HEALTHCARE

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The Auto Cell Therapy Manufacturing Opportunity: Lowering CoGS & Driving Scale

March 5, 2024

- **Bottom Line: We see significant potential for autologous cell therapy market with 19 FDA approved cell and gene therapies today and many more in the pipelines.** To understand the opportunity for Life Science Tools (LST) and Biopharma companies involved in this manufacturing challenge, we examined profit scenarios and workflow improvements on reducing significantly high cost of goods sold (CoGS) of cell therapies ranging between $120k - $300k+ per dose today to below $100k in the next few years and the potential to reach below $25k longer term with transformational innovations (in Tools) according to select MEDACorp KOLs. We outline our key takeaways below and in the following detailed report:
- **Biopharma companies are poised to gain the most gross margin upside as CoGS for auto engineered cell therapies are reduced.** In pharma, we expect gross margins on CAR-T products to evolve towards the 80%+ as list prices increase and CoGS decrease via process improvements and product volume scale reduces the impact of labor overhead.
- **LST and bioprocess tools companies to benefit from increases in cell therapy volumes, even with net of dilution as a % of total profit share.** We estimate the CAR-T US market in NHL and MM expanding from $2.4Bn in 2023 to $6.8Bn in 2029. While Tools will likely see a decrease in % profit share to pharma as cost is taken out of manufacturing, commercial expansion of cell therapies will drive significant incremental revenue to LST in absolute dollars. Among our LST coverage universe we expect A (OP), DHR (Cytiva, OP), RGEN (OP), TECH (OP), MASS (OP), and CYRX (MP) to see the most upside as CAR-T volumes scale.
- **LST companies can't afford to miss out:** Opportunities for LST and bioprocess companies reside in reducing costs for viral vectors and providing analytical tools innovation for QA/QC, followed by solving bottlenecks in key cell expansion and transduction steps. QA/QC and lot release for cell therapy may turn out to be the most promising innovation area for LST companies with early emergence of innovators and little standardization.
- **In Biopharma, we anticipate manufacturing and commercial scale benefits will drive market equilibrium toward a few large companies, much like vaccines.** Those companies well down the path to optimizing manufacturing, including Kite (GILD, MP), JNJ (OP, Risinger), BMY (MP, Risinger), and NVS (Not Rated), have the most to gain, profit-wise, from economies of scale, and should be willing to pay more for acquisition of innovative programs than nascent competitors.

Reason for report:
INDUSTRY UPDATE

S&P 500 Health Care Index: **1,700.53**

Companies Highlighted

A, ACLX, BNTX, CYRX, DHR, GILD, MASS, RGEN, TECH, TMO, TSBX, TSVT, WAT

Puneet Souda
(212) 277-6091
puneet.souda@leerink.com

Daina M. Graybosch, Ph.D.
(212) 277-6128
daina.graybosch@leerink.com

Rabib S. Chaudhury, Ph.D.
(212) 277-6268
rabib.chaudhury@leerink.com

Philip S. Song
(212) 404-4587
philip.song@leerink.com

Michael Sonntag
(212) 277-6048
michael.sonntag@leerink.com

Isabella Prugue
(212) 277-6126
isabella.prugue@leerink.com

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The Auto Cell Therapy Manufacturing Opportunity: CoGS and Scale

We believe the autologous, engineered cell therapy market for both Biopharma and Life Science Tools (LST) bioprocessing will be a key growth driver over the next five to ten years as fundamental innovation in Tools beyond process and workflow improvements helps reduce significantly high cost of goods sold (CoGS) of cell therapies ranging between $120k - $300k+ per dose today to below $100k in the next few years with some MEDACorp KOLs seeing the potential to reach below $25k with transformational innovations. While the largest beneficiaries from the lowering of costs and scaling up will be the Biopharma companies and their margins, we believe Tools companies will drive significant scale and volume for their products in the longer term as the $38.1Bn cell and gene therapy market matures in oncology and emerges in autoimmune diseases.

We believe understanding the CoGS structure of manufacturing autologous (auto), engineered cell therapies is a prerequisite (for both investors and companies) to gaining an understanding of where the pain points and bottlenecks exist in manufacturing today—representing opportunities of the future. Within LST, we believe that following companies are likely to have varying degree of exposure to innovation and expansion in cell therapy bioprocess manufacturing and analytical tools and services: DHR (OP), RGEN (OP), TECH (OP), TMO (OP), Miltenyi Biotech (Private), SRT3-DE (Not Rated), MKKGY (Not Rated), TRUMY (Not Rated), RVTY (Not Rated) and AVTR (Not Rated) among bioprocess manufacturing tools; Agilent (A, OP), DHR (OP), TECH (OP), TMO (OP), WAT (MP), MASS (OP), and MTD (Not Rated) among bioanalytical tools and LGAZY (Not Rated), CYRX (MP), OXB-LON (Not Rated), and BLFS (Not Rated) within services. Within Biopharma, we see the benefit accruing to autologous CAR-T, TCR-T, TIL and gene therapy manufacturers, including numerous others in our coverage as they scale up commercial manufacturing: TSVT (OP) / BMY (MP, Risinger), LEGN (Not Rated) / JNJ (OP, Risinger), ACLX (OP) / GILD (MP), AUTL (Not Rated) / BNTX (OP), TSBX (MP), ADAP (MP, Chang), IMTX (OP, Chang), BLUE (MP, Foroohar), CRSP (OP, Foroohar), RCKT (OP, Foroohar), and KYTX (OP, Smith). We also expect manufacturing innovation to benefit allogenic cell therapy manufacturers, but with lower absolute impact given the lower starting CoGS per dose.

Key Takeaways:

1. **Biopharma companies are poised to gain the most gross margin upside as CoGS for auto, engineered cell therapies (which we will refer to as "CAR-T" for simplicity going forward) are reduced and as therapy volumes scale up.** Among biopharma, we expect gross margins on CAR-T products to evolve towards the 80+% mark as list prices increase and CoGS decrease via operational efficiency, process improvements, and scale.

2. **Among our Tools coverage universe we expect Agilent, DHR, RGEN, TECH, and MASS to see the most upside as CAR-T volumes scale, while select cell therapy leaders including Miltentyi (Private) maintain their market position.** Among innovators and early-stage growth companies, we see MASS seeing upside from cell therapy scale up and emerging private growth companies including analytical tech at Accellix and Axion Biosystems and production systems at Cellares.
3. **Increases in cell therapy volume should benefit LST companies longer term, even net of dilution as a % of total profit share.** For example, from a CAR-T $2.4Bn US market in NHL and MM in 2023, we estimate the market expanding to $6.8Bn in 2029. While Tools will likely see a decrease in % profit share to pharma as cost is taken out of manufacturing, commercial expansion of cell therapies will drive significant incremental revenue to LST in absolute dollars (Figure 2). More specifically, we estimate that higher drug volumes enabled by adoption of automation and operational efficiencies available today can yield 70%+ growth in LST US TAM over the next five years for commercial non-hodgkins Lymphoma (NHL) and multiple myeloma (MM) markets.
4. **Opportunities for LST companies** reside in reducing costs for viral vectors and providing analytical tools innovation for QA/QC, followed by solving bottlenecks in key cell expansion and transduction steps. **QA/QC and lot release for cell therapy may turn out to be the most promising innovation area for LST companies** with early emergence of innovators so far. With little standardization today, LST companies not involved today are likely to miss out.
5. **As labor is the largest cost driver for CAR-T today, scale, achieved through expansion of current products to earlier-line settings and development or acquisition of new products, is the most important driver of Biopharma profitability, in our view.** As companies finalize optimization of initial manufacturing capacity, we expect most will follow a path like Kite to expand manufacturing footprint in a way that enables rapid and flexible scale-up in capacity, followed by strategic product acquisition and development to build scale, e.g., Kite licensing of anito-cel from Arcellx. Achieving the same end of scale, BioNTech took a different path through their licensing / manufacturing partnership with Autolus (LINK for discussion; AUTL, Not Rated). We expect this trend will continue with Biopharma's next looking to innovative cell therapy programs in solid tumor and autoimmune indications to build scale. Pressuring profitability, however, are scale bottlenecks, with US system capacity constraints being the most pressing challenge in our view (LINK, LINK for more discussion). See LINK for our recent discussion with Kite management on their capacity buildout.
6. **In Biopharma, we anticipate requirements for manufacturing and commercial infrastructure will drive toward a market equilibrium of a small number of large companies, much like vaccines.** Those companies well down the path to

