Recipharm

Turning Oncolytic Viruses into Manufacturable Cancer Therapies

Oncolytic virus development requires more than increasing viral yield. The manufacturing process must preserve the product's identity, infectivity, potency, and function as it moves from research scale into GMP production. Raw materials and consumables, intermediate stability, and product-specific analytical methods are among the most important considerations when designing a scalable process. Addressing these elements early can minimize avoidable process changes and comparability risk, while a flexible CDMO partner can tailor equipment, suppliers, and development strategies to the needs of each product rather than forcing it into a fixed platform.

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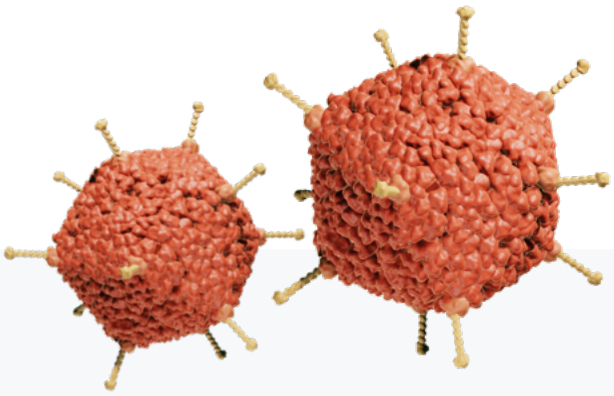


Preserving the Biology Through Manufacturing

Oncolytic viruses are designed to selectively infect and destroy tumor cells while also stimulating immune responses that can contribute to antitumor activity. Depending on the product, their function may involve infection, replication, tumor-cell lysis, immune activation, or expression of an engineered therapeutic payload. This combination of biological activities creates both therapeutic promise and significant manufacturing complexity.

For developers, the challenge is not simply to produce more virus. It is to establish a scalable, controlled, and reproducible process that preserves the characteristics responsible for the product's intended activity. Changes to raw materials, consumables, equipment, temperature, hold times, filtration conditions, or other process parameters may influence the virus in ways that are not immediately evident but will be detected at some point during development and scale-up with well-developed analytical methods.

Many developers possess deep knowledge of their virus and its mechanism of action but have less experience translating a research lab process into a practical GMP manufacturing strategy. The drug developer remains the expert in the specific product, while the contract development and manufacturing organization (CDMO) contributes expertise in cell culture, viral manufacturing, process development and technology transfer, analytical development, scale-up, quality systems, and GMP execution. Successful development depends on bringing those areas of knowledge together while maintaining close and transparent communication throughout the program.

Designing for GMP Before Reaching GMP

Manufacturability should be considered once a program moves beyond its earliest exploratory experiments. Waiting until clinical manufacturing to address materials, equipment, analytics, and scale can lead to expensive redevelopment at a stage when changes are more difficult to implement leading finally to delay of clinical study start.

A laboratory process is generally developed to answer scientific questions and generate limited quantities of material. Researchers may use the container, reagent, or consumable that is readily available because it is sufficient for the immediate experiment. That approach can become problematic when the process must be transferred to a CDMO or scaled to hundreds or thousands of liters.

Raw materials and consumables should therefore be selected with future manufacturing requirements in mind. Developers do not need to operate large-scale equipment during early development, but they should use small-scale versions made from the same or comparable equipment expected to be used later. A one-liter biocontainer, for example, may be appropriate for development if it is constructed from the same material as the larger system anticipated for GMP production.

The same principle applies to culture media, feeds, infection- or transfection-enhancing components, and other critical raw materials and reagents. Materials should be available from suppliers that can support larger quantities, appropriate quality grades, suitable documentation, and continuity through clinical and potentially commercial manufacturing. Particularly important is the compliance for TSE/BSE (transmissible spongiform encephalopathies / bovine spongiform encephalopathy) status for raw materials during early product development, if it is on the critical GMP/clinical path.

This is particularly important for live biological systems. Differences in material composition, supplier processes, or impurities can affect cell growth, infection efficiency, viral productivity, or product quality. A seemingly minor material substitution can therefore introduce significant process variability.

Material and equipment selections made early do not necessarily need to remain unchanged throughout the product life cycle. However, choosing scalable options from the outset reduces the number of changes that must later be evaluated, justified, and supported through additional development and comparability work.

Although each oncolytic virus requires a product-specific development strategy, three considerations repeatedly emerge during the transition from research production to scalable GMP manufacturing: the suitability and availability of raw materials and consumables, the stability of process intermediates, and the robustness of analytical methods used to monitor the process and characterize the product.

These areas are closely connected. A material change may alter the product, but without reliable analytical methods, the impact may be difficult to detect. A process may produce acceptable material at small scale but fail during scale-up because intermediate hold times become longer. A result that appears to indicate a process failure may instead reflect variability in the analytical method.

Intermediate Stability as a Hidden Scale-Up Constraint

One of the most easily overlooked differences between a research process and a large-scale manufacturing process is time.

