# Ultra-Scale Down Models: A Review

*Bhavana NR* [1], *Pooja Muralidas* [1], *PR Shivadarshini* [1], *Dr Trilokchandran B* [2]

*Department of Biotechnology, RV College of Engineering, Bangalore, India*

## Abstract

Ultra scale-down (USD) models have emerged as indispensable tools, addressing challenges in process development and optimization. This review delves into the transformative potential of Ultra Scale-Down (USD) models, exploring their applications, benefits, limitations, and future directions. As industries deal with more complicated manufacturing processes, the integration of USD models into development pipelines becomes crucial. This approach holds the potential to reduce timeframes, cut costs, and enhance the overall efficiency of various processes, contributing to advancements across diverse fields. Envision transforming intricate manufacturing not through colossal machinery but by harnessing the capabilities of tiny vials and microfluidic chips. This encapsulates the essence of ultra scale-down (USD), an innovative approach that downsizes the landscape of process development. Essentially, USD duplicates pivotal elements of large-scale processes on a considerably smaller scale, typically employing milliliter-sized volumes. While USD is still advancing, and its potential to transform process development is evident. Embracing miniaturization, researchers and engineers unleash efficiency, cut costs, and hasten the launch of innovative products.

**Keywords:** Ultra Scale-Down (USD) models, Downstream processing, Cell-based therapies, Early-stage optimization, Real-time applications, Personalized medicine

## 1. Introduction

There are significant obstacles to the development and large-scale production of biopharmaceuticals, and the Ultra Scale-Down (USD) process addresses some of these challenges by providing a more representative platform for process optimization. Innovative techniques like CAR-T cell therapy, stem cell treatment, and gene therapy are examples of cell-based therapies that have great promise for treating a variety of illnesses, from cancer to autoimmune diseases and genetic problems. The success of these

therapies hinges not only on the therapeutic properties of the cells but also on the efficiency and scalability of the manufacturing processes [3].

USD models provide an economical and efficient way to learn about the intricacies involved in large-scale production by downsizing and replicating crucial processes in the manufacturing process on a smaller scale. For bioprocess engineers and researchers, USD models are a vital resource that bridges the gap between bench-scale experimentation and large-scale production. A plethora of benefits come with the ultra scale-down (USD) process, including faster and more economical development cycles through experimenting with small samples, early troubleshooting and data gathering, increased efficiency and yield through micro-scale optimization, and achieving meaningful results with reduced material requirements, making it especially valuable for precious materials or limited samples.

The applications of the ultra scale-down (USD) process are extensive, reaching across various industries. In biopharmaceutical manufacturing, USD is instrumental in streamlining processes such as protein purification, filtration, and crystallization. In chemical engineering, it facilitates the scaling up of new chemical reactions and separation methods. Furthermore, in the realm of food and beverage production, USD plays a crucial role in designing efficient processes for food processing and extracting key ingredients. Ultra Scale-Down (USD) processes not only address challenges in biopharmaceutical development but also hold the key to unlocking the potential of innovative cell-based therapies, emphasizing the critical link between therapeutic properties and scalable manufacturing efficiency [2].

## 2. USD Models

Ultrascale-down tools and methods enable manufacturing research to be conducted using milliliter quantities of precious material at an early stage of product development. This allows for rapid insight into the performance of full-scale processes as well as the impact of the engineering environment on process materials. This makes it possible for process scientists and bioprocess engineers to create and evaluate manufacturing routes at an early stage of development. It depends on research and understanding of the unit operation as a whole, taking into account not only the conditions within the large-scale machinery but also the effects of material transfer via pumps and valves during the biomanufacturing process.

Traditionally, scaling-down processes involved pilot plants or small-scale setups, which, due to the substantial amounts of biological material required, remained expensive. Recently, ultrascale-down (USD) tools have emerged, covering various techniques in cell bioprocessing. The use of small material volumes in USD devices enables high-throughput experimentation, which is particularly beneficial for the cell-based industry, where cellular material is costly to produce. This allows early-stage identification

and understanding of both the mechanical and biological responses of candidate cells to processing stimuli, facilitating the design of robust bioprocesses.

Ultra Scale-Down (USD) models, as a standard practice, involve the utilization of microfluidic devices, lab-on-a-chip platforms, or scaled-down versions of larger equipment. Microfluidic devices, characterized by their intricate networks of microchannels and chambers, enable the manipulation and analysis of small volumes of fluids, allowing researchers to emulate key aspects of larger-scale processes on a smaller scale. Lab-on-a-chip platforms, designed to integrate multiple laboratory functions onto a single chip, offer a compact and controlled environment for studying various aspects of cell therapy operations. Scaled-down versions of larger equipment, on the other hand, involve the replication of industrial-scale apparatus in a more compact form, ensuring that critical parameters and conditions are maintained on a smaller scale. This approach is particularly valuable for mimicking the challenges and complexities encountered during the manufacturing of cell therapies [4].