optimizing commercial manufacturing, including Kite (GILD), JNJ, BMY, and NVS (Not Rated), have the most to gain, profit-wise, from increased scale, and should be willing to pay more for acquisition of innovative programs than nascent competitors. Though some companies may attempt to enter by acquiring smaller companies, like AZN (OP, Berens) did recently with their acquisition of Gracell and BioNTech with their Autolus partnership, we believe their path to profitability will be long. An important catalyst here will be Autolus profit in 2025, as the company will launch with an automated process (akin to our “Milestone 2” scenario) that Autolus management believes will be profitable at the smaller scales of their lead indication for obecabtagene autoleucel (obe-cel).

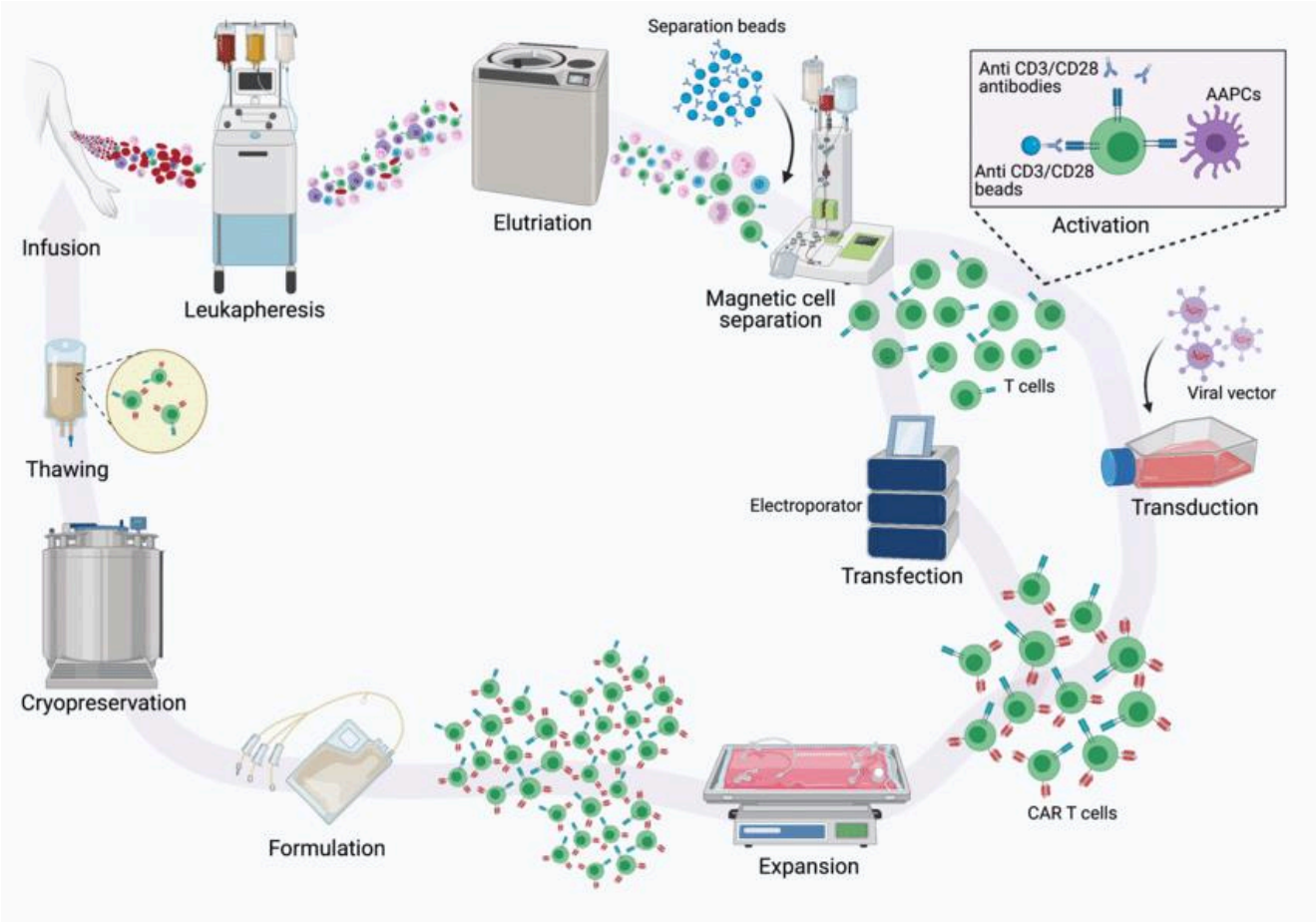
OUR AUTO CAR-T MODEL

We built a bottom-up CoGS model for auto, engineered CAR-T manufacturing and found that overhead, cell expansion fixed costs, and transduction (i.e., viral vector) are the primary drivers of current outsized CoGS in cell therapy manufacturing, with the largest opportunities to optimize costs today in cell expansion and transduction. Our model takes a comprehensive line-by-line bottoms-up approach to individual consumables, fixed, and labor cost components across manual and automated unit operations and was constructed through iteration with KOL/industry feedback (leveraging our MEDACorp network), and triangulation with reported and top-down estimates from various commercial therapies.

Biopharma stands to gain a larger profit share as commercial markets expand, with process and scale improvements in their manufacturing. We estimate that present margins across the commercial non-hodgkins Lymphoma (NHL) and multiple myeloma (MM) spaces to be ~60% and foresee that figure expanding to over 80% stemming from operational efficiency improvements, price increases, and scale-up of volume. In process development, automation will play a key role in reducing costs and improving out-of-spec rates. Viral vector was a common discussion point with our MEDACorp KOLs and we believe that switching to suspension culture-derived vector can reduce vector sourcing cost by up to 90%, albeit, for current manufacturers, at the cost of clinical trials and with regulatory risk for equivalence testing to switch from adherent vector processes. As such, early-development companies are at an advantage in that they can begin with the most up-to-date processes like suspension vector from the process design stage.

