Designing for Commercial Scale: A Rapid and Scalable Lentiviral Manufacturing Approach

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Director Innovation, Analytical and Process Development

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Built on Stability, Committed to Your Success

Investment to support our clients' needs

CDMO built to deliver from early development through commercialization across a global network

Viral Vectors | Small Molecules

AAV, LVV, Adeno

Strategic Facilities Mitigating Potential Supply Chain Risks

SMALL MOLECULE
NORTH AMERICA
Rancho Cordova, CA, USA
Company Headquarters
Manufacturing Plant
Process R&D Center

El Dorado Hills, CA, USA
Contract Analytical Services

GENE THERAPY
NORTH AMERICA
King of Prussia, PA, USA
Viral Vector Manufacturing Plant

SMALL MOLECULE
NORTH AMERICA
La Porte, TX, USA
Manufacturing Plant
Process R&D Center

SMALL MOLECULE
EUROPE
Swords, Ireland
Manufacturing Plant
Process R&D Center
Particle Engineering Lab

GENE THERAPY
EUROPE
South of Paris, France
Viral Vector Manufacturing Plant
Large-scale Manufacturing

SMALL MOLECULE
ASIA
Sejong, South Korea
Manufacturing Plant

Daejeon, South Korea
Process R&D Center

Committed to support our clients **deliver life-impacting medicines for patients** around the world

Mission

We are committed to changing the world through our unwavering dedication to lifesaving therapies.

We enable our partners with cutting-edge technologies, expertise, and customer centricity, allowing them to bring breakthrough treatments to patients and deliver happiness and health to stakeholders everywhere

Vision

The most trusted global partner in the delivery of innovative medicine

Manufacturing Capability Snapshot

3 Plug-and-play viral vector manufacturing platforms

Specializing in **AAV, LV-based, Adeno**, and other viral modalities

LVV *ex vivo* to *in vivo* approach

2 Locations: France and US

100+ Number of total cGMP batches produced over AAV, Lentivirus, and Adenovirus

9 Vector suites + Formulation and Fill/Finish suites

3-5 Week Avg. Batch Production

8 Months from plasmid to cGMP release using our LVV and AAV platforms

Up to: **500 L** Adherent process

2 x 1,000 L Suspension process

Overview & Technical Narrative

From Proven *Ex vivo* Manufacturing to *In vivo* Drug-Product Readiness

1

Defining Our LentiSure™ Platform:

A proven and scalable *ex vivo* LVV manufacturing platform built on years of clinical experience.

2

Our Approach from *Ex vivo* to *In vivo*:

Building on our *ex vivo* LVV track record, we are evolving to drug-product standards with strengthened purity, potency, and CMC control.

3

Redefining LVV Downstream for *In vivo* Applications:

Addressing yield limitations and impurity constraints to meet drug-product–level expectations.

4

Scalable Performance & Manufacturing Readiness:

Demonstrating robustness, cost efficiency, and yield from bench scale through 50 L.

SK pharmteco

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USP: Engineering Biological Control for Commercial Scalability

A modular, fully single-use upstream platform designed for robustness, flexibility, and scale consistency

Controlled Biological Foundation

- In-house cGMP HEK293T MCB / WCB
- Serum-free culture
- Standardized quadruple-plasmid system
- Proprietary transfection reagent

