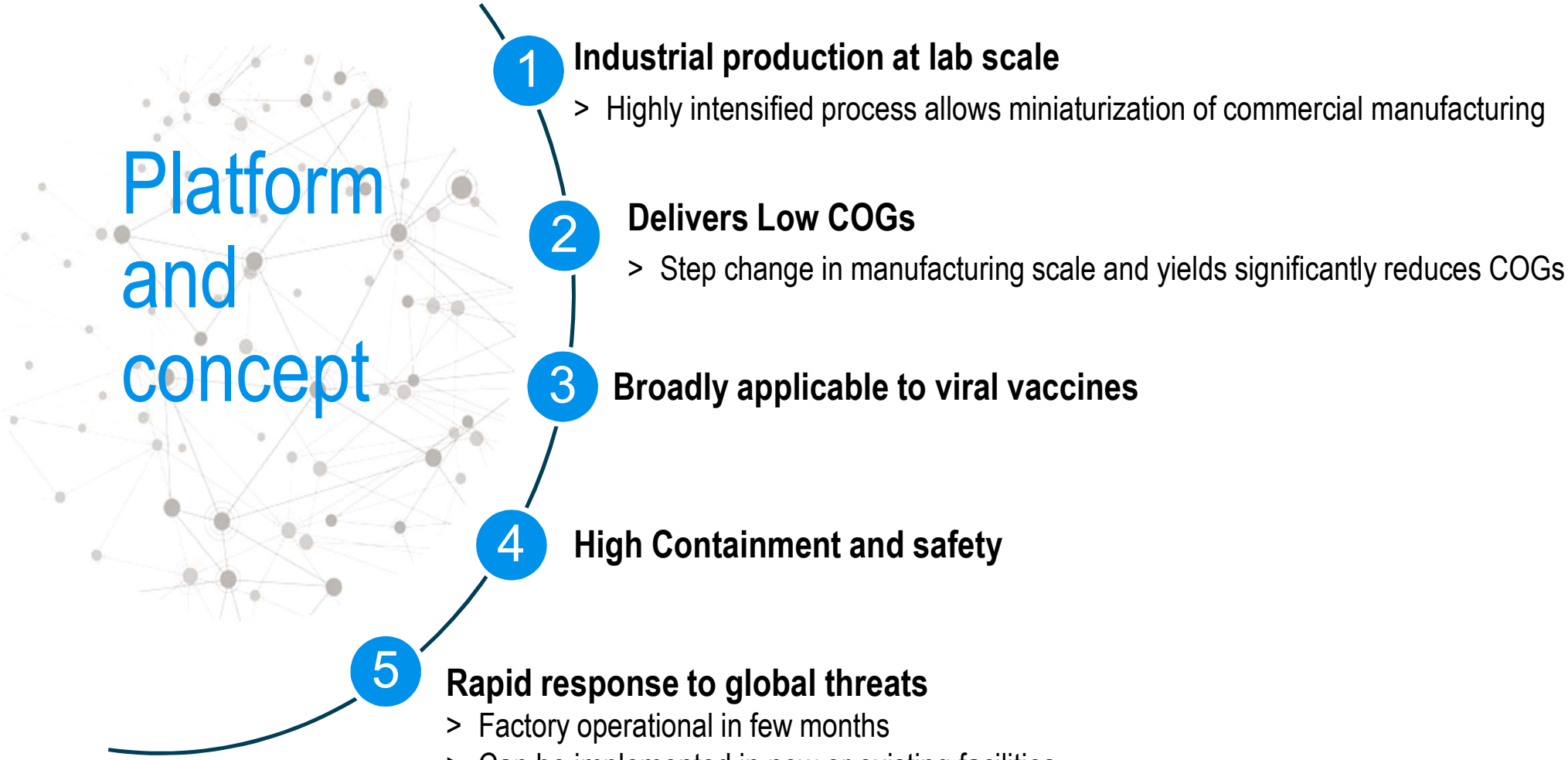
OmniVax vaccine manufacturing platform should deliver trivalent sIPV at a CoG of

**~$ 0.15 per dose**

# Vaccine Manufacturing at Laboratory Scale

- Facility design ongoing with engineering company
- Challenge Biosolve estimations:
  - ~ 1,000 m² flexible facility with 2 ”Micro-facility” skids
  - CAPEX < EUR 10M capable of …
  - … delivering 40M doses trivalent IPV vaccine / year

# Summary of platform and concept



# Acknowledgements

***"Humanity's greatest advances are not in its discoveries, but in how those discoveries are applied to reduce inequity."***
**Bill Gates**

BATAVIA biosciences

C. Yallop
A. Luitjens

Natrix™

John Chickosky
Renaud Jacquemart

UNIVERCELLS