While Tools will likely see a decrease in % profit share to pharma as cost is taken out of manufacturing, commercial expansion of cell therapies will drive significant incremental revenue to LST in absolute dollars. More specifically, we estimate that higher drug volumes enabled by adoption of automation and operational efficiencies available today can yield **70%+ growth in LST TAM over the next 5 years for commercial non-hodgkins Lymphoma (NHL) and multiple myeloma (MM).** As discussed above, LST vendors of closed and automated systems such as Cytiva (DHR), Miltenyi Biotech (Private), Lonza (LZAGY, Not Rated) Cocoon, Cellares (Private), and future competitors will be key to near-term process improvement in CAR-T and viral vector manufacturing. However, **significant whitespace remains in LST to address bottlenecks that have not yet been fully solved today, with QA/QC one particular example**. As discussed further in this note, there is still little standardization across different manufacturing processes and therapies, and future innovation in LST has the potential to drive faster process times, better scalability, and lower contamination risk even beyond the scenarios described in this report.

Figure 1. Autologous CAR-T Therapy Manufacturing Workflow



Note: workflow similar for auto TCR-T cell therapy
Source: Blood Cancer Discovery – AACR Journals, Leerink Partners

Methodology and CoGS Scenarios

As a bottom-up model, we first developed a deep understanding of the auto CAR-T cell manufacturing process (see Appendix) qualitatively via literature review and discussions with two MEDACorp KOLs (one with a cell manufacturing process design background in big pharma and one with a background in the manufacturing tools space). We then built up our labor / fixed / variable cost bases from primary and secondary sources. For labor overhead, we determined personnel overhead via a LinkedIn assessment of manufacturing personnel Kite Pharma (GILD) and ascertaining what proportion of staff (~1,000 total on the website) were directly on the production line what proportion are off the line, i.e. overhead to the process.

We perform our analysis based on our view of three paradigms during an auto. CAR-T manufacturing process evolution: (1) early scale up, (2) optimized process, and (3) scaled-up

process (Table1). Starting from Milestone 1, we to present an optimized process wherein operators may realize cost savings from *operational* efficiencies (Milestone 2), and then a future optimized case wherein operators realize both *operational* and *scale-based* efficiencies (Milestone 3). Beyond Milestone 3, there remains whitespace to further process optimization, i.e. upstream automation, improving QC processes, and higher transduction efficiency requiring a lower multiplicity of infection for the vector product; these steps represent upside to our current assumptions.

Table 1. Manufacturing Scenario Overview

Design parameter	Milestone 1: Early scale-up	Milestone 2: "Optimized" process	Milestone 3: Scaled up "optimized" process
Process time	30 days	16 days	16 days
Out of spec (batch failure) rate	13%	5%	5%
Process automation	Fully manual	Partially automated (downstream)	Partially automated (downstream)
Vector manufacturing method	Adherent	Suspension	Suspension
Vector procurement	In-house	In-house	In-house
Vector quality	Standard	Standard	Standard
Equipment utilization	63% (transduction 100%)	63% (transduction 100%)	63% (transduction 100%)
Manufacturing facility scale	900 doses/year	900 doses/year	2,300 doses/year
Capital equipment avg. useful life	10 years	10 years	10 years
Facility CapEx	$40M / 20 years	$40M / 20 years	$200M / 20 years
CoGS per dose	$269k	$163k	$89k

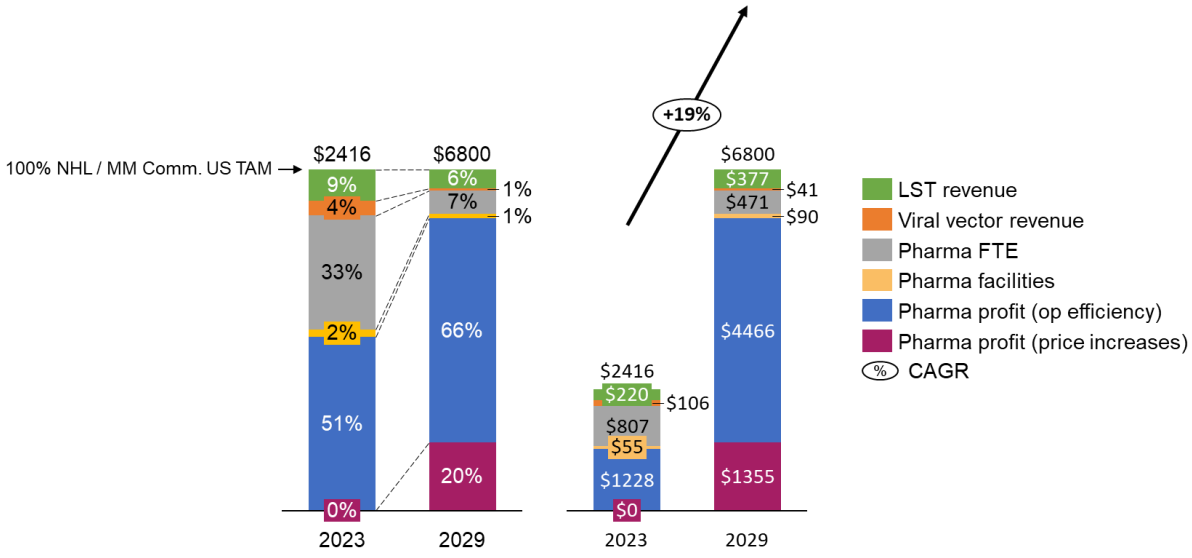
Note: we believe Kite is close to Milestone 3, but we estimate CoGS per dose ~$115K, given recent capacity build for even greater scale (~$500M CapEx and capital equipment avg. useful life of five years).
Source: Leerink Partners estimates

Profit Pool Analysis Indicates Increased Upside to Both Pharma and LST Over Time, but we Expect Biopharma to Retain Majority of Upside

Considering the US commercial non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) markets both at present (2023) and in 2029, we believe that manufacturing process optimization and scale up will increase incoming cash to both Biopharma and LST, though the share of cash in-flow will shift towards the former (Figure 2). We believe that TAM for commercial NHL / MM autologous CAR-T therapy will

expand to approximately $6.8Bn in 2029, with pharma gross profit margins increasing to 86% from 51% today. The biggest driver for this increased margin is that the introduction of process automation in addition to higher scale across the sector, which would increase full-time equivalent (FTE) labor efficiency both on production lines and as overhead. While increased operational efficiency will enhance pharma bottom lines, the LST sector is poised to assume a lower share of the profit pool, but an increased overall revenue as the market expands.

