Disruptive micro-facility for affordable vaccine manufacturing

Case study for sIPV polio vaccine

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Abstract

Vaccines are the sole preventative measure to eliminate poliomyelitis. The traditional biologic production in stainless steel bioreactors is limited by high capital expenditures and does not provide a sustainable or cost-effective solution for the future. Univercells aims to change the paradigm and produce biologics using small-scale integrated systems, providing a more affordable and flexible approach. The production of a polio vaccine candidate using this compact system paves the way for a worldwide production of affordable vaccines and biologics.

Biologics for all

We notice an increasing demand for affordable biologics such as vaccines, a demand reinforced by the continued efforts of global immunization campaigns.

In the case of poliomyelitis, a renewed global immunization effort is combining the use of the OPV and IPV by producing a injected inactivated vaccine using attenuated strains.

Due to its high infectivity, Polio vaccine needs to be handled in highly contained environment to ensure operators and environment safety. Facilities complying with GAP III safety levels being usually very complex and expensive to build and operate, new technologies are called for to implement cost-effective sIPV production facilities.

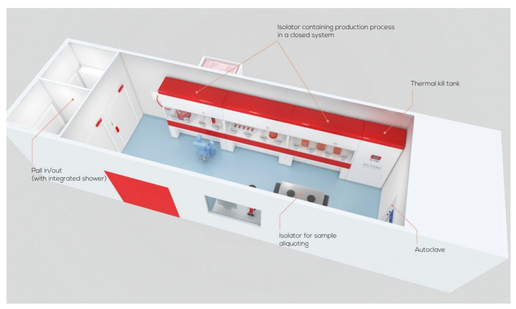
To circumvent the limitations of traditional bioproduction methods (eggs, cell factories or micro-beads), Univercells envisioned a down-scaled high-performance production process, leading to low-footprint infrastructures more affordable (CAPEX & OPEX) and flexible, whilst achieving high productivity of vaccines.

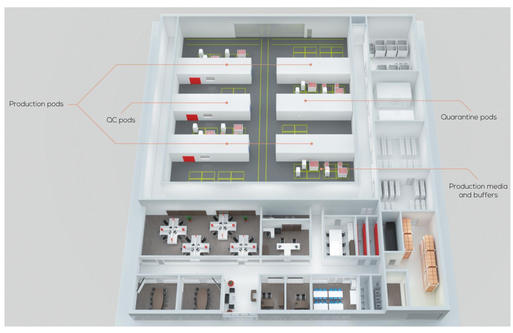
NevoLine™ micro-facility concept

Univercells designed a self-contained, single-use, closed, low footprint and automated continuous manufacturing platform for GMP pilot and commercial-scale virus production (figure 1). Self-contained upstream and downstream modules reduce the facility CAPEX, while reducing OPEX at the same time through automation and downsized continuous processing.

The first application was developed with Bill and Melinda Gates Foundation funding to meet the goal of reducing the cost of manufacturing inactivated attenuated polio vaccine to U.S. $0.15/dose, presented here.

Figure 1: NevoLine single-use manufacturing platform, and its containment in BSL3 POD & POD-based facility





Materials and methods

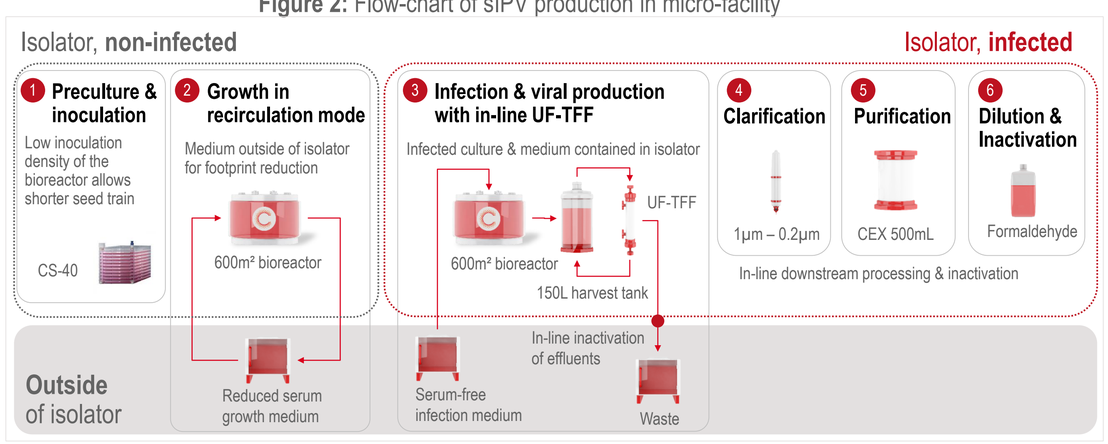
- Bench-scale fixed-bed bioreactor (scale-X™, surface: 2.4m² available for cells);
- Carriers made of 100% pure non-woven hydrophilized PET fibers;
- Vero cells grown serum containing media, infection in serum-free media;
- Sabin attenuated polio strains;
- Cell nuclei count on carriers estimated by crystal violet staining;
- Polio virus production estimated by ELISA assay (D-antigen content) and TCID50.
- Two steps purification (single step enhanced filtration & single step high affinity CEX chromatography)
- CoGs calculation using BioSolve 2017 (BioPharm Services)

Results

1. Process flow chart

To deliver a low-footprint production unit, Univercells designed a complete sIPV production process of small enough volume & footprint to fit into an isolator (figure 2), based on intensification and chaining technologies.