Robust & Modular by Design

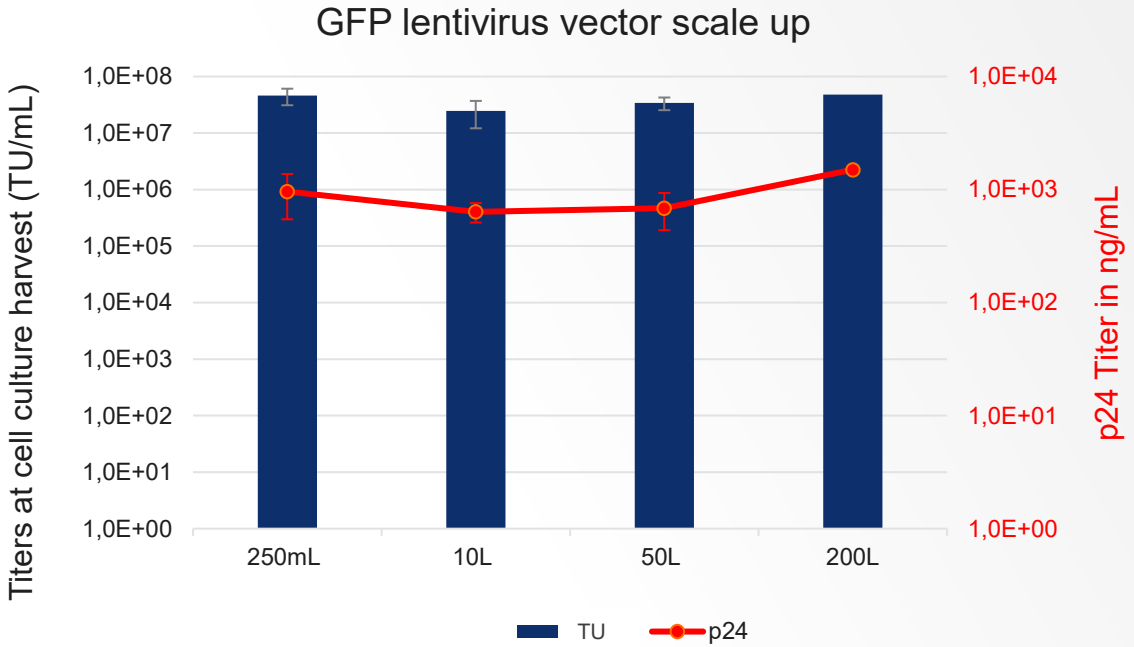
- DoE-optimized DNA/cell and plasmid ratios
- Standardized transfection parameters
- Fully single-use closed architecture
- Compatibility with customer cell lines and plasmids

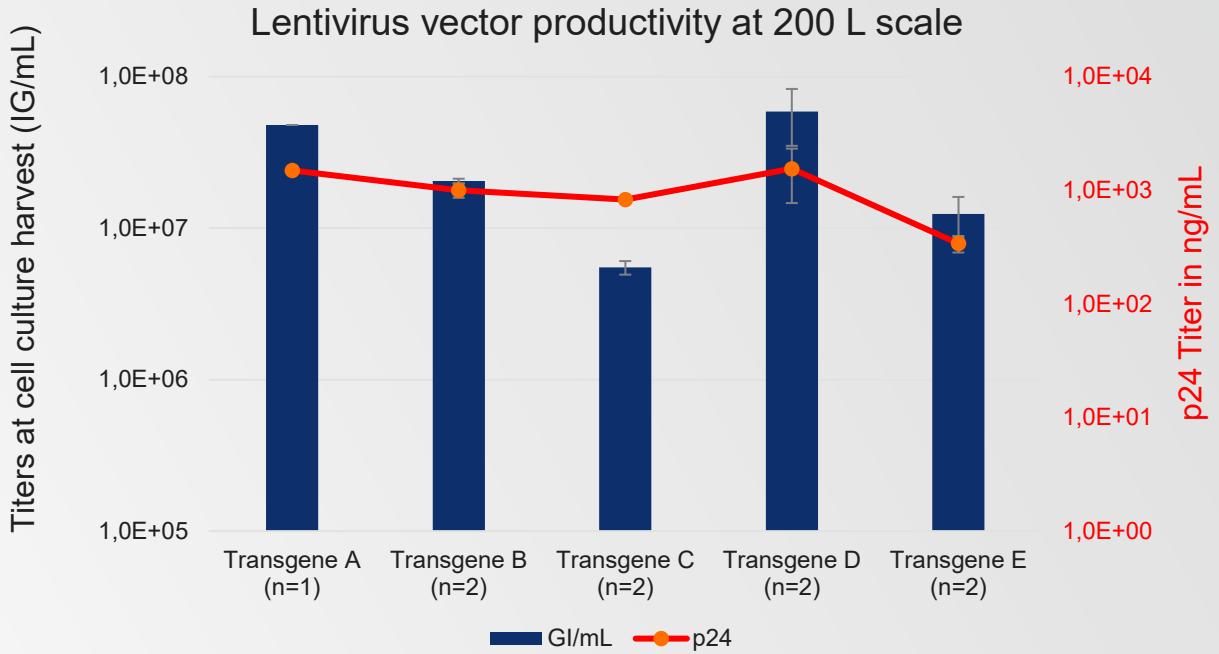
Scalable Performance Demonstrated

- Consistent titers across scales
- Harvest titers up to 5.9×10^7 IG/mL
- No loss of infectivity during scale-up
- Demonstrated scalability to 200 L