Figure 2. NHL / MM Commercial Profit Pool Analysis in 2023 vs. 2029 Projection



TAM: Total Addressable US Market for CAR-T in NHL and MM (additional upside from indications still in development)
LST: Life Sciences & Tools
FTE: Full-time equivalent labor

We chose commercial NHL and MM markets as we believe they are relatively predictable from a total addressable market (TAM) projection point-of-view and we have the most robust dataset for these indications and in this commercial setting. The 2023 condition for the market assumes a mix of manufacturing processes and scales with some operators being more advanced in process automation and viral vector manufacturing technology while we assume that by 2029 the field will have shifted in process / vector technology as well as scale (see Table 1).
Note: Pharma facilities = capital expense
Source: Leerink Partners estimates

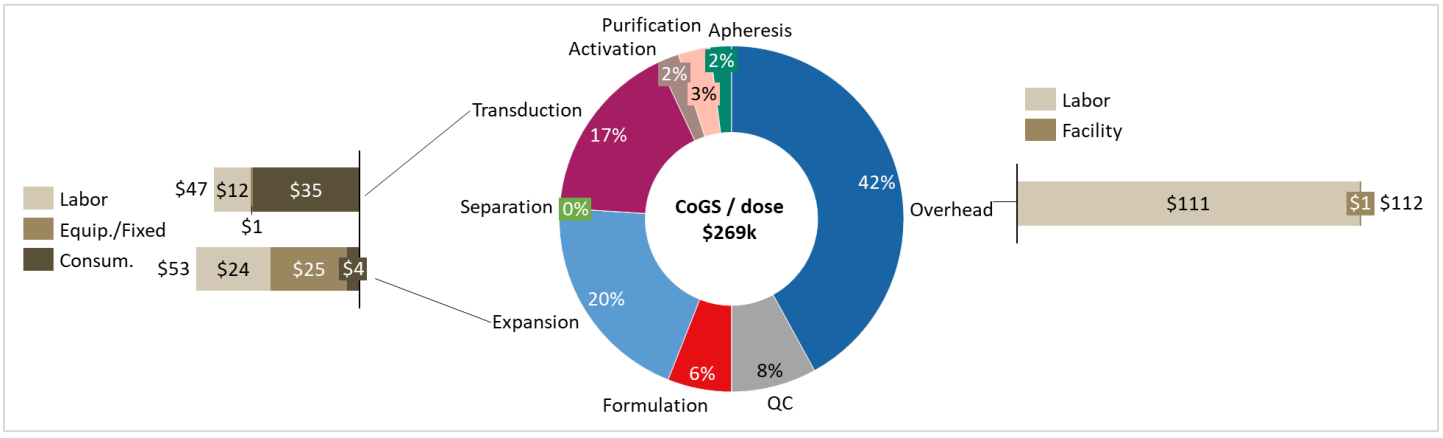
The scope of our analysis here focuses on the commercial market; but the pre-commercial arena still provides a significant opportunity for LST. There are only a few commercial cell & gene therapies today (19 FDA-approved), the sector has been one of the fastest growing biologic drug categories in recent years, and we expect growth to continue over the next decade. According to data released from Charles River Laboratories (CRL, Not Rated), cell/gene therapy made up ~35% of biologics R&D projects (2022) in the overall

industry's drug development pipeline (pre-clinical through Phase III). This figure compares to 22% in 2016, for a ~20% 5-year CAGR. According to Repligen, there are > 500 cell / gene therapy candidates across >2,000 active clinical trials; of these candidates, Danaher estimates that >200 are in late-stage clinical trials today, with >40% of trials in oncology. RGEN estimates a $5B+ TAM opportunity for cell / gene therapy growing 25%+ annually (as of 2023).

Early Manufacturing Profitability Gated Both by Process and Scale

We believe that most CAR-T cell operators who manufacture products in-house follow our base process (Milestone 1, Table 1) as of FY2022. These companies potentially include 2seventy / BMY, Legend (LEGN, Not Rated) / JNJ, and Novartis, though the extent of this alignment certainly varies across these manufacturers. We know that Kite (Gilead) recently introduced process automation as well as an in-house suspension vector process as of 4Q22, and with their scale, puts them closer to Milestone 3 (PR#1, PR #2), with more capex (~$500M we estimate) invested for future program expansion. Figure 3 illustrates the base process CoGS breakdown by process step, with a total cost of $269,000 per dose. New CAR-T entrants may launch with processes closer to Milestone 2, as they assume more modern processes in clinical development; an example of this is Autolus, as management tells us they will launch with automated manufacturing, efficient training facility, and slim labor overhead.

Figure 3. Milestone 1 Breakdown of Cost by Process Step (absolute figures in $'000s)



Note: Estimates include out-of-spec costs.
Source: Leerink Partners estimates

The top three CoGS drivers within this Milestone 1 scenario:

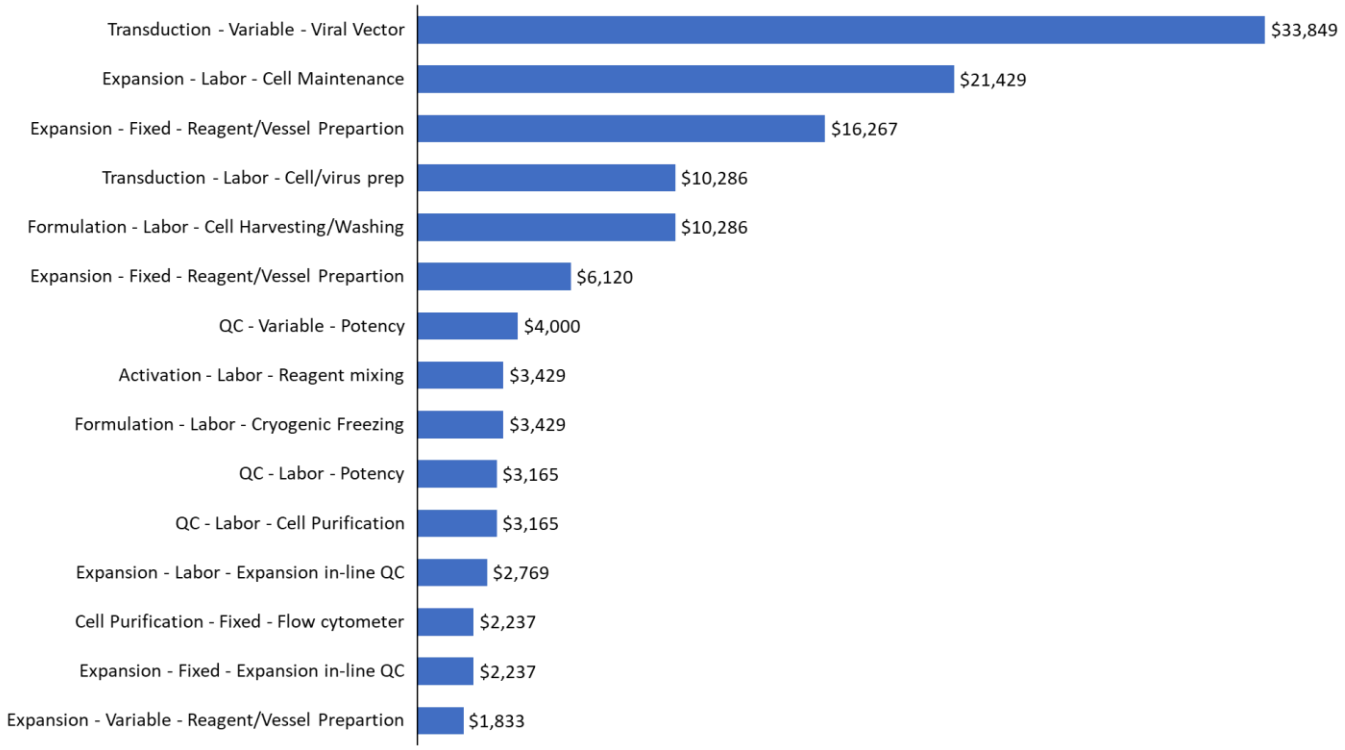
1.) **Transduction**

2.) **Expansion**

3.) Overhead

Viral vector cost is the single largest variable cost contributor in the Milestone 1 process (Figure 4), accounting for over 10% of the overall cost with just one consumable item. The underlying causes for this high cost are the diseconomies of scale with respect to manufacturing viral vectors using adherent culture methods. The labor and material-intensive nature of this process is reflected by high costs in the cell expansion step which accounts for ~20% of the overall process, as expansion requires multiple manual inputs as well as significant resource usage (e.g., media exchanges) over the course of this part of the process.