Figure 2: Flow-chart of sIPV production in micro-facility



2. Cell growth & fixed-bed homogeneity

Cultivation of Vero cells in medium with serum was carried out in 2.4m² compact fixed-bed bioreactors achieving high cell density. Cell dispersion results show homogeneity in the fixed bed, ensuring even and predictable growth throughout the structure (figure 4). Thanks to its unique compact structure, scale-X bioreactors seeded with cell densities a quarter of that needed for traditional systems grow nearly 50-fold to reach a final concentration of 200,000+ cells / cm² (figure 3).

Figure 3: Growth of Vero cells cultivated in scale-X bioreactor (2.4m²) (Two sets of experiments in two labs)

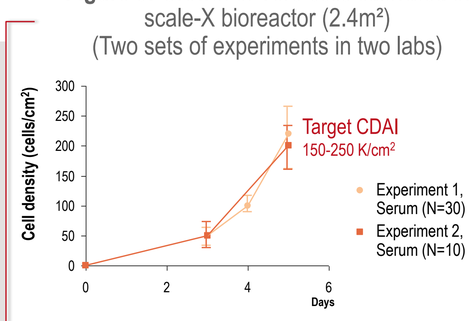
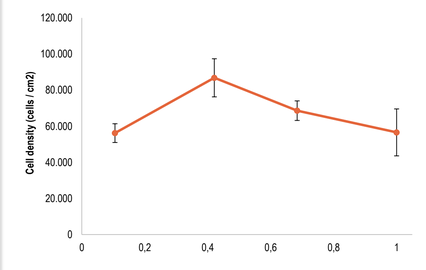


Figure 4: Fixed-bed vertical dispersion in scale-X bioreactor



3. Purification

First steps of purification, i.e. DNA removal step, pH adjustment and clarification, are performed in-line with positive results. In-line single step purification using CEX chemistry participates in improving overall downstream processing recovery yield & high purity.

Results of downstream processing steps for PV2 & PV3 demonstrate good overall yield, maintaining high product purity (results for PV1 are being generated):

- HC-DNA concentration after CEX meets WHO requirements (spec <100pg DNA/dose)
- Total protein concentration either meets (PV2) or is very close to (PV3) WHO requirements (spec <0.1 µg TP/DU).

4. Productivity

The process was developed on the three strains of sIPV, achieving promising productivity and purity results (table 1). The overall process achieves high productivity, delivering an equivalent of 0,5 million doses of trivalent at 600m² scale (based on a ratio S1/S2/S3).

Table 1: Overall process productivity at 600m² scale

Serotype	Doses / batch
PV1	~6.8M
PV2	~0.8M
PV3	~2.0M

5. CoGs

Based on the process data obtained thus far (table 1), CoGs calculations of trivalent sIPV production were performed using BioSolve software. Results achieved at small scale thus far predict a drug product Cost of Goods close to reaching the BMGF target of <$0.15 / dose, to be attained with further process development and optimization of operations both to increase the cell lines productivities and the DSP yields.

Table 2: Estimated annual productivity of trivalent sIPV, using 600m² scale

# trivalent doses / year	43M
# doses / batch	525,000
# microfacilities	4
Production CAPEX	$13M
# batches / year	88 (22 / microfacility)

Conclusions

> The successful implementation of intensification and chaining for sIPV production led to a drastically reduced equipment size, enabling the process to be operated within a closed system, in a low footprint isolator, called micro-facility system, NevoLine.

> Thanks to improved recoveries, the intensified process achieves high productivity, delivering 525,000 doses of trivalent sIPV per batch.

> With Univercells NevoLine technology, viral vaccines such as polio can be produced in a miniaturized fully-contained isolator for increased safety, leading to a tremendous impact on the factory design, CAPEX and cost of manufacturing.

Perspectives

> Based on the successful implementation of the intensification and chaining concepts for sIPV, we think NevoLine will provide tremendous value for many applications, like and without limitation:

i. Other viral vaccines for human and veterinary uses
ii. Rapid deployment manufacturing capacities to face outbreaks
iii. Production of gene vectors needed for the ever-increasing gene therapy segment

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