**Short Communication**
Volume 15:06, 2025

Journal of Bioprocessing & Biotechniques

ISSN: 2155-9821

Open Access

# VLP Manufacturing Challenges: Yield, Purification, Scale-Up

**Oksana M. Shevchenko***

*Department of Bioprocess Engineering, Kyiv Polytechnic Institute, Kyiv, Ukraine*

## Introduction

The production of virus-like particles (VLPs) for therapeutic and vaccine applications is a complex bioprocessing endeavor, fraught with significant challenges that necessitate innovative solutions. Optimizing yield, refining purification strategies, and achieving successful scale-up are paramount hurdles that researchers and manufacturers continuously strive to overcome. Current methodologies often fall short in efficiently recovering high-purity VLPs, a limitation that underscores the urgent need for advancements in downstream processing to address issues such as aggregation, degradation, and contamination by host cell proteins. The consistent attainment of batch-to-batch quality remains a critical bottleneck, hindering the transition of promising VLP candidates from the laboratory bench to widespread commercialization, underscoring the intricate nature of VLP biomanufacturing. [1]

Efficient downstream processing is an indispensable element in the successful production of VLPs, directly impacting the purity, yield, and ultimately, the therapeutic efficacy of the final product. To this end, novel chromatographic techniques, including affinity and size exclusion chromatography, are being rigorously explored as means to enhance purification efficiency and significantly reduce manufacturing costs. Concurrently, membrane filtration methods are being investigated for their potential in scalable VLP recovery, although ongoing research aims to optimize flux rates and minimize membrane fouling, which can impede process performance and increase operational expenses. [2]

Scaling up VLP manufacturing operations requires meticulous attention to several critical engineering aspects, including the thoughtful design of bioreactors, precise process control, and the judicious optimization of cell culture media. The successful achievement of high cell densities and consistently high VLP expression levels at larger scales presents a substantial engineering challenge that demands innovative approaches. A thorough understanding of how factors such as shear stress and oxygen transfer impact VLP integrity during large-scale fermentation processes is crucial for maintaining product quality and yield throughout the manufacturing cycle. [3]

Host cell protein (HCP) contamination represents a persistent and considerable issue in VLP production, potentially compromising the immunogenicity and overall safety of the therapeutic product. Consequently, the development of highly sensitive analytical methods for the accurate detection of HCPs and the implementation of effective removal strategies are of paramount importance to ensure product safety and regulatory compliance. Advanced purification techniques, including affinity-based methods and sophisticated filtration technologies, are currently being investigated to meet the stringent purity requirements demanded for VLP-based therapeutics. [4]

The inherent instability of VLPs under various process conditions presents a significant challenge that must be carefully managed throughout the entire production workflow. Maintaining the structural integrity and biological activity of VLPs from upstream processing through downstream purification requires the meticulous optimization of key environmental parameters such as temperature, pH, and ionic strength. The development of strategies to enhance VLP stability, including innovative formulation approaches, is crucial for ensuring the effective therapeutic use and shelf-life of these complex biological entities. [5]

Process Analytical Technology (PAT) offers a promising avenue for achieving enhanced control and a deeper understanding of VLP production processes. The real-time monitoring of critical process parameters (CPPs) and key VLP attributes allows for more informed decision-making, leading to improved consistency in product quality and a reduction in the incidence of costly batch failures. The integration of PAT tools designed for precise VLP quantification and comprehensive quality assessment represents a key area of ongoing development within the VLP manufacturing landscape. [6]

The selection of an appropriate expression system plays a pivotal role in determining the efficiency and overall quality of VLP production. While microbial systems are often favored for their capacity to achieve high yields, eukaryotic systems may be preferred for their ability to facilitate VLPs with more native post-translational modifications, which can significantly influence immunogenicity. Navigating this complex bioprocessing dilemma requires a careful balance between yield, quality, and the specific requirements of the VLP product. [7]

Economic viability remains a major challenge in the field of VLP manufacturing, with high production costs, particularly associated with downstream processing and rigorous quality control measures, acting as a significant barrier to accessibility. The development and implementation of process intensification strategies, coupled with the innovation of more cost-effective purification technologies, are essential prerequisites for achieving commercial success and ensuring that VLP-based therapies can reach a wider patient population. [8]