Figure 4. Viral Vector is the Largest Individual Cost Component in the Base Case Scenario



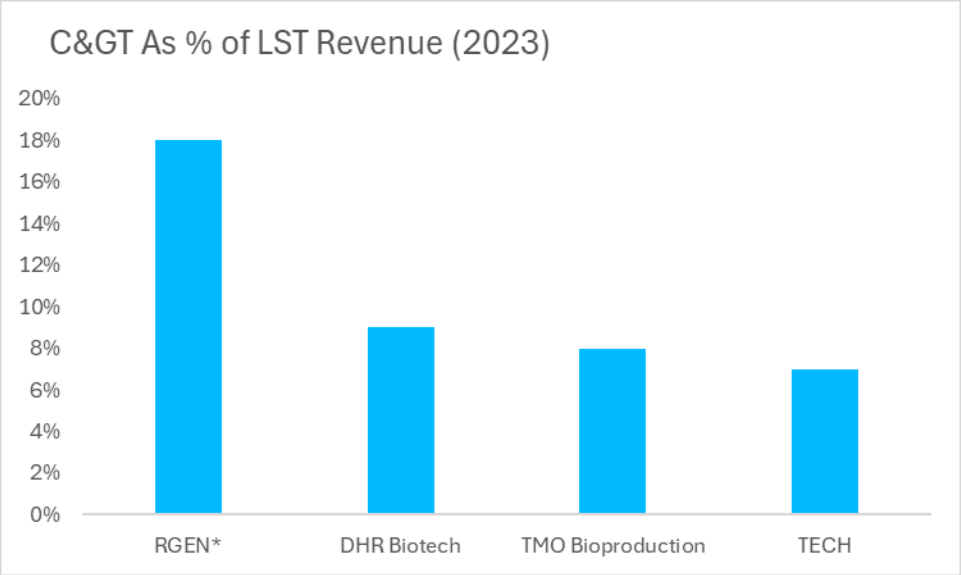
Source: Leerink Partners estimates

Cell expansion makes up an outsized proportion of upside / downside process time variability due to its relative higher share of labor hours and equipment costs, particularly in a manual manufacturing process. Expansion occurs over the course of 3-6 days, with regular media exchanges/refreshes (media need to be periodically removed and replenished during incubation), usually over the course of a larger seed train (transferring the cell culture to progressively larger vessels), typically beginning with a smaller T-flask (itself in

incubators) to a larger production reactor. In a more manual process, liquid handling and media exchange are handled by techs in a biosafety cabinet—a highly manual and time-intensive step. Media exchange can be partially automated from bioreactor platforms from Cytiva and Sartorius, which support perfusion, and automated control and monitoring abilities (i.e., bags fitted with in-line pH and DO sensors, control tower for the rocker). Media exchange can also be partially automated by liquid handling equipment, such as from Wilson Wolf.

We believe that CoGS estimates in the literature have underestimated the impact of overhead at present-day scales (see LINK, with $80k / dose estimate at 5,000 dose / year scale. In our model, labor-related overhead contributes to ~42% of the overall cost. As a process scales up, overhead will become an increasingly small piece of the overall cost (see next section), though processes with even lower scales than the base process would be subject to a significant cost malus.

Figure 5. Cell & Gene Therapy as % of Life Science Tools Revenue



Note: RGEN includes viral vectors and mRNA vaccines. TMO represents an estimate. DHR and TMO as % of total company sales are <3% and <1%, respectively.

Source: Leerink Partners, Company filings

Milestone 1 Process Sensitivity Analysis

Given that we are estimating dollar figures for cost components, we assessed the impact of imprecision/uncertainty in our assumptions and variability by company in our model. The sensitivity analysis below examines how deviations in process design inputs impact our estimated cost per dose across each step in the cell therapy process (Table 2).

Table 2. Upside/Downside Sensitivity Process Parameters vs. Base Process

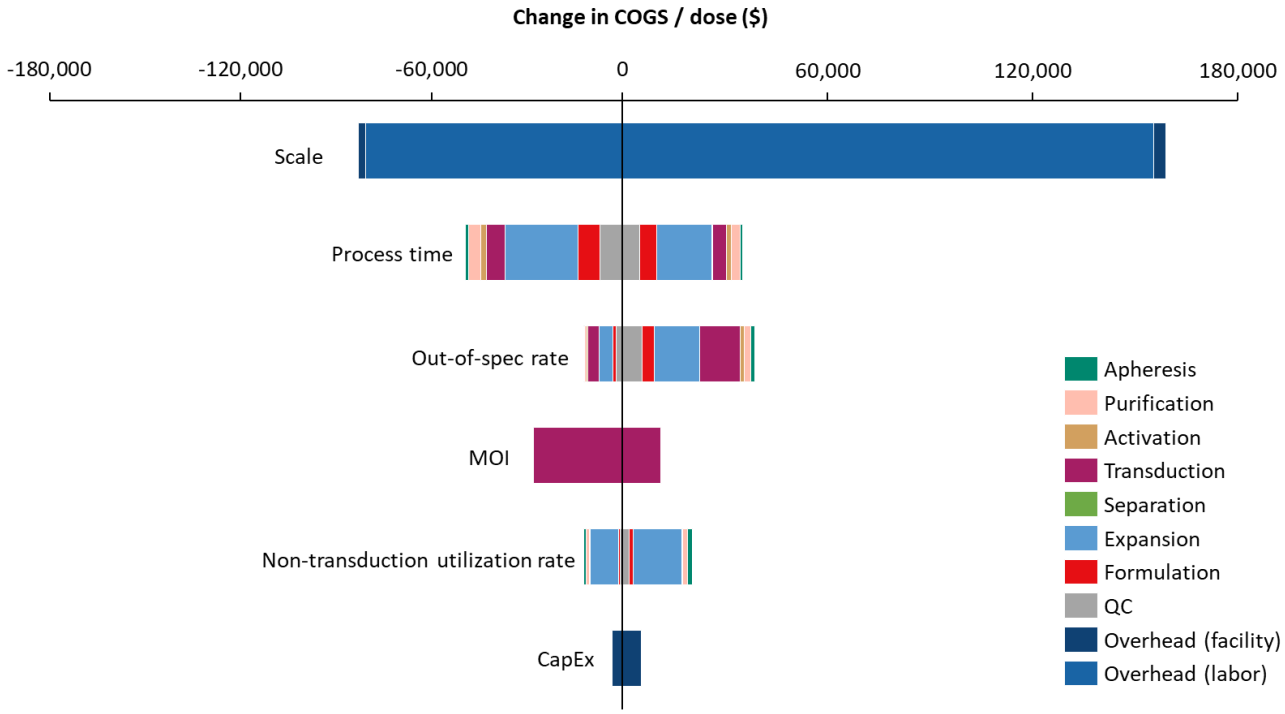
Variable	Lower cost	Higher cost	Base
Turnaround time (days)	16	40	30
Out of spec rate	5.0%	30.0%	12.5%
Manufacturing scale (doses/year)	2,500	450	900
Multiplicity of infection	2.5	8	6
Non-transduction utilization	100%	40%	63%
Facility capex	5	200	40

Scenarios deviate from base case assumptions to levels that we believe are reflective of real-world upside/downside ranges for each input.