## 3. Applications of USD models

The miniaturisation of the models can be applied to the following:

a. An initial pilot study has to be done to study the effectiveness of the process. By employing USD models, it is possible to optimise the cell culture media, along with various process parameters such as pH, temperature, agitation rate, velocity of the stirrer, etc., to identify the optimal conditions for cell growth and optimum production of the product, as it is the main objective of upstream and downstream processing.
b. The uniform distribution of nutrients or oxygen and the study of the same are essential to understanding its implementation in a large scale bioreactor, as they are required for even growth of the cells and also as the requirements vary as per the stage of the cell.
c. They are mainly used in performance studies to validate the working of chromatographic columns and the filters at a smaller scale to identify the optimising conditions.
d. Useful for viral inactivation and mAb purification, to enable the study of steps in its production and allow for a quicker and more cost effective development.
e. There will be many parameters affecting the process. However, analysing these parameters on a large scale adds to the initial cost; hence, these USD models are used to evaluate the robustness of the manufacturing process.

## 4. Real time applications of USD models

Ultra Scale-Down (USD) models have become integral in real-time applications across industries. They play a pivotal role in biopharmaceutical process development, optimize drug formulation and delivery, and facilitate point-of-care testing through portable devices. In the dynamic realm of bioprocessing, USD models contribute to real-time monitoring, adaptive control strategies, and the advancement of personalized medicine applications. Their integration with lab-on-a-chip technology enhances precision in real-time monitoring and control, ensuring accuracy in studying cell composition changes over time. In essence, USD models provide a versatile approach to streamline processes, offering insights that drive efficient and dynamic decision-making in various applications.

As the field witnesses a surge in advanced therapies, such as cell and gene therapies, advancing through early- and late-stage clinical development, there is a pronounced emphasis on establishing scalable and resilient manufacturing processes. While a significant portion of research and development in this sector has focused on overcoming upstream challenges, particularly in large-scale cell expansion, equal attention is crucial for the advancement of large-scale harvesting and downstream processing operations.

### 4.1 Challenges Faced by Existing Cell-Based Therapies

The rapid growth of the cell and gene therapy fields in recent decades reflects their potential to address previously unmet patient needs by treating and curing diseases. The cell therapy industry, in particular, has witnessed substantial growth, with 728 clinical trials underway by the second quarter of 2016. Despite the approval and marketing of several cell therapy products worldwide, challenges, particularly related to cell manufacturing, have led to the failure of many small and medium-sized companies attempting clinical trials. The intricate relationship between the product and process in cell therapies poses challenges, including exposure to various stresses during processing, which can result in DNA damage, genomic alterations, physiological changes, cell death, and physical damage. Additionally, the need for robust processes to ensure the quality and integrity of the cells throughout processing is crucial for the successful commercialization of cell-based therapies [6].

Manufacturing difficulties arise from the biological complexity of cells, a limited understanding of their mechanisms, challenges in product characterization, and inherent variability in starting materials. These challenges highlight the importance of understanding the impact of processing conditions on cell health and the development of scalable and efficient manufacturing processes for cell-based therapies. Addressing these challenges is vital for ensuring the economic feasibility of the cell therapy sector. It involves creating a resilient, clearly outlined, and scalable manufacturing procedure that safeguards the potency, identity, viability and purity of the ultimate live cell product.

## 4.2 Application in the field of Cell-Based Therapies

Dedicated efforts in the research and development of Downstream Processing (DSP) demand attention toward efficient process development, comprehension of critical process parameters (CPPs), and the utilization of bench-scale technologies replicating full-scale operations. Ultra Scale-Down (USD) tools are proving to be invaluable assets in this context, facilitating the exploration of diverse manufacturing hydrodynamic environments and geometries with minimal resources. This accelerates cost-effective and time-efficient experimental phases in the pursuit of advancing DSP methodologies.

These models offer cost-effective screening capabilities, allowing the assessment of cell lines' susceptibility to diverse operating conditions, which is particularly crucial during the early stages of discovery and process development. With a minimal requirement for cell quantities, aligning with the often limited availability in initial stages, USD models enable efficient and resource-conscious experimentation. Their versatility is evident in the detailed characterization of cell responses to specific processing conditions, providing essential insights into cellular behavior throughout different manufacturing stages. Facilitating the evaluation of processing conditions' impact on cell damage and morphological changes, they contribute to a comprehensive understanding of their effects on cellular behavior [15].