Productivity Across Volumes and Transgenes

LentiSure maintains infectious titer and productivity from bench to pilot scale





Demonstrated scalability:

- Comparable infectious titers from 250 mL to 200 L
- No significant loss of productivity during scale-up
- Stable p24 levels across volumes

Robustness Across Transgenes:

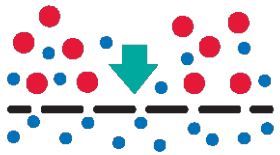
- Consistent performance across multiple constructs
- Titers up to 5.9 × 10^7 IG/mL at 200 L
- No construct-specific productivity collapse

DSP: High-Recovery, Scalable Purification by Design

Single-use DSP strategy engineered to preserve infectivity and maximize manufacturing efficiency

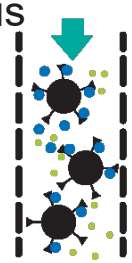
1 Protecting Vector Integrity Early

- Optimized single-use clarification train
- High-capacity filtration strategy
- 0.2 μm filtration to protect AEX membrane
- Controlled shear exposure



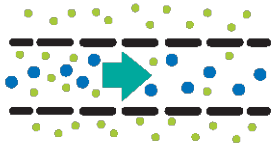
2 Membrane-Based AEX for Scalable Recovery

- Single-use membrane chromatography
- High load capacity
- Reduced residence time, minimizing vector degradation
- High recovery of infectious particles



3 Efficient Concentration & Manufacturing Readiness

- Single-use TFF/Diafiltration
- Controlled buffer exchange
- Concentration without infectivity loss
- Removal of residual DNA and process-related impurities
- Reduced process time and footprint



Maintained Infectivity and Controlled Recovery Through DSP

From harvest to drug product without significant infectivity loss

Scan to explore a real-world LentiSure case study.

Follow us on LinkedIn for our upcoming white paper on ex vivo LVV manufacturing.

Harvest Performance

Comparable harvest titers:
- 3.7 x 10^7 IG/mL at 50 L
- 2.9 x 10^7 IG/mL at 200 L

- No major scale-related drop

Drug Substance Intermediate Concentration

Effective downstream concentration
- Infectious titer maintained post-purification:
  - 4.3 x 10^9 IG/mL at 50 L
  - 4.0 x 10^9 IG/mL at 200 L