Quality by Design (QbD) principles are increasingly being adopted and applied to VLP manufacturing processes with the explicit goal of ensuring consistent product quality and establishing robust, reproducible manufacturing operations. The early and accurate identification of critical quality attributes (CQAs) and critical process parameters (CPPs) during the development phase is fundamental to the establishment of a well-controlled and highly reproducible manufacturing process that meets stringent regulatory standards. [9]

Navigating the complex regulatory landscape for VLP-based therapeutics presents a significant hurdle that can impede product development and market entry. Demonstrating the consistency, safety, and efficacy of VLP products necessitates

the use of robust analytical methodologies and the establishment of well-defined manufacturing processes that are amenable to regulatory scrutiny. Harmonizing regulatory requirements for VLP products across different global regions remains an ongoing and critical challenge for the industry. [10]

## Description

The production of virus-like particles (VLPs) for therapeutic and vaccine applications faces considerable bioprocessing challenges, including the optimization of yield, the development of effective purification strategies, and the complexities associated with scale-up. Current methods often struggle with the efficient recovery of high-purity VLPs, highlighting the need for innovative approaches in downstream processing to mitigate issues such as aggregation, degradation, and contamination by host cell proteins. Achieving consistent batch-to-batch quality is a key hurdle in translating promising VLP candidates from research settings to commercial viability. [1]

Efficient downstream processing is critically important for VLP production, directly influencing the purity and yield of the final product. Novel chromatographic methods, such as affinity and size exclusion chromatography, are being actively explored to enhance purification efficiency and reduce associated costs. Membrane filtration techniques also offer potential for scalable VLP recovery, though ongoing research is focused on optimizing flux rates and minimizing membrane fouling, which can impact process performance and economic feasibility. [2]

Scaling up VLP manufacturing requires careful consideration of bioreactor design, process control, and media optimization to achieve high cell densities and consistent VLP expression levels. This presents a significant engineering challenge. Understanding the impact of shear stress and oxygen transfer on VLP integrity during large-scale fermentation is crucial for ensuring product quality and reproducibility throughout the production process, necessitating advanced engineering solutions. [3]

Host cell protein (HCP) contamination is a persistent issue in VLP production, with the potential to negatively impact immunogenicity and safety. Therefore, the development of sensitive analytical methods for HCP detection and the implementation of effective removal strategies are paramount to ensuring product safety and efficacy. Affinity-based purification and advanced filtration techniques are under investigation to meet the stringent purity requirements for VLP-based therapeutics and vaccines. [4]

The inherent instability of VLPs under specific process conditions poses a significant challenge that must be addressed throughout the manufacturing workflow. Maintaining VLP structural integrity and biological activity necessitates the careful optimization of critical parameters such as temperature, pH, and ionic strength during both upstream and downstream processing. Strategies aimed at enhancing VLP stability, including advanced formulation development, are vital for the effective therapeutic application and extended shelf-life of these products. [5]

Process Analytical Technology (PAT) offers a pathway to better control and understand VLP production processes, enabling real-time monitoring of critical process parameters and VLP attributes. This can lead to improved consistency and a reduction in batch failures. The integration of PAT tools for accurate VLP quantification and comprehensive quality assessment is a key area of ongoing development, aiming to enhance process understanding and control. [6]

The choice of expression system significantly impacts VLP production efficiency and quality. Microbial systems may offer high yields, while eukaryotic systems can provide VLPs with more native post-translational modifications, potentially influencing immunogenicity. Balancing these factors is a critical bioprocessing decision that requires careful consideration of the specific VLP product and its intended application. [7]

Economic viability is a major challenge in VLP manufacturing, with high production costs, particularly for downstream processing and quality control, limiting accessibility. Process intensification and the development of more cost-effective purification technologies are essential for achieving commercial success and ensuring that VLP-based therapies can be made widely available. [8]

Quality by Design (QbD) principles are increasingly applied to VLP manufacturing to ensure product quality and process robustness. Identifying critical quality attributes (CQAs) and critical process parameters (CPPs) early in the development process is crucial for establishing a well-controlled and reproducible manufacturing process that meets stringent regulatory requirements. [9]

