



New trends in vaccine upstream processing

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NON CONFIDENTIAL

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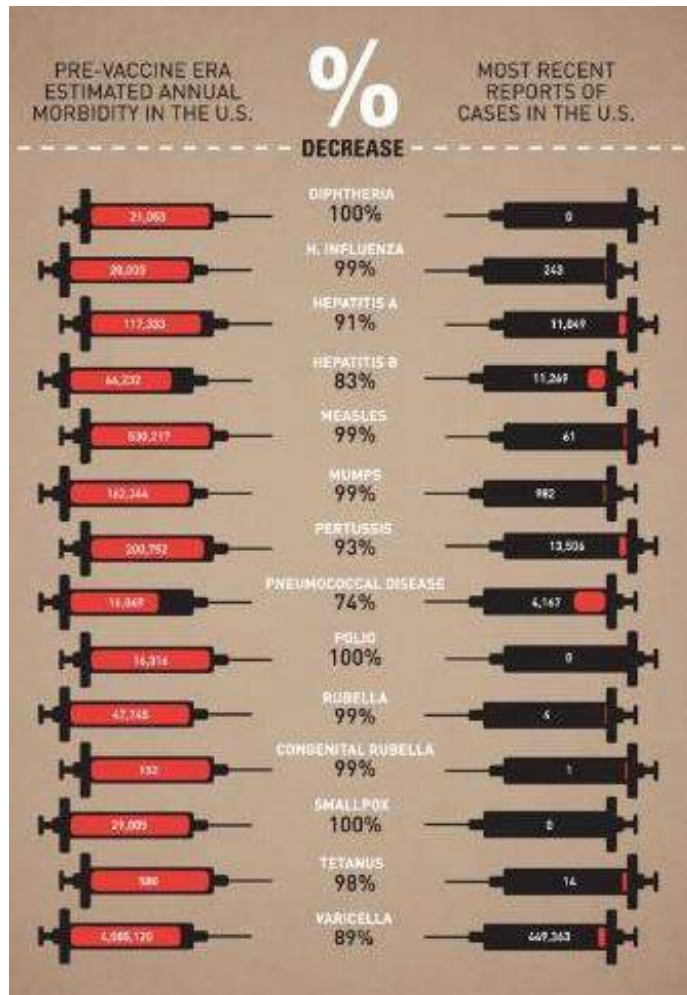


A. Vaccine
manufacturing today





Vaccines are the most efficient tools to prevent infectious diseases, yet a number of factors prevent global coverage



Global immunization

- > Averts ~ 2 to 3 million deaths every year (of DTP and Measles)
- > An **additional 1.5 million deaths** could be avoided, by improving vaccination coverage
- > An estimated **19.4 million infants** worldwide are still missing out on basic vaccines

Insufficient supply and late availability (i.e.)

- > Prevnar in 2011, USA
- > BCG in 2015, France
- > Meningitis C in 2015, Africa
- > DTP in 2015, India

Crisis

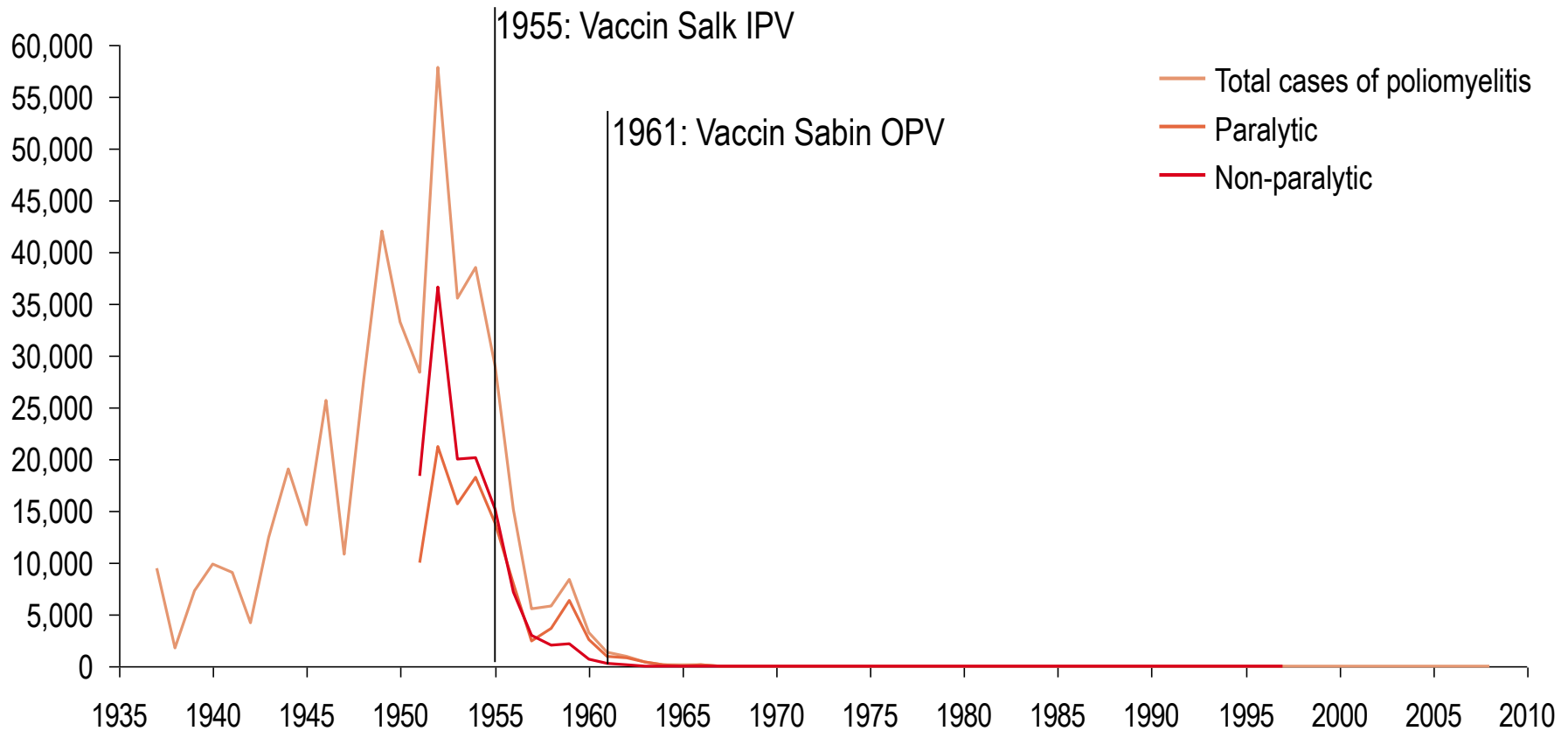
- > Zika virus spread
- > Ebola epidemic