Process Efficiency

15 % - 30% Overall yield

- Controlled recovery from harvest to DS intermediate
- Stable across scale

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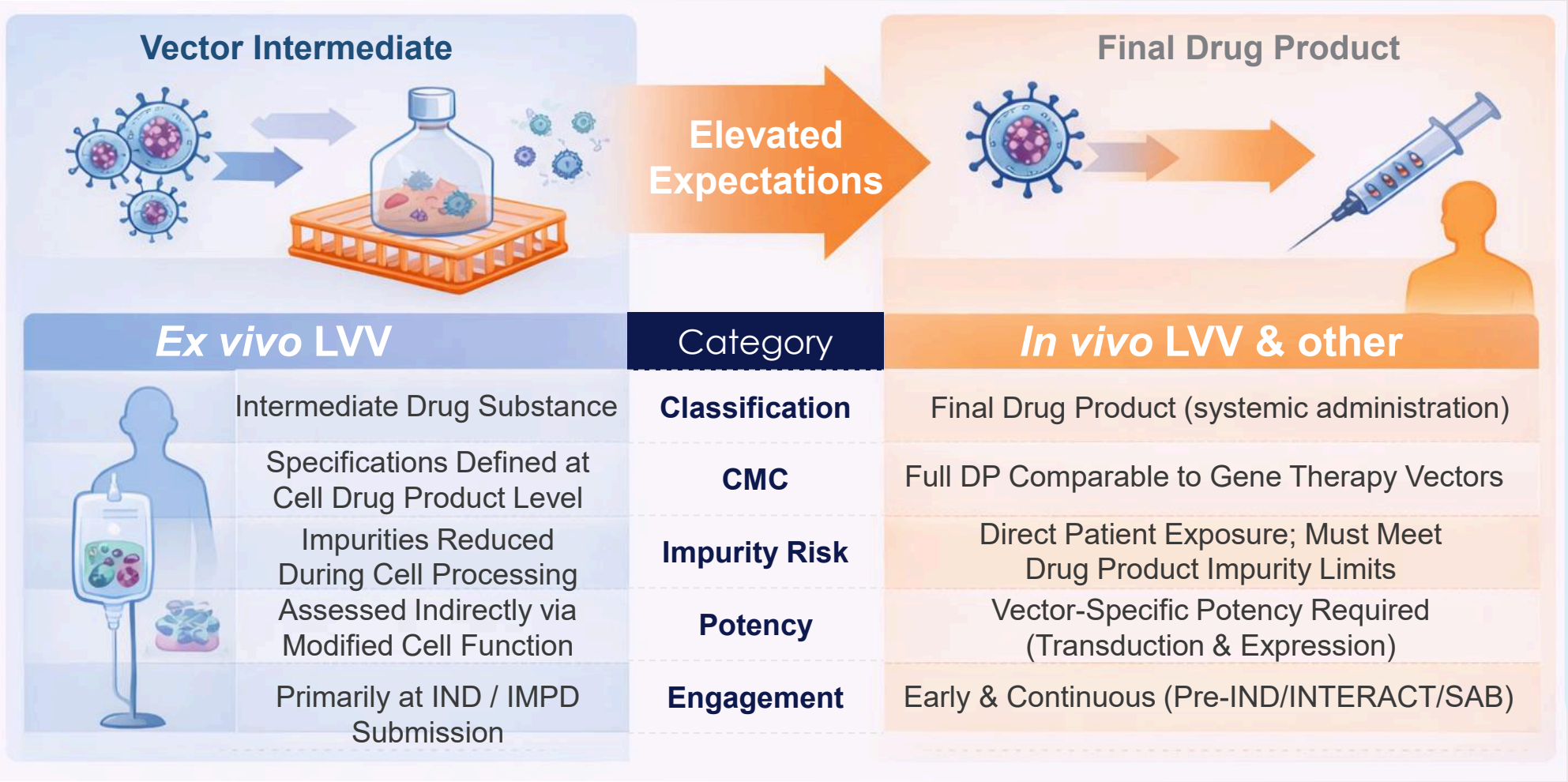
Shift in Regulatory Burden From Drug Substance to Drug Product

Implications for Manufacturing, CMC, & Analytical Strategy



Ex vivo LVV	Category	*In vivo* LVV & other
Intermediate Drug Substance	**Classification**	Final Drug Product (systemic administration)
Specifications Defined at Cell Drug Product Level	**CMC**	Full DP Comparable to Gene Therapy Vectors
Impurities Reduced During Cell Processing	**Impurity Risk**	Direct Patient Exposure; Must Meet Drug Product Impurity Limits
Assessed Indirectly via Modified Cell Function	**Potency**	Vector-Specific Potency Required (Transduction & Expression)
Primarily at IND / IMPD Submission	**Engagement**	Early & Continuous (Pre-IND/INTERACT/SAB)

Key Milestone:

SK pharmteco successfully manufactured and released both ***ex vivo*** and ***in vivo*** lentiviral products for clinical use, demonstrating capability across drug substance and drug product manufacturing.

In vivo CAR-Ts: Barriers to Entry

Identifying the Key Biological and Manufacturing Bottlenecks

Tropism & Cell Selectivity

- Off-target transduction of non–T-cell populations (e.g., macrophages or NK cells) may trigger uncontrolled cytokine release and systemic inflammation.
- Unintended antigen recognition on healthy tissues (e.g., low-level HER2 expression) can result in fatal on-target/off-tumor toxicity.
- Achieving strict T-cell–specific tropism is essential to minimize immune-related adverse events.

Regulating Expression

Current LVVs often rely on strong, constitutive promoters, leading to poorly regulated expression kinetics.

