Bioprocess Modelling of Upstream Viral Vector Production Enhancement

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Introduction

High Cost and Low Supply in Vector Manufacturing

- There are approximately 800 ongoing clinical trials involving virus products, which all require significant manufacturing capacity. This number is expected to grow 10x by 2026[1].
- There is a gap between current demand and available manufacturing capacity, even if additional planned capacity comes online (Figure 1).

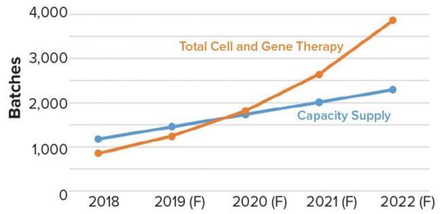


Figure 1. Cell and Gene Therapy Supply and Demand

[1] *https://bioprocessintl.com/manufacturing/emerging-therapeutics-manufacturing/capacity-analysis-for-viral-vector-manufacturing-is-there-enough/*

- High production costs and limited manufacturing capacity of cell and gene therapy vectors continues to be a significant barrier to producing affordable and widely accessible therapies[2] (Table 1).

Table 1: Affordability of Cell and Gene Therapies

Drug Application	Patient Cost (USD)
Spinal muscular atrophy	$2,125,000
Inherited retinal disease	$850,000
Acute lymphocytic leukemia	$475,000
Mantle cell lymphoma	$373,000

[2] *https://www.primetherapeutics.com/research/cost-management-for-sky-high-high-cost-gene-therapy/*

Increasing upstream manufacturing yields is imperative to meet production demands and increase affordability.

- To mitigate these major challenges associated with cell and gene therapy production, manufacturers can employ the use of **upstream process additives** during the production step to optimize product yield, the cost of which needs to be assessed.
- **Through bioprocess modelling**, the impact of process additives on both manufacturing yields and resulting cost of goods sold (COGS) can be evaluated.

Modelling Methodology

- BioSolve Process 8.3 software (Biopharm Services Ltd.) was used to model a generic upstream (USP) transfection based viral vector production process.
- The model was used to **assess yearly COGS and upstream crude dose cost savings associated with using upstream process additive technology** to boost manufacturing yields.
- The model consisted of a seed train, followed by three 500L production bioreactors (Figure 2).

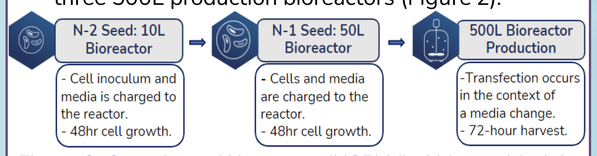


Figure 2. Overview of Upstream (USP) Viral Vector Model

Key Modelling Assumption:

- Only USP unit operations were modelled due to variability in downstream processing techniques between viral vector production processes.

Small Yield Enhancements Lead to Large COGS Savings

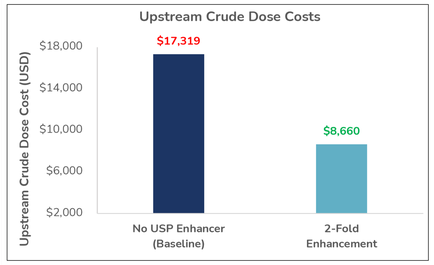


Figure 3. 2-Fold Yield Enhancement Savings

- A 2-fold enhancement in yield reduced upstream crude dose cost by 50%.

Case Study: Process Modifications Enabled by a 2-Fold Yield Enhancement

After assessing the impact of a 2-fold enhancement in yield on our modelled upstream viral vector production process (Figure 3), we then assessed whether it would be economically feasible to:

1. **Reduce the Number of Production Bioreactors**
2. **Reduce the Size of Production Bioreactors**

Case Study Results: 2-Fold Viral Vector Yield Enhancement

- The goal of the following case study was to assess **the economic feasibility** of manufacturing **process modifications enabled by a 2-fold enhancement** in USP yield.

Scenario 1: Reducing Number of Production Bioreactors

- The first scenario of the case study identified the economic feasibility **of reducing the number of production bioreactors from 3 to 2** when a 2-fold enhancement in upstream yield was achieved.
- The annual COGS, crude dose cost and throughput of doses per year was studied (Table 2). The % change breakdown of annual COGS, was also modelled (Figure 4).

Table 2: Reducing Number of Bioreactors Results

USP COGS Comparison	Baseline Process	2-Fold Yield Enhancement
Production Bioreactor Yield (Particles/L)	1.50E+13	3.00E+13
Number of Production Bioreactors	3	2
Annual COGS (USD)	$110,410,775	$74,469,075 *(-33%)*
Throughput (Doses/Year)	6,375	8,500 *(+33%)*
Crude Dose Cost (USD)	$17,319	$8,761 *(-49%)*

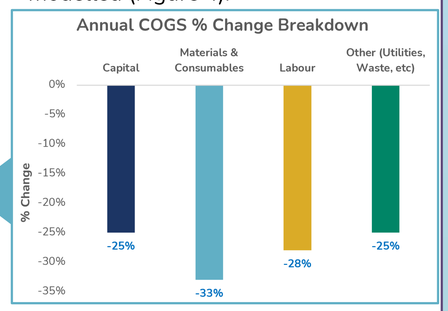


Figure 4: COGS % Change Breakdown

- The modelling results showed that running one less bioreactor was economically feasible when exhibiting a 2-fold enhancement in yield.
- **Upstream crude dose cost** was **decreased by 49%,** as **throughput was increased by 33%.**
- **Annual COGS** associated with USP production was **reduced by 33%.**