Serving as a flexible platform for testing various operating conditions, these models empower researchers to optimize processes and identify conditions that balance efficiency and minimize cell damage. They are also known for their swift adaptability to changing parameters, assisting researchers in responding promptly to evolving requirements and conditions in cell-based therapy manufacturing. By simulating large-scale operations with minimal material, USD models enhance researchers' understanding of processes, facilitating the development of resilient and scalable processes crucial for commercial viability in cell-based therapies.

## 5. Benefits of USD models

The USD model stands out as a highly innovative solution, bringing numerous advantages that reshape how we efficiently approach large scale production. Process optimisation often requires changing certain materials to see if they fit in the process. This could incur a lot of costs for the initial studies. By employing USD models, it enables the reduction of expensive raw materials required for process testing and promotes cost-effective process development. As the processing volume is on a smaller scale, it enables a faster development and testing cycle, especially in the biopharmaceutical industry. Due to the smaller scale, parallel testing of the same process for different conditions can be done, which is very essential for testing

the efficiency of a process. At this non-resource-intensive production level, problems and challenges with the design can be identified, which helps mitigate risk during scale-up. For the growth of cells or product formation, specific parameters such as pH, temperature, agitation levels, etc. are required to be studied. USD models facilitate rapid and systematic screening of these parameters. The performance characteristics of the designed bioreactor can be studied, which helps in the scale up of the bioreactor in a more predictive and efficient way [16].

## 6. Limitations of USD models

Navigating the complexities of scale-up processes poses unique challenges, particularly when transitioning from the small scale of USD models to their larger counterparts. The small scale of the USD models need not necessarily replicate the large scale characteristics. There might be changes in mass transfer, mixing characteristics, or fluid dynamics that may lead to significant changes. USD models often simplify the geometries of the scale-up factor, which also contributes to the change in mass transfer and fluid dynamics. In processes involving cells, they respond to different environments in a varied manner. Hence, the behaviour of the cell may not be the same in both cases. There is different behaviour exhibited at different scales. For every process that exists, irrespective of scale, dynamic changes occur over time. USD models may not capture the dynamics of a large scale representation at a smaller scale. Some of the equipment parts may not be available in their smaller counterparts, which can restrict the small scale modelling. Assumptions and simplifications are often used to model the USD model, which often hampers the sensitivity of the process [17].

## 7. Future perspectives of USD models

Assumptions and simplifications as limitations can be overcome by using artificial intelligence as a predictive model. It can be trained by putting the data from the large-scale models in place to enable efficient scaling down. 3D cell culture systems are the next generation of cell culture, where the cells are allowed to grow and interact with the extracellular framework as opposed to 2D, which relates to monolayer culture. Future USD models can help model the 3D cell culture environment and enhance personalized medicine applications [9]. Many of the patients express a range of diseases, and using effective personalised treatment can help in rapid recovery. USD models can help in the customisation of therapeutic products and in the rapid screening of these products in patient-specific applications. On-site production and optimisation of the therapeutics enable testing the effectiveness of the drug and the development of a portable model. This can help in the design of point-of-care scale-down models. The

dynamic nature of processes as a limitation can be overcome by using real-time monitoring on USD models. This could be used for adaptive control strategies, ensuring consistent product quality.

Lab-on-a-chip technology is an upcoming nanoscale aspect that employs miniaturisation similar to USD models and integrates several laboratory operations, such as PCR and DNA sequencing, on a single ship. By employing this technology, accurate development of USD models can be done with enhanced monitoring and control [8]. The composition of the cell changes with time, and the changes in metabolism and byproducts vary with the stage of the cell. Studying this by using USD models can help design the cultural conditions and media formulation, which can then be used in other USD models.

## 8. Conclusion

Ultra Scale-Down (USD) models have emerged as revolutionary tools, presenting solutions to various challenges in the realms of biopharmaceutical development and downstream processing, spanning multiple industries from biopharmaceutical manufacturing to chemical engineering. These models offer a versatile and economically efficient platform. Despite the persisting challenges in cell-based therapies, USD models are instrumental in their mitigation by facilitating early-stage optimization, real-time applications, and opening avenues for progress in personalized medicine. Looking forward, the potential for enhanced capabilities and expanded applications of USD models lies in overcoming limitations through the integration of artificial intelligence and the adoption of cutting-edge technologies such as 3D cell culture and lab-on-a-chip.

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