- > Urgent need for **increased production capacity** and **cheaper vaccines**
- > The global vaccine market will reach **USD 48 bn in 2021**, and 90% in the developed countries
- > **Emerging countries** must be able to **manufacture their own vaccines more efficiently**



Vaccination is the only option to eradicate poliomyelitis, for a major impact on global health

Recorded cases of paralytic and non-paralytic poliomyelitis, USA, 1935-2010





Vaccine Manufacturing Today...



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

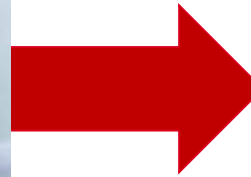
- > Some vaccines are manufactured in bioreactors – **scaling up**
- > Barrier: **Extremely high CAPEX**
- > Reduced risk: Limited aseptic manual operations
- > **Production capacity**↑↑, **cost**↑↑



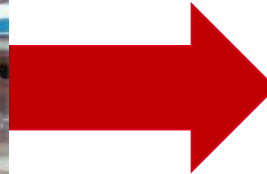


The majority of vaccine **manufacturing techniques** are still based on lab-scale principles “**outscaled**” to manufacturing scales

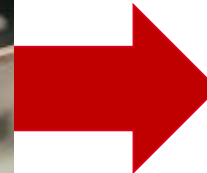
- T-Flasks



- Roller Bottles



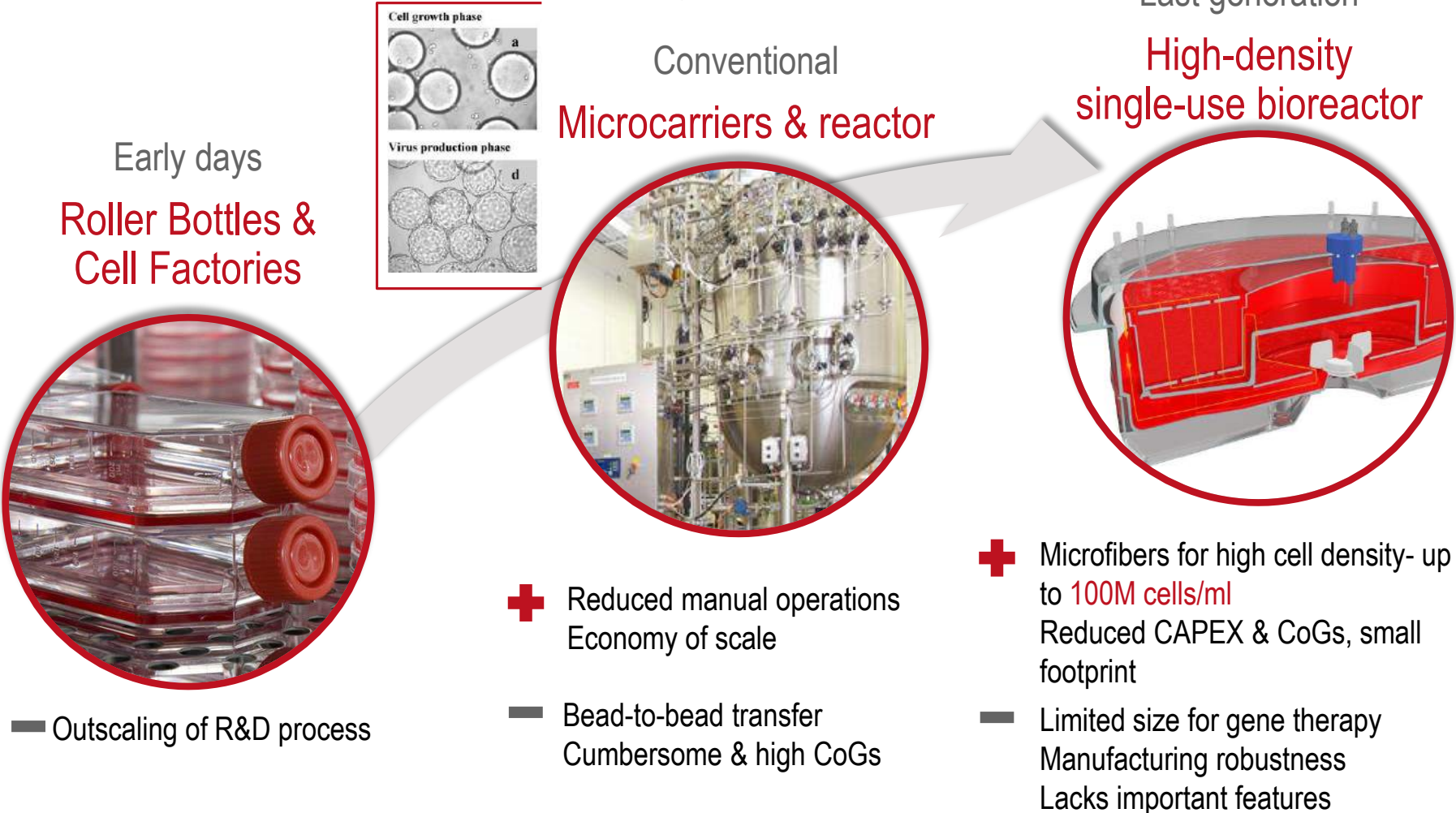
- Eggs...