I. Underexpression → loss of potency & persistence

II. Overexpression → cytokine release syndrome or tissue damage

III. Variable expression → heterogeneous potency & unpredictable safety profiles.

Manufacturing & Dosing Challenges

- *In vivo* LVVs represent the final drug product (DP) rather than an intermediate, imposing stricter CMC and analytical expectations.
- Requires robust vector quality and durability to ensure consistent *in vivo* performance.
- Variability in transduction efficiency, T-cell expansion kinetics, and host immunity affects potency and comparability across patients. Neutralization of transduced cells before expansion.

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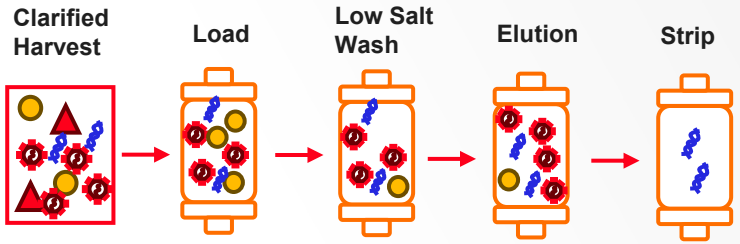
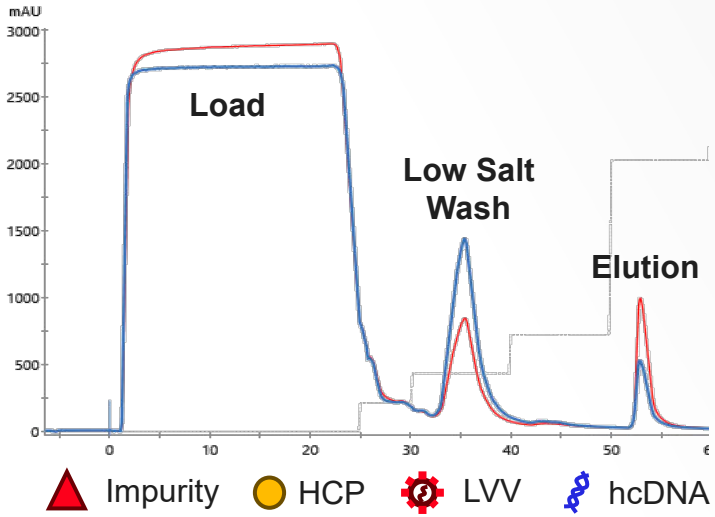
Dissecting AEX Chromatography

Why Traditional AEX Constrains LVV Manufacturing

Goal: Identify why resin-based AEX limits LVV recovery and scalability and what must change to unlock higher yields.

Traditional IEX Process





~20% Total LVV Recovery

Comparison of IEX Technologies

Attribute	Packed-Bed Resin	Membrane Adsorber
Mass Transfer	Diffusion-limited	Convection-driven
Recovery	**15–40%**	**60–90%**
Throughput	**Slow, batch-limited**	**>5× faster**
Back Pressure	Increases at High load	Minimal
Residence Time	**2-4 min**	**0.1 min**
Cost & Flexibility	High COGs, rigid hardware	Disposable, cost-efficient

Impact of Process Optimization on LVV Elution

Elution	VP/mL	Total VP	%VP of Load
Traditional	1.1E+08	4.6E+08	17%
Optimized	**4.6E+08**	**1.9E+09**	**70%**

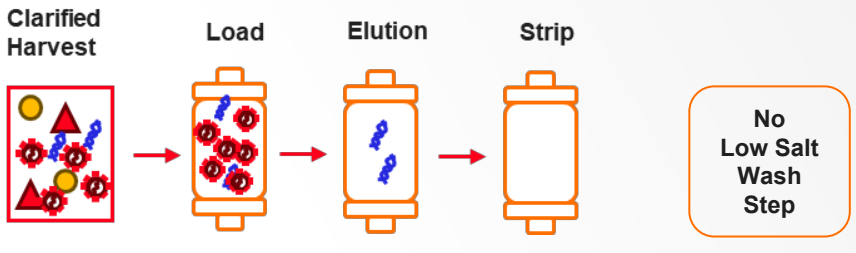
Even with optimization, resin-based AEX remains diffusion-limited thus capping LVV recovery, extending cycle times, and driving high COGs.

