New trends in vaccine upstream processing

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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
- DPTP 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

Source: Univercells
**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

Sources: (MMWR), Summary of Notifiable Diseases.
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 **asceptic manual operations**
> **Production capacity↓↓ ,cost ↑**

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

Source: Univercells
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

- **Early days**
  - Roller Bottles & Cell Factories
  - Outscaling of R&D process

- **Conventional**
  - Microcarriers & reactor
  - Reduced manual operations
  - Economy of scale
  - Bead-to-bead transfer
  - Cumbersome & high CoGs

- **Last generation**
  - High-density single-use bioreactor
  - Microfibers for high cell density - up to 100M cells/ml
  - Reduced CAPEX & CoGs, small footprint
  - Limited size for gene therapy
  - Manufacturing robustness
  - Lacks important features

Source: Univercells
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

<table>
<thead>
<tr>
<th>Old paradigm</th>
<th>New paradigm</th>
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<td>Centralized manufacturing for developed economies (e.g. USA, EU, Japan)</td>
<td>Distributed manufacturing for local markets (e.g. Asia, Africa, Latin America)</td>
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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

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

Source: Univercells
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

**Low-footprint, high-performance process**

- Use of high-density fixed-bed bioreactors operated in perfusion, and high-performance chromatography columns

**Intensification**

- 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

**Value creation**

**Chaining**

- The perfusion process and the integration of steps allow continuous operation from cell culture to clarification and capture

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

Business opportunities in LMICs

### Unmet needs

- 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

### 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

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

**Univercells bioreactor main features & benefits**

- **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

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**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

Source: Univercells
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**

![Image of cell entrapment kinetics graph]
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

Scale-out of lab principle to industrial scale

> 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

*Roller bottle

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

**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

Source: Univercells
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

Chained production process in closed system
1st containment layer of poliovirus

Condensed footprint of the chained process allows containment into isolator, which is the primary containment
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

<table>
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<th><strong>We offer</strong></th>
<th><strong>Features</strong></th>
<th><strong>Benefits</strong></th>
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<td><strong>Customizable solutions for viral production</strong></td>
<td>&gt; Intensified &amp; cost-effective manufacturing process</td>
<td>&gt; High production capacity at very low COGS and limited CAPEX</td>
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<td>&gt; Adapted to any viral-based product requirements</td>
<td>&gt; Minimized risks</td>
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<td>&gt; Rapid implementation / production revamping</td>
<td>&gt; Broadly applicable to viral vaccines</td>
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<td>&gt; Record time-to-market</td>
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<td>&gt; Rapid response to epidemics &amp; global threats</td>
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**Cost-efficient technology**...  

...suited for viral production revamping
Acknowledgements

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