High-density fixed-bed single-use bioreactors represent the optimal solution in viral culture, yet leaving room for improvement

Evolution of cell immobilization technologies





B. Univercells mission
How to make biologics
available to all

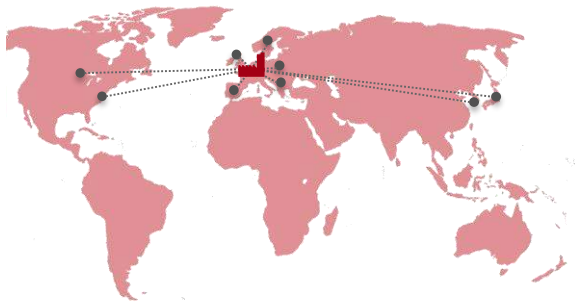


Univercells exists to make **biologics available and affordable** to all – Its mission embodies the ongoing industry **paradigm shift**

Biologics for all – Industry paradigm shift

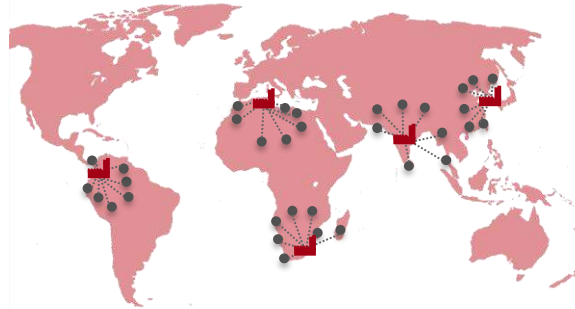
Old paradigm

Centralized manufacturing for developed economies
(e.g. USA, EU, Japan)



New paradigm

Distributed manufacturing for local markets
(e.g. Asia, Africa, Latin America)



Paradigm shift supported and **promoted by all health-related NGOs and academics**, i.e. WHO, BMGF, Wellcome Trust and MIT, UCL

Univercells **mission** supported by **key strategic partnerships**

Viral vaccines

- > **Bill & Melinda Gates Foundation** (BMGF) – Grant for integrated micro facility for vaccine production in GAVI countries

Monoclonal antibodies

- > **Network in LMIC countries** through Key Opinion Leaders, Strategic Consulting firms, WHO and other NGOs

