ReciBio Pharm

Cell and virus banking in OV development and manufacturing

Five considerations for planning your program

INTRODUCTION

Oncolytic viruses (OVs) are rapidly emerging as an important tool for treating cancer. They can be specifically engineered for tumor cell selectivity and enhanced immune stimulation to lyse cancerous cells or deliver a therapeutic payload. OVs remain largely in the clinical trial phase, with more than 120 clinical trials utilizing OVs conducted in 2021[1]. Nevertheless, the results of these studies are highly promising, hinting at the technology's future potential.

OVs offer significant advantages to patients, particularly as they allow them to avoid more invasive treatment options — such as surgery or radiation therapy — and their associated side effects. However, the modality faces unique challenges, particularly when it comes to development and manufacturing at the required scale. Careful consideration, and sometimes trial and error, is required to develop efficient and robust processes to ensure a commercially viable product.

This article explores the key considerations for starting a cell and virus seed bank for infection-based OV production processes. Additionally, developers and manufacturers need to take into account to make sure these vital substrates are ready as early as possible to streamline OV manufacturing.

Generating cell and virus banks for OV production

For OV development and manufacturing, robust processes for cell and virus banking are essential to deliver well-characterized starting materials needed throughout the lifecycle of the OV production process. Master cell or virus banks (MCB/MVSS) are derived from the expansion of a cell or virus clone, with working banks (WCB/WVBs) made once the master has been completed.

Planning considerations

There are many aspects that OV manufacturers will need to consider when establishing cell and virus banks:

1 Determining parameters and bank size

Developers must decide on the key cell and virus banks parameters for each starting material. A typical MCB will be established with 300–500 vials, with WCBs comprising 500–1,000 on average.

Comparable vial numbers are expected for master virus banks. Further considerations include:

- A clear understanding of substrate source and origin
- Prior exposure to animal-derived components
- Clonality and characterization of seed materials
- Bank size — projected future use and needs
- Minimum cell density or minimum virus titer
- Filling volumes
- Recovery after a freeze-thaw cycle
- Timeline readiness for GMP manufacturing
- Requirements of permitting, shipping and logistics.

2 Performing pre-GMP feasibility studies

Banking feasibility studies should be carried out on starting materials prior to GMP production to minimize risk of unexpected occurrences later on. These studies aim to ensure that cell expansion and viability, as well as system productivity, are all acceptable for GMP by performing a non-GMP verification run. This is performed by taking cells to the early culture stage through a number of passages or by performing a full process simulation for the cell or virus bank.

Other studies that can be performed include ensuring that dimethyl sulfoxide (DMSO) in cell and virus bank formulation does not pose unacceptable toxicity risk, and determining if controlled freezing and thawing can maximize cell recovery.

3 Characterizing cell and virus banks

There are strict regulatory requirements for the testing of production cell and virus banks. As such, preparation of the sampling plan and release testing panel should be considered in the manufacturing of starting material to ensure compliance.

The release and characterization panel will depend on the cell line, virus seed and whether any animal-derived product has been used in production (including fetal bovine serum). Testing may also require non-infected control cells to determine the presence of adventitious agents for full characterization.[2,3,4]

It is recommended to consult with the relevant regulatory agency to confirm the specified testing parameters of the substrate, especially when using a novel cell or virus. Common testing per regulatory guidance includes:

- Identity
- Microbial safety (sterility, mycoplasma)
- Adventitious virus safety (*in vitro/in vivo*, PCR-based)
- Retrovirus detection (TEM, PBRT)
- Testing for specific viruses of the substrate origin
- Performing genetic stability/construct confirmation (restriction digest, sequencing).

4 Amplifying virus seed material

Occasionally, insufficient material is produced in the first production run. In this case, manufacturers should consider a further amplification step for the virus seed during the starting cell expansion for the drug substance. If this is required, the infectious titer of this material must be available at the time of batch infection.

5 Considering long-term storage conditions

In a best-case scenario, the culture medium used will be sufficient to ensure cell stability during freezing, storage at long term and thawing. However, in some cases, additional excipients may be required. Other long-term storage considerations include:

- Determining the best containers for cell banks (typically cryovials) and viral seeds (cryovials or glass vials)
- Planning for additional needs of material used in the characterization and quality control testing as well as stability studies.

CAREFUL PLANNING IS KEY TO CREATING EFFECTIVE BANKS

Well-generated cell and virus banks are crucial to ensuring consistent production of OV therapies, from development to post-launch commercial manufacturing.

With so many factors that need to be considered to ensure quality and regulatory compliance, the expertise and experience provided by a specialized OV contract service partner can be invaluable.

Explore our virotherapy insider: Deep dive into GMP manufacturing of oncolytic viruses to review the critical steps involved in OV development, manufacturing, testing and the important considerations that must be made throughout.

References

1. *Cook M, Chauhan A. Clinical Application of Oncolytic Viruses: A Systematic Review. Int J Mol Sci. 2020;21(20):7505. Published 2020 Oct 12.*
2. *https://file.wuxuwang.com/yaopinbz/EP3/EP3_1998__13.pdf*
3. *https://www.ema.europa.eu/en/ich-q5a-r1-quality-biotechnological-products-viral-safety-evaluation-biotechnology-products-derived*
4. *https://www.fda.gov/media/76255/download*

About us

Introducing ReciBioPharm, Recipharm's biologics business combining the capabilities of acquired CDMOs Arranta Bio, GenIbet and Vibalogics. Our expanded biologics drug development and manufacturing services encompass technologies based on live viruses and viral vectors, live-microbial biopharmaceutical products, recombinant proteins, nucleic acid-based mRNA and plasmid DNA production.

Established in 1995, Recipharm's manufacturing, fill & finish, and delivery-device services encompass a wide variety of drug dosage forms and modalities. Recipharm is an industry leading CDMO with over 30 facilities and 9,000 employees globally – supporting companies that are developing small molecules, biologics, and drug-device combinations. The company operates development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US.

recibiopharm.com

ReciBio Pharm