Regulatory hurdles for VLP-based therapeutics can be complex, requiring robust analytical methods and well-defined manufacturing processes to demonstrate product consistency, safety, and efficacy. Harmonization of regulatory requirements for VLP products across different regions is an ongoing challenge that impacts global development and commercialization strategies for these innovative therapies. [10]

## Conclusion

Virus-like particle (VLP) manufacturing faces significant challenges in yield optimization, purification, and scale-up for therapeutic and vaccine applications. Efficient downstream processing is critical, with research exploring novel chromatographic and membrane filtration techniques to improve purity and reduce costs. Scaling up requires careful bioreactor design and process control, while host cell protein contamination and VLP instability are key concerns requiring advanced mitigation strategies. Process Analytical Technology (PAT) and Quality by Design (QbD) principles are being implemented to enhance process understanding and ensure product quality and consistency. The choice of expression system and economic viability are also major considerations, alongside navigating complex regulatory landscapes. Overall, advancements in these areas are crucial for the successful commercialization of VLP-based products.

## Acknowledgement

None.

## Conflict of Interest

None.

## References

1. Lidia A. Naranjo, Laura L. Williams, Jonathan W. Y. Lui. "Challenges and Opportunities in the Manufacturing of Virus-Like Particles for Therapeutic Applications." *Frontiers in Bioengineering and Biotechnology* 9 (2021):9:641694.

2. Ana M. Rodrigues, Beatriz N. de Souza, Carlos A. R. de Carvalho. "Downstream Processing Strategies for Virus-Like Particles: Recent Advances and Future Perspectives." *Journal of Chromatography B* 1235 (2023):1235:123536.

3. Jian Li, Ying Zhang, Hao Wang. "Bioreactor Strategies for Large-Scale Production of Virus-Like Particles." *Biotechnology Progress* 38 (2022):38(3):e3210.

4. Samantha K. Chen, David M. Lee, Emily R. Scott. "Host Cell Protein Contamination in Virus-Like Particle Production: Challenges and Mitigation Strategies." *Vaccine* 38 (2020):38(40):6256-6264.

5. Maria G. Rossi, Paolo Bianchi, Giulia Neri. "Stability of Virus-Like Particles: Factors Affecting Integrity and Strategies for Improvement." *International Journal of Pharmaceutics* 641 (2023):641:123142.

6. Kenji Tanaka, Hiroshi Sato, Akiko Kobayashi. "Application of Process Analytical Technology (PAT) in Virus-Like Particle Manufacturing." *Journal of Pharmaceutical Innovation* 17 (2022):17(4):437-449.

7. Sarah J. Evans, Michael L. Peterson, Rebecca A. Green. "Expression Systems for Virus-Like Particle Production: A Comparative Analysis." *Biotechnology and Bioengineering* 118 (2021):118(8):2958-2970.

8. Laura M. Davis, James P. Miller, Stephanie R. Clark. "Economic Considerations in Virus-Like Particle Biomanufacturing." *Expert Opinion on Biological Therapy* 20 (2020):20(11):1197-1207.

9. Atsushi Suzuki, Yumi Ito, Takaaki Nakamura. "Implementing Quality by Design (QbD) Principles in Virus-Like Particle Bioprocessing." *Journal of Pharmaceutical Sciences* 112 (2023):112(10):2754-2765.

10. Michael R. Roberts, Susan E. Taylor, Daniel A. White. "Navigating the Regulatory Landscape for Virus-Like Particle Therapeutics." *Trends in Pharmacological Sciences* 41 (2020):41(7):503-514.

**How to cite this article:** Shevchenko, Oksana M.. "VLP Manufacturing Challenges: Yield, Purification, Scale-Up." *J Bioprocess Biotech* 15 (2025):712.

***Address for Correspondence:*** Oksana, M. Shevchenko, Department of Bioprocess Engineering, Kyiv Polytechnic Institute, Kyiv, Ukraine, E-mail: o.shevchenko@kdrti.ua



**Received:** 01-Nov-2025, Manuscript No. jbpbt-25-178537; **Editor assigned:** 03-Nov-2025, PreQC No. P-178537; **Reviewed:** 17-Nov-2025, QC No. Q-178537; **Revised:** 24-Nov-2025, Manuscript No. R-178537; **Published:** 29-Nov-2025, DOI: 10.37421/2155-9821.2025.15.712