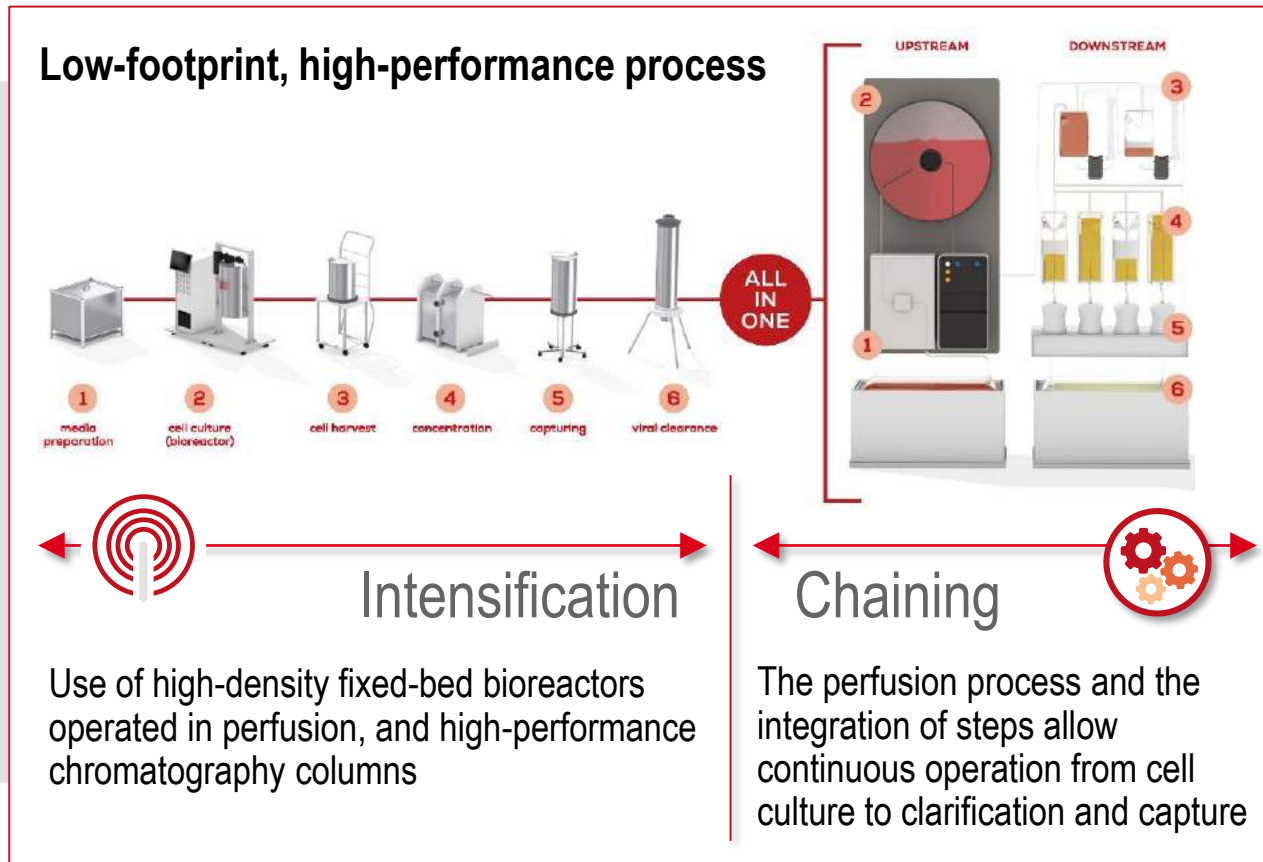
Enzyme Replacement Therapies

- > **Private health insurance companies** to leverage biosimilar platform to dramatically reduce the cost of orphan drugs, to be produced in hospitals



This is achieved by bringing out the **best of technology innovations** allowing a **rapid deployment** of **low CAPEX/OPEX** production facilities

Technology-driven affordability by applying chemical engineering rules



Value creation

- > Dramatic reduction of **CAPEX & OPEX**
- > Rapid deployment of multiproduct facilities with a capacity of:
 - 5-40M doses/year for Vaccines
 - 50-500 kg/year for mAbs
 - Up to 5 kg/year for rec Enzymes



Univercells ambition is to provide **integrated solutions**, to enable the commercialization of **high quality vaccines and biosimilars in LMICs**

Business opportunities in LMICs

Extremely low biologic treatment rates in LMICs

- > Prohibitive price per patient
- > Low availability due to unadapted production capacities