Tripling LVV Recovery with Optimized IEX Chromatography

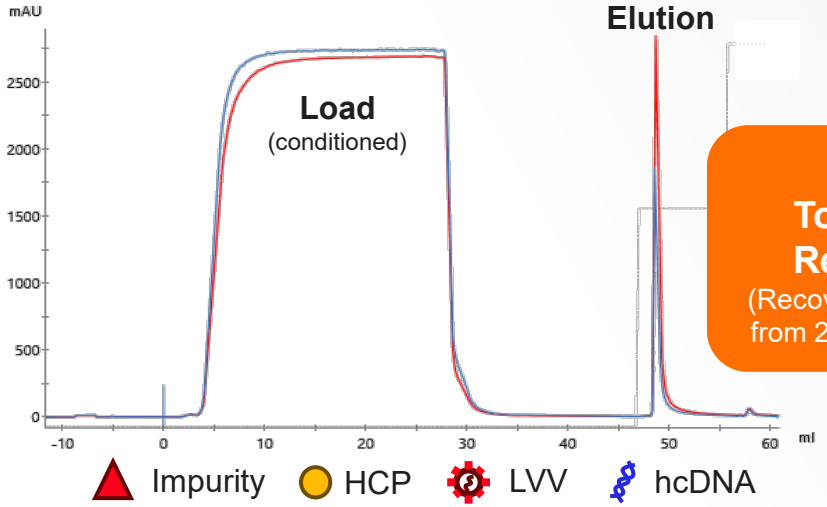
Driving Recovery from 20% to 70% Through High-Throughput Convective IEX Membrane Chromatography

Goal: To overcome diffusion-limited recovery, we evaluated convective membrane-based IEX as an alternative capture strategy.

SK pharmteco's Improved Process:

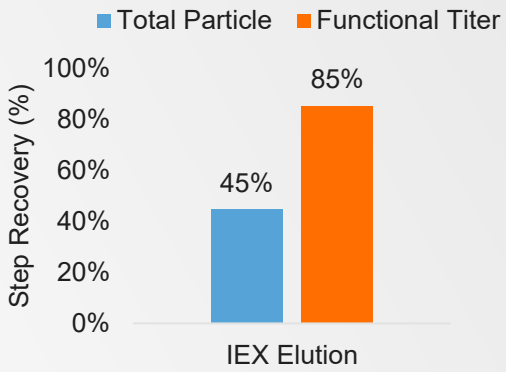


No Low Salt Wash Step

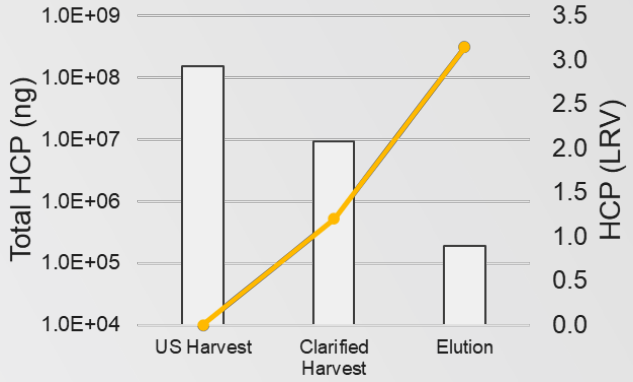


≥70% Total LVV Recovery
(Recovery increased from 20% → ≥ 70%)

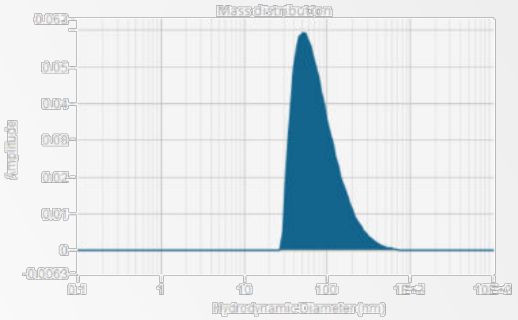
Improved Yields



Reduced Residuals



Intact Virus



Summary:

- Achieves 98% HCP clearance (99.7% from harvest).
- **> 85% TU recovery** across runs.
- ≥ 70% overall LVV yield.
- **<2h processing time**, enabling simplified operations.

Convective membrane flow eliminates diffusion constraints, enabling high-throughput viral capture with improved impurity resolution.