Scenario 2: Reducing Size of Production Bioreactor

- The case study also explored the economic feasibility of **reducing the size of the production bioreactor from 500L to 300L** when a 2-fold enhancement in USP yield was achieved.
- Even with a 200L reduction in bioreactor size, a 2-fold enhancement in yield enabled a **20% increase in crude doses** produced per year, and a **17% reduction in upstream crude dose cost.**
- In addition, reduction of bioreactor size led to **significant reductions** to the **environmental footprint** of the manufacturing process.
- **Plastics usage** per batch was reduced **by 24%,** and **water usage** per batch was **reduced by 6%.**

Table 3. Reducing Size of Bioreactor Results

USP COGS Comparison	Baseline Process	2-Fold Yield Enhancement
Size of Bioreactor (L)	500L	300L
Bioreactor Yield (Particles/L)	1.50E+13	3.00E+13
Batches per Year	51	51
Throughput (Doses/Year)	6,375	7,650 *(+20%)*
Crude Dose Cost (USD)	$17,319	$14,293 *(-17%)*

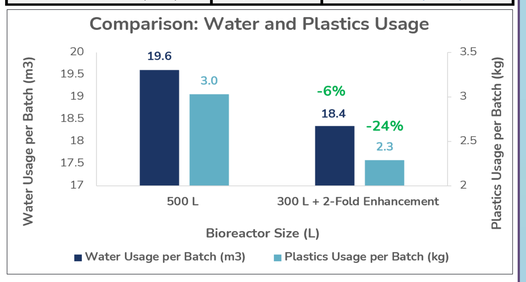
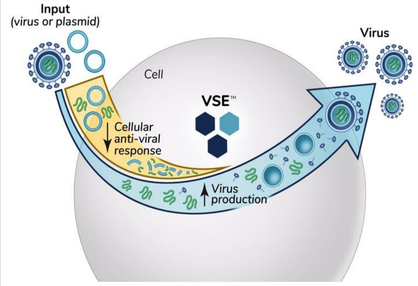


Figure 5: Environmental Footprint Reduction

Virica's Yield Enhancement Technology: VSE™s



- Virica's Viral Sensitizer technology, also known as VSE™s, are proprietary small molecules that **boost upstream viral production** in replicating and non-replicating viral vectors by uniquely altering cellular signaling to **curb antiviral defenses.**
- VSE™ compounds have been shown to boost viral manufacturing yields multi-fold for both replicating and non-replicating viral vectors.

VSE™s Are Easily Incorporated Into the Manufacturing Process

- Virica's VSE™ formulations are integrated into manufacturing processes as a **simple upstream media additive.**
- VSE™s are added before or at time of transfection/infection.
- VSE™ concentrations **decrease to non-detectable limits in the final product** because the compounds are rapidly metabolized by the cells and filtered out using traditional purification methods.

VSE™s Enhance Viral Vector Manufacturing Yields

AAV Manufacturing

- 8 VSE™s were screened for the ability to improve production of AAV2 in HEK293 SF suspension cells **(3rd party collaboration).**
- Unoptimized shaker flask formulation development data **indicates 2+ fold enhancement** in yield with 6/8 compounds (Figure 6).

Lentivirus Manufacturing

- Virica has used its unique high-throughput methodology to identify a multi-VSE™ formulation that is able to **enhance the production of third generation lentivirus** up to **7.4-fold** in adherent HEK293T cells across multiple production formats (Figure 7).

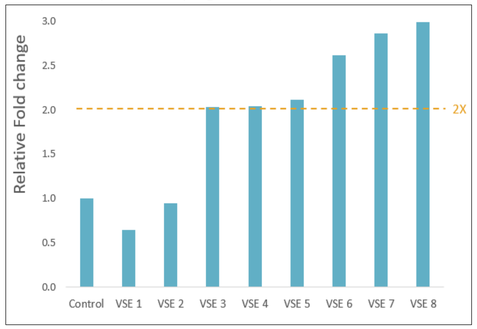


Figure 6: VSEs™ Enhance AAV2 Production

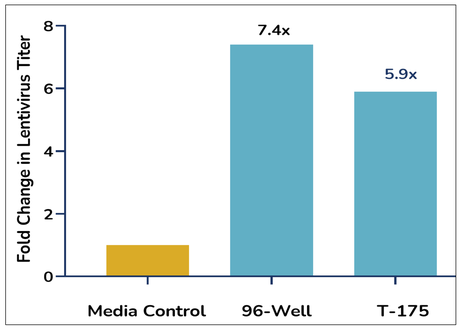
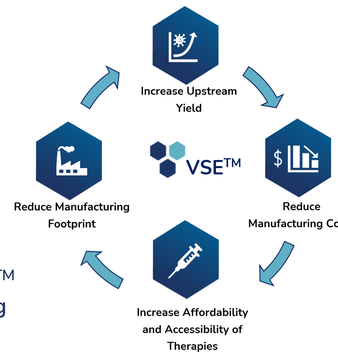


Figure 7: VSEs™ Enhance LV Production

Conclusion

- The modelled COGS savings associated with using **upstream process additives** to enhance viral vector production demonstrated the potential to both **address growing demand** and to **produce more affordable and accessible cell and gene therapies.**
- **Virica's VSEs™** are small molecule upstream process additives that address the often-neglected cellular antiviral defenses to **uniquely enhance viral vector manufacturing yields.**

Virica offers partners an opportunity to customize VSE™ formulations that best suit their specific manufacturing platforms.



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