Willingness to develop in-country for-country production

Unmet needs



Barriers to bioproduction

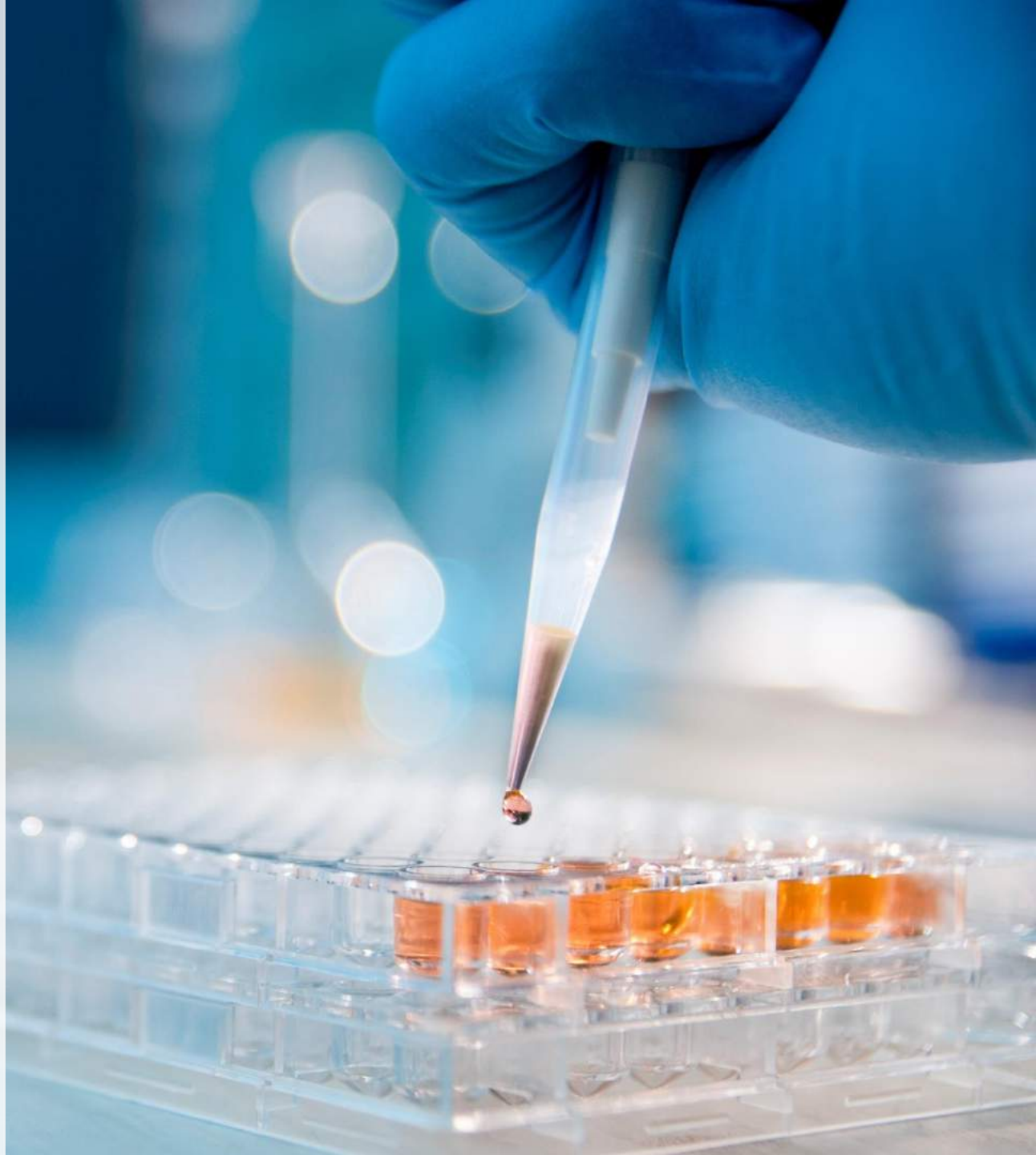


- 1 CAPEX intensive** (~100-300 m EUR)
- 2 High operational costs** preventing competitive pricing
- 3 Scarcity of technical, regulatory and clinical know-how**

Univercells solution

- > **Complete CMC**
 - Biological materials
 - Processes (USP, DSP, F&F, QC assays)
 - Documentation
- > **Microfacility**
 - Design tuned to manufacturer (includes production equipment)
- > **Technology transfer and training**
- > **Clinical/regulatory development**
 - IND submission
 - Immunogenicity (or Biosimilarity) study

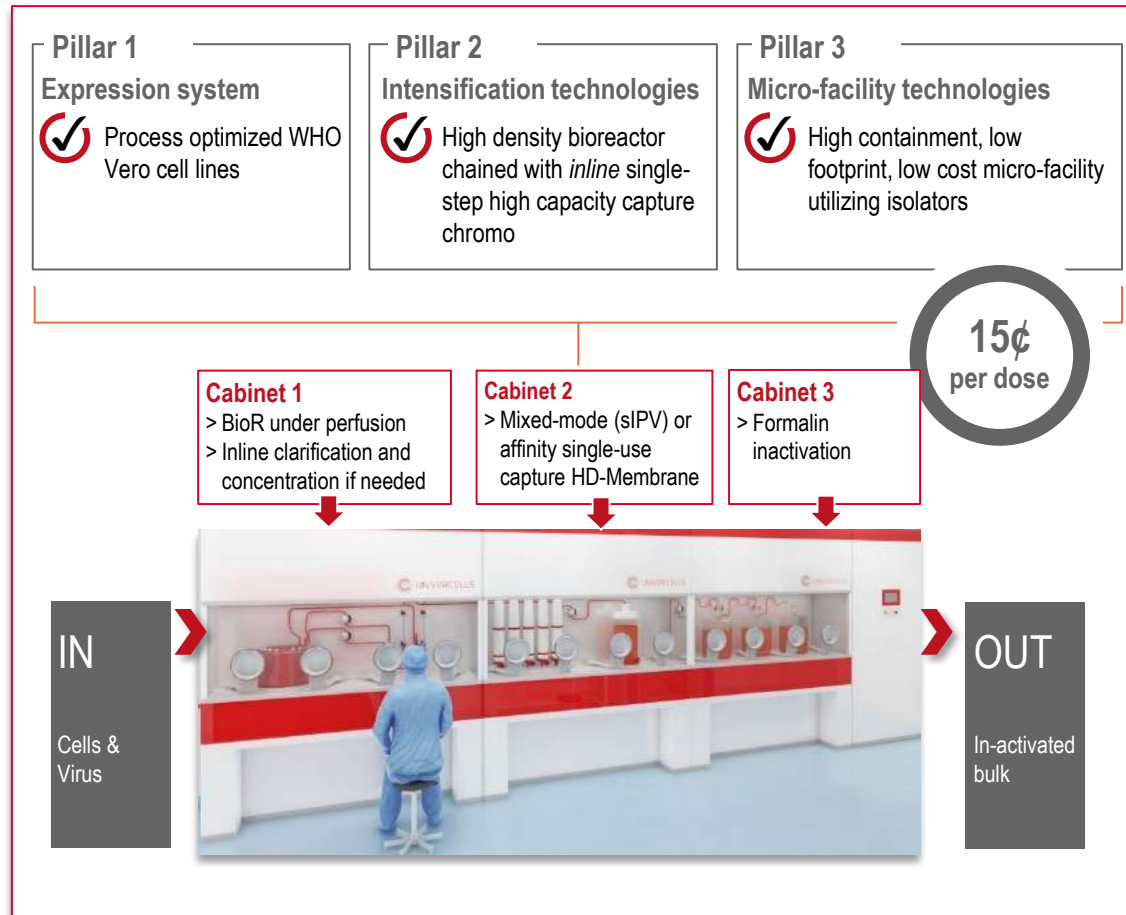
C. Innovative technology for manufacturing of viral vaccines