Source: Leerink Partners assumptions

We estimate variability of up to + /- ~$60K CoGS per dose from our base case estimate of $270K when accounting for uncertainty in input assumptions and company / batch differences (Figure 5). Scale is the biggest cost modulator, but only affects overhead cost, with no effect on our bottom-up process estimates. Out-of-spec rate is similarly disentangled from our process estimates as it is applied after tallying individual process estimates. Process time is our most sensitive process-internal factor with variability of -$12k on the upside and +$38k on the downside, though a 30% out-of-spec rate represents a “worst case” scenario. As discussed further in our appendix, our process time assumption is a key driver of labor and fixed cost estimates across each of our process steps. Cell expansion makes up an outsized proportion of upside / downside process time variability due to its relative higher share of labor hours and equipment costs, particularly in a manual manufacturing process. Non-transduction utilization of equipment is sensitive to the downside by an order of around ~+$20k due to fixed cost deleverage, all other factors constant.

Figure 6. Milestone 1 CoGS Sensitivity Analysis Around Base Case of $270K Per Dose



Source: Leerink Partners estimates

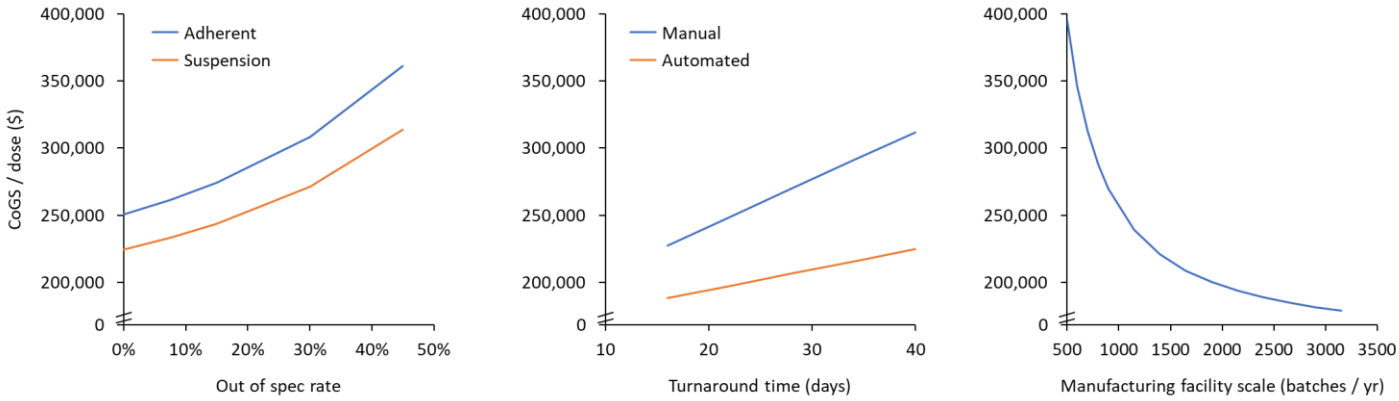
Double-click on Significance of Scale, Out-of-Spec Rate and Turn Around Time to CoGS

We found that out-of-spec rate and scale relate non-linearly to CoGS, while process time is linear, identifying potential design "cliffs." The previous sensitivity analysis provided a snapshot of how point deviations may impact the final cost output. Figure 6 illustrates trends on how process deviations may impact cost. Out-of-spec rate relates non-linearly to CoGS, indicating that a proportional increase in this variable will affect CoGs more than a proportional decrease. Given the downside risk skew, **a high out-of-spec is a major red flag for profitability and presents the largest opportunity to improve profitability**. While moving viral vector source from adherent to suspension may benefit overall cost, switching to this regime would not necessarily buffer the process from cost risks related to out-of-spec deviations.

In contrast to out-of-spec rate, scale is positively correlated with cost savings and decreases in facility output would significantly impact the per dose overhead cost, though volatility in sales volume could contribute negatively to CoGS. As a process scales up, operational efficiencies from more favorable distribution of overhead costs significantly improves per dose CoGS. That being said, if a process is built up for a certain

scale, but for whatever reason sales volume fails to match the specified scale, that overhead would have a similarly negative impact on CoGS. Process (turnaround) time scales linearly with CoGS, indicating equal upside and downside deviation risks. Switching a process towards automation decreases the rate at which deviations impact cost.

Figure 7. CoGS Sensitivity to Perturbations in Process Factors: Out-of-Spec Rate with Adherent or Suspension Vector Processes (left), Turnaround Time with Manual or Automated Processes (middle), Process Scale (right)



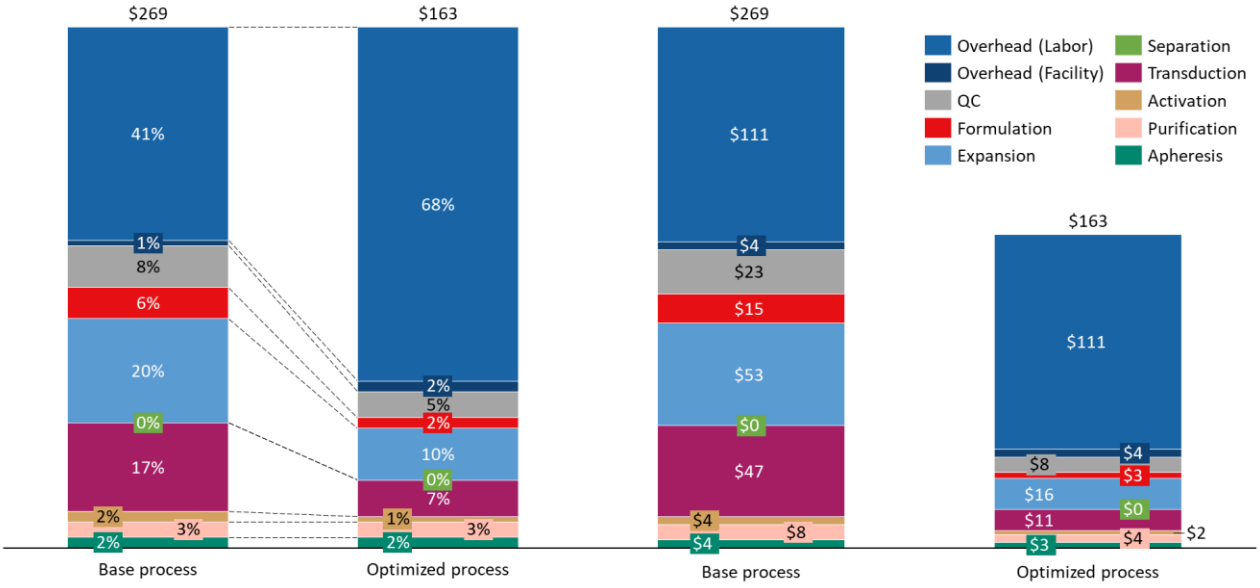
Source: Leerink Partners estimates

Process Improvements in Cell Expansion and Transduction can Drive Lower CAR-T CoGS, Independent of Scale

We model our Milestone 2 analysis based on Kite Pharma disclosures on process automation and vector sourcing to arrive at a CoGS/dose estimate of ~$163k, a decrease of 40% from the Milestone 1 process. Starting from the Milestone 1 process, the largest opportunities to optimize costs are in cell expansion and transduction, and our assertion is directionally consistent with industry and MEDACorp KOL feedback.