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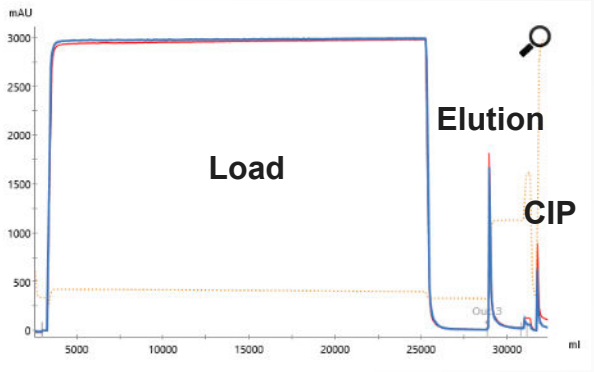
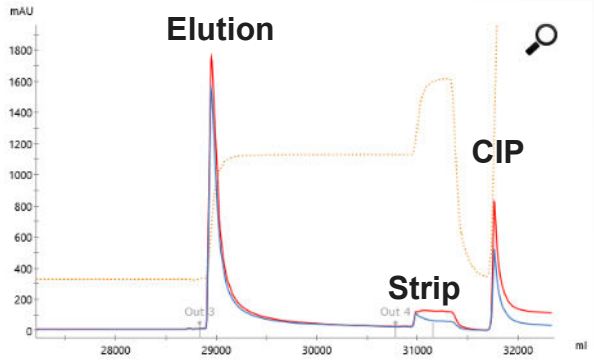
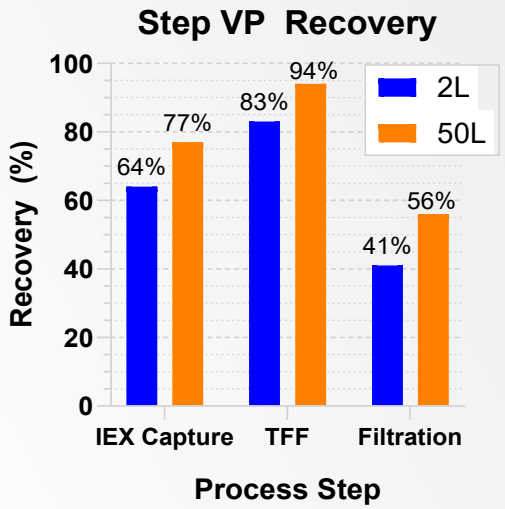
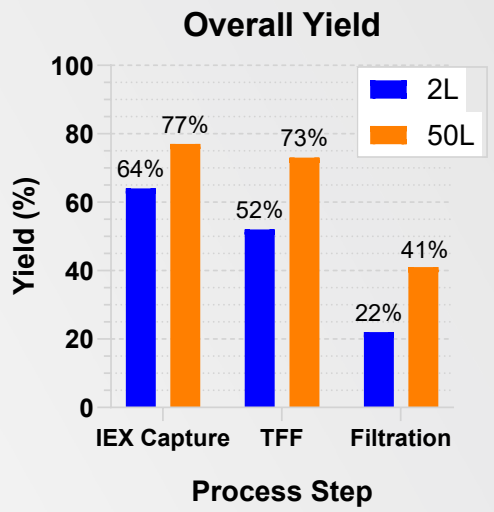
Consistent LVV Performance from Bench to 50 L Scale

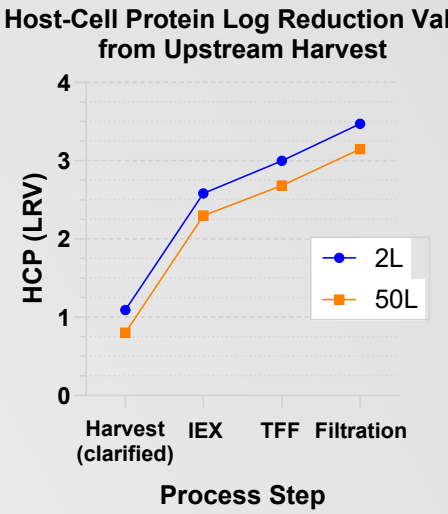
Optimized IEX Processing Delivers Robust Recovery, Purity, and Fast Processing Across Scales











Data shown represent representative internal process development runs; performance may vary by vector construct and upstream conditions.

Total DS Processing Time from Clarification to SF: 6 – 8 hrs

Optimized IEX processing maintains consistent LVV recovery, impurity clearance, and processing times from benchtop to 50 L, demonstrating scalability and manufacturing robustness.