Univercells platform will produce 40M doses/year of sIPV in a lab-scale micro-facility at a cost of USD 0.15/dose

Univercells sIPV platform



Key benefits

- > **Industrial production at lab scale**
 - Highly **intensified process** allows miniaturization of manufacturing
 - Isolator-based micro-facility for simplified infrastructure, **high containment & safety**
- > **Delivering low CoGs**
 - Target trivalent sIPV at **\$0.15 per dose**
 - Broadly applicable to viral vaccines
- > **Rapid implementation**
 - **Building footprint: <1,500m²**
 - **Target CAPEX: ~€10-€20M**
 - Factory operational in a few months
 - Implemented in new or existing facilities
 - Plug & Play system: rapidly deployed in-country-for country manufacture



Univercells bioreactor features bring **game-changing benefits** in adherent cell culture and viral production

Univercells bioreactor main features & benefits

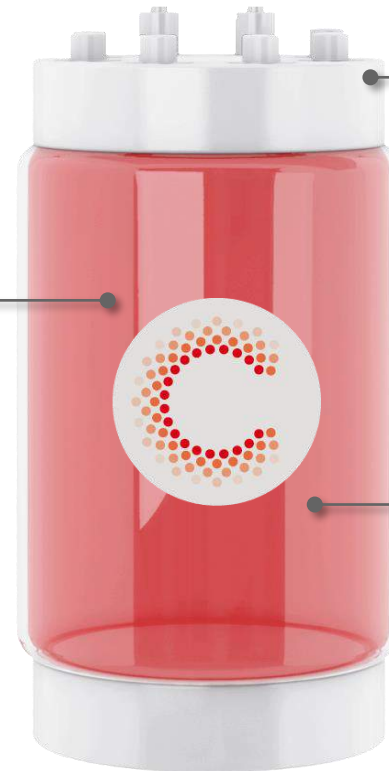
How to avoid:

- > **Scale-out** of classical adherent/suspension cell culture (cell factories, roller bottles)
- > **Large volumes** (micro-carriers & bioreactors)
- > **Manual** interventions
- > ... and related footprint, CAPEX and CoGs

Univercells high-density fixed-bed bioreactor

Cell growth & virus production

- > Proprietary structured fixed-bed
- > Stackable by design



Sterile sampling
Enabling process control in aseptic conditions

In situ freeze-thaw
Enhancing recovery of intracellular products



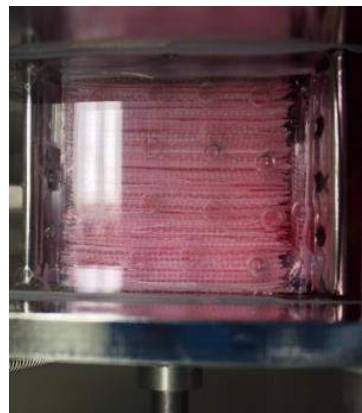
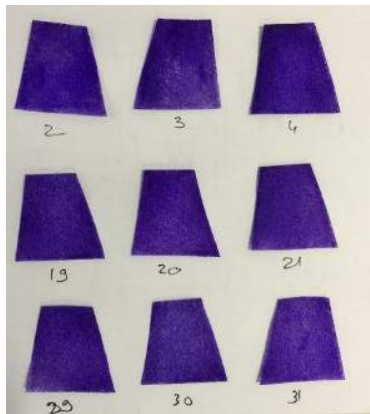
We have already achieved a **remarkable increase in yields** driven by our proprietary **high cell density, small footprint, single-use bioreactor**

Evaluation of microfiber technology – structured fixed bed with multiple embodiments