In our analysis, we contemplate an "optimized" case scenario to reflect process changes that could have a material impact on CoGS, with driving assumptions around automation, process length, vector manufacturing method, and out of spec rate (refer to Table 1 for a summary of input assumptions). Figure 7 illustrates the differences between base and optimized processes and Table 3 provides a detailed breakdown of cost differences between the two cases. Since scale remains constant in these cases, overhead also remains constant in absolute dollars, and thus comprises a larger proportion of the overall optimized process. On-line labor is rolled into each process step and so labor savings for automation are realized within each step, while overhead labor is uniquely tied to process scale. Expansion and transduction steps represent the most significant cost reduction steps due to the suspension vector change and introduction of automation.

Figure 8. Cost Contribution to Overall CAR-T CoGS / Dose in Milestone 1 (base) and Milestone 2 (optimized) Processes (assuming constant scale)



Source: Leerink Partners estimates

Table 3. Milestone 1 (base) vs. Milestone 2 (optimized) Process Model Output

Cost Breakdown by Cost Type	Base Case		Improved Case		Case Delta	
	Cost/Dose ($)	% Total	Cost/Dose ($)	% Total	Cost/Dose ($)	% Delta
Upstream Cost/Dose						
Labor Cost/Dose	$7,731	3%	$4,123	3%	($3,608)	-47%
Variable Cost/Dose	$2,161	1%	$2,133	1%	($28)	-1%
Fixed Cost/Dose	$4,767	2%	$2,544	2%	($2,223)	-47%
Total Upstream Cost/Dose	$14,659	5%	$8,800	5%	($5,859)	-40%
Transduction Cost/Dose						
Labor Cost/Dose	$10,385	4%	$5,538	3%	($4,846)	-47%
Variable Cost/Dose	$30,278	11%	$4,241	3%	($26,037)	-86%
Fixed Cost/Dose	$475	0%	$277	0%	($198)	-42%
Total Transduction Cost/Dose	$41,137	15%	$10,056	6%	($31,081)	-76%
Downstream Cost/Dose						
Total Downstream Mfg. Labor Cost/Dose	$45,058	17%	$14,556	9%	($30,501)	-68%
Total Downstream Mfg. Variable Cost/Dose	$10,425	4%	$5,859	4%	($4,566)	-44%
Total Downstream Mfg. Fixed Cost/Dose	$24,086	9%	$6,171	4%	($17,915)	-74%
Total Downstream Cost/Dose	$79,569	30%	$26,586	16%	($52,983)	-67%
Total Manufacturing Cost / Dose	$135,365	50%	$45,442	28%	($89,923)	-66%
Out-of-Spec Rate (%)	*12.5%*		*5.0%*			
Cost/Dose incl. Out-of-Spec	$154,703	57%	$47,834	29%	($106,869)	-69%
Facilities Costs	$3,638	1%	$3,638	2%		
Overhead & Misc. Labor Cost / Dose	$111,330	41%	$111,330	68%		
Total Cost / Dose	**$269,671**	**100%**	**$162,802**	**100%**	**($106,869)**	**-40%**
Cost Breakdown by Process Step						
Apheresis	$4,139	2%	$2,785	2%	($1,354)	-33%
Cell Purification	$8,256	3%	$4,263	3%	($3,993)	-48%
Activation	$4,358	2%	$2,214	1%	($2,144)	-49%
Transduction	$47,014	17%	$10,585	7%	($36,429)	-77%
Cell Separation	$224	0%	$57	0%	($167)	-75%
Expansion	$52,953	20%	$16,462	10%	($36,491)	-69%
DP Formulation	$14,929	6%	$3,129	2%	($11,800)	-79%
Batch Release/QC	$22,830	8%	$8,338	5%	($14,492)	-63%
Facilities	$3,638	1%	$3,638	2%		
Overhead	$111,330	41%	$111,330	68%		
Total	**$269,671**	**100%**	**$162,802**	**100%**	**($106,869)**	**-40%**

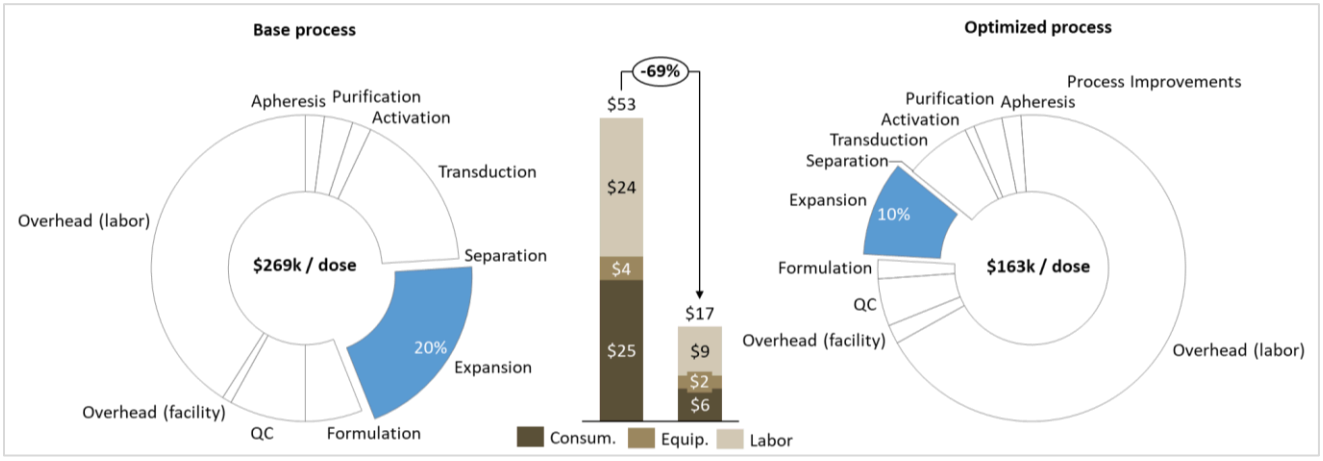
Note: Upstream refers to Apheresis, Activation, and Purification steps. Downstream refers to Separation, Expansion, Formulation, and Batch Release/QC steps.
Source: Leerink Partners estimates

Reducing Expansion CoGS via Automation Represents the Largest Cost-out Opportunity in Our Analysis of Process Improvement

Cell expansion drives the largest $ delta between our two scenarios, representing a ~$36.5k or 69% decrease in CoGS (Figure 8). This savings estimate in our model are driven primarily by increased automation applied to the cell maintenance step (i.e., the use of

modular perfusion-based systems), which significantly reduces manual labor hours required for monitoring and feeding of cell media. Note that **cell maintenance represents the most labor-intensive and time-consuming step in a manual process** (we are estimating~19 labor hours for this step) and moving to a closed/automated system here drives a ~$19K difference per dose before accounting for reduced out-of-spec rates. For reference, cell maintenance labor represents 40% of expansion CoGS in the Milestone 1 process but is largely eliminated in the optimized case scenario.