At laboratory scale, an intermediate may be generated, processed, and transferred to the next step within several hours. Researchers may therefore have little reason to determine whether it remains stable for longer periods at room temperature or under other process conditions.

The same operation can take much longer at manufacturing scale. Filtration through a larger surface area, transfer of hundreds of liters, filling, visual inspection, and other operations extend process duration. Live-virus products may also place limits on the pressure, flow rate, or shear forces that can be applied, preventing manufacturers from simply accelerating a step to reduce the hold time.

A laboratory process that can be completed within eight or 24 hours may require several days at larger scale. Temperature conditions that are practical for a small vessel may also be difficult to maintain consistently in a 200-, 600-, or 1,000-liter system.

These differences make intermediate stability a potential process constraint. A hold time that was acceptable for a small batch may become insufficient when the number of filled units increases substantially and additional operations, including visual inspection of final product vials, must be completed.

Intermediate-stability studies should therefore be incorporated into process development before scale-up. These studies can establish acceptable hold times and temperatures, identify stages at which the virus is most vulnerable, and determine whether buffer, formulation or process modifications are needed. A relatively small change introduced early may substantially improve stability and remove what could otherwise become a late-stage bottleneck.

Final drug product storage presents a related but more familiar challenge. Many live-virus products require frozen storage, potentially at –20 °C or –80 °C depending on their formulation and stability profile for the specific virus. Facilities must provide qualified freezers, alarms, backup power, redundant storage capacity, temperature monitoring, and validated shipping systems.

Temperature-excursion studies are also needed so that manufacturers can determine whether a product remains suitable for use following a related deviation. Without those data, even a relatively short excursion may result in the loss of a valuable batch. These requirements can be costly, but they are technically manageable when incorporated into the storage and distribution strategy.

Building the Analytical Strategy for the Process

Analytical methods provide the visibility needed to understand what is happening to an oncolytic virus during development, scale-up, manufacturing, storage, and release. They are effectively the eyes of the process.

Standard methods can be used to evaluate attributes and impurities common to many viral products, including identity, viral titer (total particle, genome copy, and infectious titers), host cell proteins, host cell DNA, and process-related impurities. However, many of the most important methods for oncolytic viruses are product specific.

The infection efficiency of a virus can differ depending on the viral construct and the target cell. Relevant assays may therefore require dedicated cell lines, cell banks, virus banks, reference materials, antigens, antibodies, negative and positive controls, or other reagents developed specifically for the product. Those supporting reagents and biological systems must themselves be characterized, controlled, and maintained if the method is to remain reliable throughout development.

The existence of an analytical method is not sufficient. The method must also be robust enough to produce meaningful results when transferred between laboratories, used by different analysts, or repeated over time. This approach of assay qualification and validation is applied at increasing scrutiny during clinical development.

Method variability is particularly important for live viral products because some degree of biological variability is unavoidable. Developers need enough repeated measurements to understand the normal variability of the assay and the product. Without that information, an unexpected result may be incorrectly attributed to the manufacturing process when the actual source is the test method.

A useful analytical strategy should establish what attribute each method measures, how that attribute relates to product quality or function, the expected variability of both the method and the product, whether the method can reliably detect meaningful process changes, and how it will evolve from development use to qualification and validation. This understanding allows analytical data to inform process decisions rather than create additional uncertainty. Each product-specific analytical method and needed equipment should be evaluated and challenged for its feasibility to be qualified within an QC / GMP / regulatory environment.

Using Risk Assessment to Guide Necessary Change

Some changes are inevitable when moving from a research process to a scalable GMP process. Laboratory equipment may not be suitable for larger batches. Materials may not be available in sufficient quantities or with appropriate quality documentation. Manual operations may need to be replaced with controlled and reproducible manufacturing steps.

The goal is not to avoid every change. It is to understand which changes are necessary, evaluate their potential effects, and avoid introducing changes that offer no meaningful benefit.

A product-specific risk assessment should identify differences between the incoming process and the proposed GMP process, materials, equipment, and parameters that may affect viral structure or function, gaps in analytical coverage, scale-dependent changes in processing time or temperature, potential sources of product and method variability, and the evidence needed to demonstrate that the product remains comparable.

Critical process parameters (CPPs), critical material attributes (CMAs), and critical quality attributes (CQAs) can then be linked through the analytical strategy to control the production process, even at commercial stage. This framework helps determine which process parameters require close control and which analytical methods are needed to confirm that changes have not altered the product.

Risk assessment should be an ongoing activity rather than a one-time exercise performed at project initiation. As process understanding develops, new information may change the relative importance of individual parameters or reveal previously unrecognized sources of variability.

Engaging Regulators While the Field Evolves

Oncolytic viruses remain a comparatively young therapeutic class, and scientific and regulatory understanding continues to develop alongside individual products. Product-specific considerations, particularly those involving mechanism of action and potency, may not be addressed by detailed prescriptive guidance.