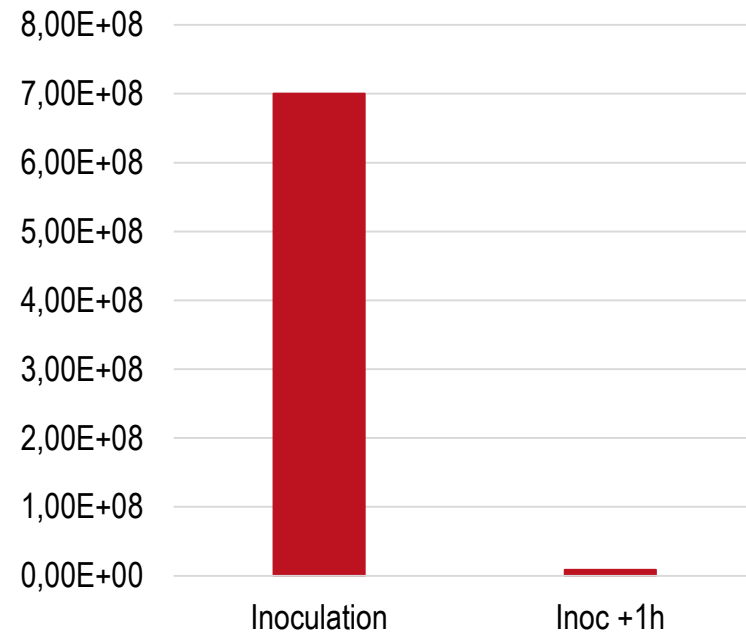


Benefits of a structured bed

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



Cell Entrapment Kinetics

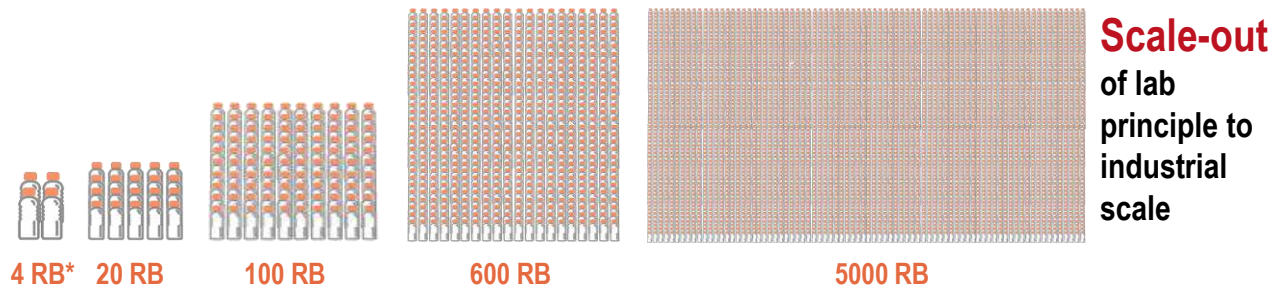




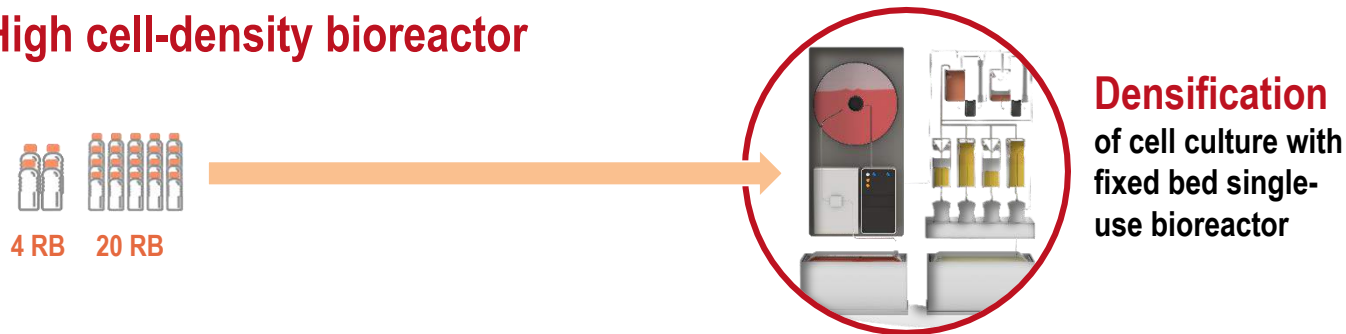
Cell culture is performed in a **bioreactor** to significantly increase **cell-density**, as a way to replace traditional manufacturing process

Increase efficiency in cell culture – Single-use fixed-bed Bioreactor

Traditional manufacturing



High cell-density bioreactor



*Roller bottle

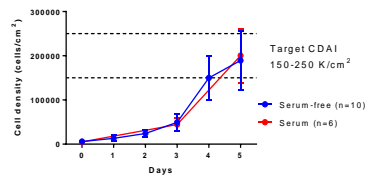
- > **Limited innovation in current vaccine manufacturing**
 - Over 80% of viral vaccines are still manufactured by the scaling out of lab-scale systems
- > **A fixed-bed bioreactor significantly increases cell density**
 - Allows low seeding density and biomass multiplication by up to 500x
 - Offers 500m² of surface in <50L bioreactor



Summary of current sIPV Process development in closed system at small scale

BILL & MELINDA GATES foundation

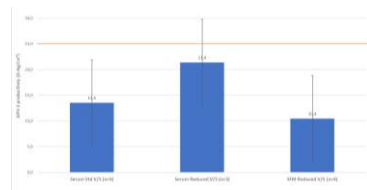
Cell growth



- > Univercell's Bioreactor design allows using a low cell density at inoculation & to reach the targeted cell density for subsequent infection

✓ Successful Cell Growth in New BioR design at small scale

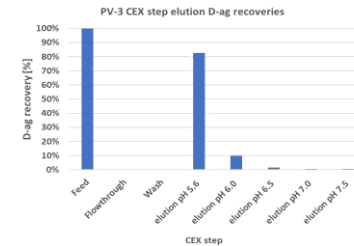
Viral Productivity



- > Following increase in volumetric productivity has been demonstrated vs spin tubes
- > **PV3**, ~ 21 to 33x increase
- > **PV2**, ~36x increase
- > **Next**: Further PD for robustness, scaling up & yield improvement

✓ Expected volumetric productivity in New BioR design at small scale

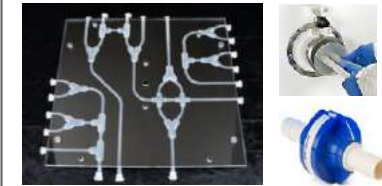
Purification



- > Natrix' HD-Sb membrane delivers **expected performance for PV3**
- > High binding capacity – (>50 000DU/mL Mb)
- > Good HCP clearance – (<0.1µg HCP/DU)
- > D-antigen recovery >90%
- > **Next**: Confirm results for PV3 & PV2 at larger scale