Go Deeper: *In Vivo* & *Ex Vivo* LVV Manufacturing

Explore the full technical strategy behind our optimized LVV platform

Prefer to read?

Download our white paper:

Revolutionizing Lentiviral Vector Manufacturing for In Vivo & Ex Vivo CAR-T

Scan to access

Prefer to listen?

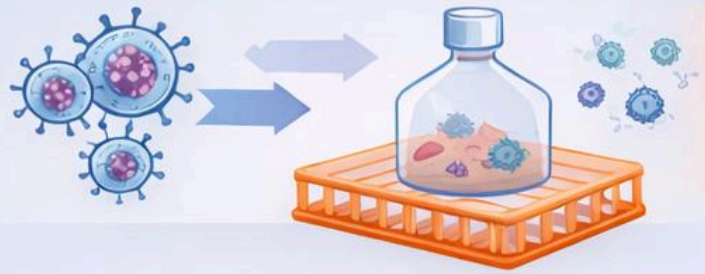
Watch our on-demand webinar:

Enhancing LVV Manufacturing: Eliminating the Barriers to In Vivo and Ex Vivo CAR-T Delivery

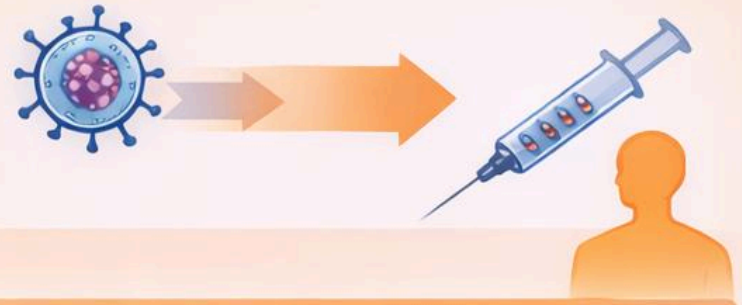
Scan to watch

From Platform Excellence to *In Vivo* Drug-Product Readiness

Vector Intermediate



Final Drug Product



Ex vivo LVV – LentiSure Platform

- Controlled biological foundation
- Modular, single-use, designed for robustness
- High-recovery DSP with membrane-based AEX
- Maintained infectivity from harvest to drug product
- Demonstrated scalability from bench to 200 L

In vivo LVV – Platform evolution

- From vector intermediate to systemic drug product
- Gene-therapy–level regulatory expectations
- Breaking the IEX bottleneck
- High-recovery membrane-based purification (~70%)
- Scalable platform supporting in vivo CAR-T development

SK pharmteco

Thank You

Meet us at booth #203 to learn how we can support your program requirements.

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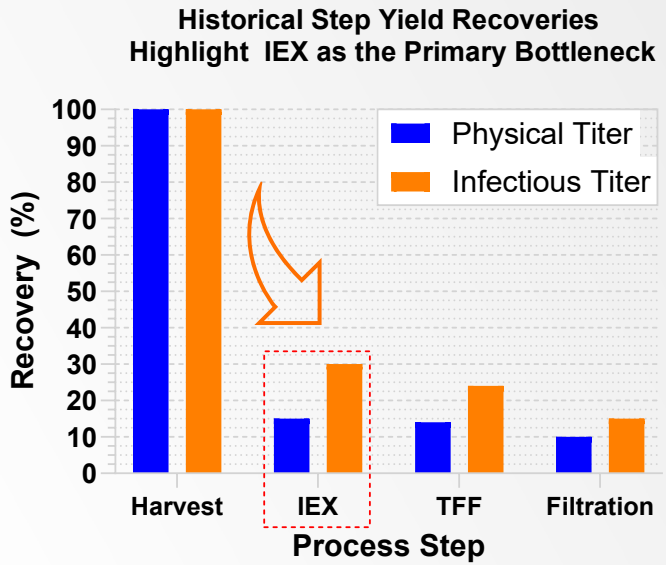
Lentiviral Vector (LVV) Downstream Is Yield-Limited by IEX Recovery

IEX remains the dominant loss point despite downstream optimization



Even with downstream optimization, IEX recovery remains the dominant constraint on LVV yield (typically 15-30% LVV recovery).