Biopharma developers and manufacturers should not respond by waiting for regulators to define a universal approach. Early engagement can provide an opportunity to present the proposed development, analytical, and potency strategies, explain the available data, and obtain feedback while the program remains adaptable.

Such interactions are particularly valuable when the mechanism of action involves several biological activities, the potency strategy uses multiple assays, product-specific cell systems or reagents are required, established acceptance criteria are limited, a process change may affect clinically relevant attributes, or the program uses an approach for which little precedent exists.

Open scientific exchange benefits both the program and the broader field. Regulators gain insight into emerging technologies, while developers receive feedback on whether their proposed control strategy provides adequate evidence of identity, quality, consistency, and biological activity.

Tailoring the Manufacturing Solution to the Product

The client possesses knowledge of its specific virus that cannot be replaced by general manufacturing experience. At the same time, the sponsor may not have the equipment, personnel, quality systems, regulatory, or scale-up experience needed to translate that virus into a clinical or commercial product.

The most effective CDMO relationship combines these complementary areas of expertise. The developer remains closely involved in decisions affecting the product, while the manufacturing partner provides the infrastructure and experience needed to establish a practical GMP process.

At Recipharm, this collaboration is based on adapting the manufacturing approach to the individual product rather than adapting every product to a fixed platform. We do not automatically impose a preferred supplier, filter, bioreactor, consumable, or process simply because it is already part of an internal platform. However, we will consult the customer in a proactive and productive manner if process changes should be considered or are even regarded as mandatory.

When an existing element of the customer's process is working and can support the required scale and quality, changing it may introduce risk without providing a corresponding benefit. Recipharm has access to different types of equipment and manufacturing lines, enabling the selection of the option that best fits the incoming process.

The same principle applies to suppliers. When an established supplier can support the required quantity, quality, and documentation, that supplier can be incorporated into the program, including through addition to Recipharm's approved supplier list where necessary. Alternatives are recommended when an existing material or supplier cannot support GMP manufacturing or future scale, or when data indicate that a change could improve the process.

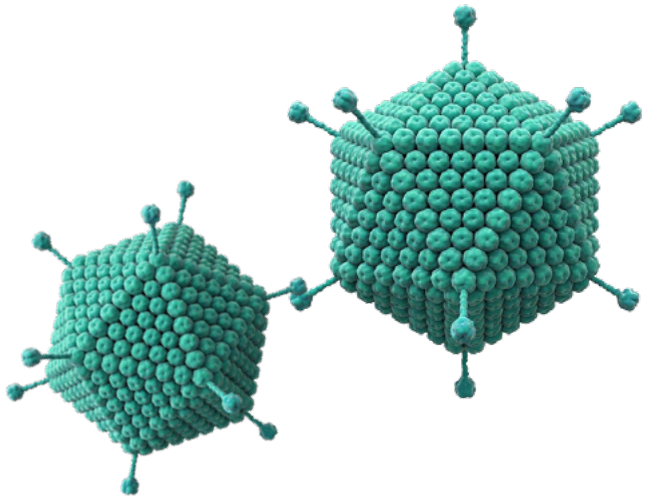
This approach combines flexibility with scientific discipline. It does not mean preserving a research process unchanged. It means changing what must be changed, retaining what remains appropriate, and using risk assessment and analytical evidence to guide each decision.

The value of that flexibility can be particularly visible during technology transfer. In one example involving an already commercialized product with an established process and supplier network, Recipharm transferred the process, manufactured process performance qualification (PPQ) batches, and released drug substance in less than nine months. The established nature of the program was an important factor in that timeline, but the ability to accommodate the existing process and suppliers avoided unnecessary redevelopment.

Transparent communication is equally important. Sponsors need clear visibility into their programs, including unexpected results, emerging risks, and decisions that may affect the product. Maintaining that openness allows the developer and CDMO to evaluate challenges together and protects the product knowledge established before outsourcing.

Recipharm also encourages customers, where appropriate, to share clinical information with the teams working on their programs. Connecting manufacturing personnel with the intended indication and patient need reinforces the importance of execution at every level of the organization.

Turning an oncolytic virus into a manufacturable therapy ultimately requires more than viral production capacity. It requires an early strategy for materials, intermediate stability, analytics, scale-up, and regulatory engagement, together with a manufacturing partner capable of understanding and accommodating the needs of the specific product. By preserving what already works, changing only what the evidence supports, and maintaining close collaboration throughout development, sponsors can reduce avoidable risk while advancing complex oncolytic virus therapies toward patients.



About Recipharm

Recipharm is a leading contract development and manufacturing organisation (CDMO). We operate development and manufacturing facilities in France, Germany, India, Italy, Portugal, Spain, Sweden and the US and are continuing to grow and expand our offering for our customers. We are supporting pharmaceutical companies with our full service offering, taking products from early development through to commercial production. For over 30 years, we have partnered with our clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again. We conduct our business as we always have and continue to deliver value for money with each customer's needs firmly at the heart of all that we do.