✓ Encouraging results at small scale for a 1step purification

Closed System



- > Every production step is linked together by closed manifolds & connectors to have a fully **Closed System**
- > The production process is designed to have a **linked upstream, downstream & inactivation** process to allow **continuous processing** between inoculation and inactivation

✓ Conceptual design of linked closed process

> With current small scale yields, **Univercells process would yield:**
 – @500m² / 37L FB and 2x250L medium in perfusion, ~650DU/mL in 250L
 – **~4.2M doses/run in crude harvest**

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



All intensified production unit steps are linked together in a **chained process into a closed system** which is contained **inside an isolator**

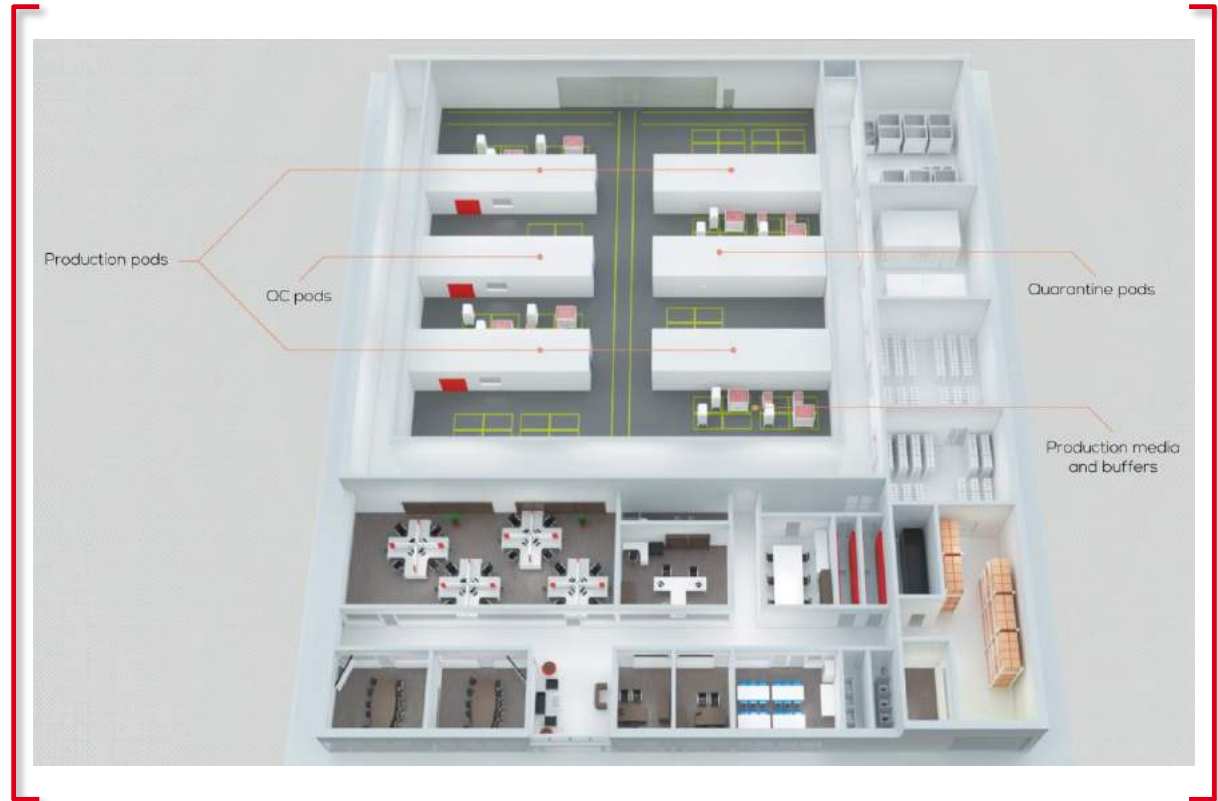
First micro-facility system to be delivered in Q4 2018





Micro facilities allow GAP III compliance with CAPEX reduction

- > **Complete containment solution** is proposed as to ensure entire process is contained
 - Production pods
 - QC pods
 - Quarantine pods for storage of inactivated quarantined bulks
- > The conceptual design highlights the **small GAP III surface required to produce 40M doses trivalent sIPV/year** with 4 MicroFacility systems
- > This low GAP III surface allows a **reduction of the associated CAPEX** (~\$10-20M for the complete facility as depicted below)



D. Conclusions –
Benefits of intensified
manufacturing platform





Univercells provides **customizable solutions for viral production**, enabling rapid implementation of novel biomanufacturing capabilities

Our offering for viral production

We offer

Customizable solutions for viral production

Human & veterinary vaccines, gene therapy, oncolytic viruses

Features

- > **Intensified & cost-effective** manufacturing process
- > **Adapted to any viral-based product** requirements
- > **Rapid implementation / production revamping**

Benefits

- > **High production capacity at very low COGS and limited CAPEX**
- > **Minimized risks**
- > **Broadly applicable to viral vaccines**
- > **Record time-to-market**
- > **Rapid response to epidemics & global threats**

Cost-efficient technology...

...suited for viral production revamping

Acknowledgements



C. Yallop
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John Chickosky
Renaud Jacquemart

BILL & MELINDA
GATES foundation

“Humanity’s greatest advances are not in its discoveries, but in how those discoveries are applied to reduce inequity.” – Bill Gates



UNIVERCELLS

Biologics
available to all !