Figure 9. Comparison of Cell Expansion CoGS / Dose in Milestone 1 (base) vs. Milestone 2 (optimized)



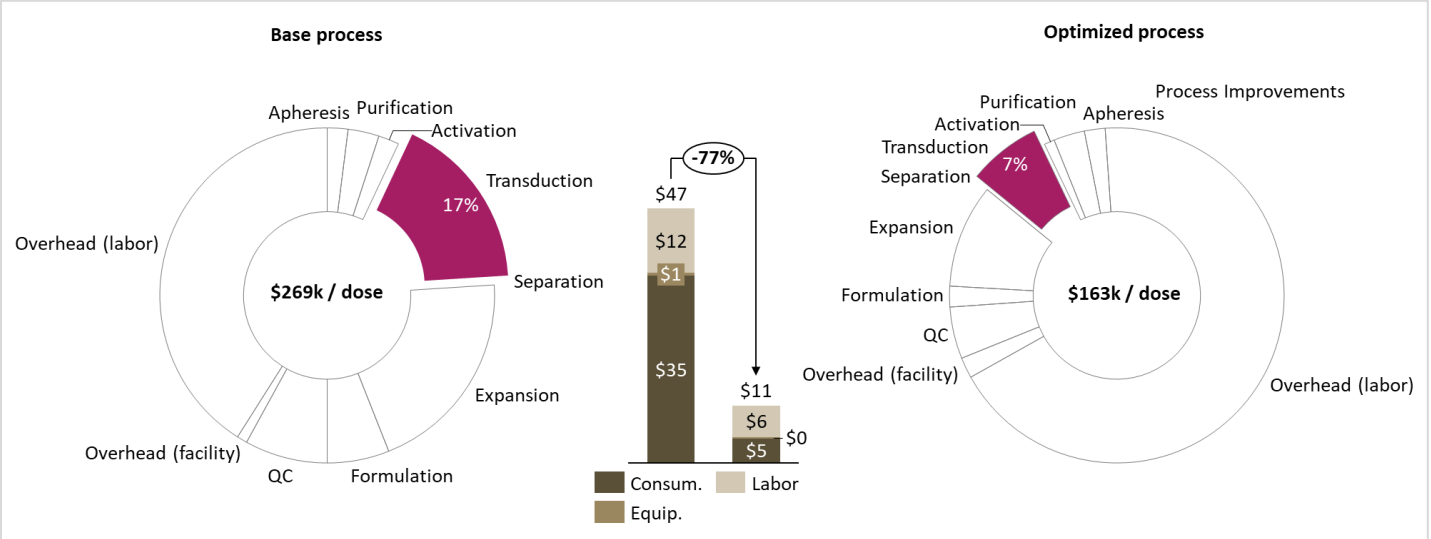
Source: Leerink Partners estimates

Despite the benefits of automation in the optimized process, cell expansion still drives the greatest share of costs excluding overhead in both scenarios, with 20% of total costs or $53K/dose in our base case, but a meaningfully reduced cost of $16K/dose in our optimized case scenario. Fixed/equipment costs (i.e., bioreactors) drive outsized CoGS in addition to labor and are relatively static across the two scenarios given less benefit to be gained from process optimization/automation (albeit lower in the optimized process purely as a function of leverage on shorter process length). For reference, the equipment cost of the bioreactor makes up ~30% of total expansion costs in the base case and ~50% of expansion costs in the optimized case-- incidentally also representing the largest individual cost component in the optimized case overall at $7.8K/dose. Recall, in our earlier Foundations conf 2023 C&GT Panel note (see here), KOLs identified moving to closed-loop systems (such as in Lonza Cocoon) as the lowest hanging fruit in terms of addressing cost early, with one KOL indicating that doing so can yield up to a ~10x improvement in CoGS.

Moving to a Suspension-based Vector is an Important Path to Reduce Manufacturing CoGS today, but Regulatory Risks May Pose Challenge

As shown in Figure 9, cell expansion drives the second largest $ delta between our two scenarios, representing a ~$36.4K or 77% decrease in Transduction CoGS. Savings are almost exclusively attributed to the use of suspension-based viral vector manufacturing to yield a cheaper viral vector in the optimized scenario given improvements in yield, scale, and full / empty capsid ratio, as opposed to adherent-based techniques in the base process. We acknowledge that in-process changes, however, have to be submitted to regulatory bodies such as FDA and likely require clinical equivalency testing— thus posing a major hurdle especially when the drugs is already commercialized. As such, pre-commercial CAR-T operators would be best served by designing their processes to include suspension-based vector from the start in order to realize cost savings sooner.

Figure 10. Comparison of Transduction CoGS / Dose in Milestone 1 (base) vs. Milestone 2 (optimized process)



Source: Leerink Partners estimates

Viral Vector Costs Remain Significant

Our conversations with industry leaders have repeatedly highlighted viral vector as a major source of capacity constraint and ultimately costs. Holding all other factors constant, we estimate that moving to a suspension-based technique can reduce vector cost by an order of over 8x to an estimated $3.8K/dose. According to our analysis, transduction represents an outsized 17% of total costs or $47K/dose (vector representing ~64%) in our Milestone 1 process and is significantly reduced to ~7% of total costs or $11K/dose (vector representing ~37%) in our Milestone 2 process, with reduced vector costs making up 72% of

reduced CoGS. During our 2023 Foundations conf, Dr. Peter Marks keynote and C&GT and Biologics Panel KOLs unanimously agreed that reducing the cost of the viral vector will be key to driving down CAR-T manufacturing CoGS long term. Links are here and here.

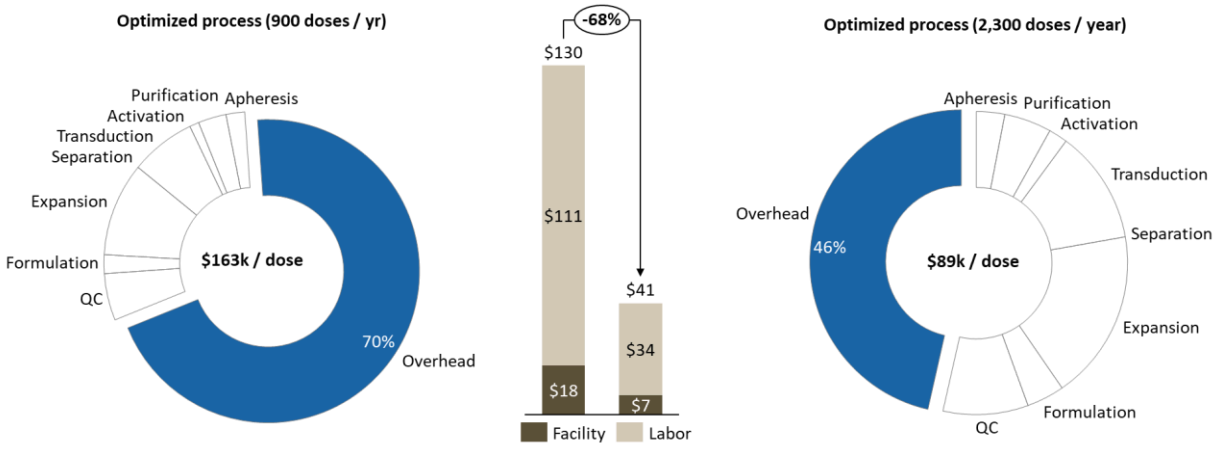
We'd consider the range between our base and optimized processes as broadly representative of the scope of process improvement in commercial therapies today. Although we acknowledge there is a degree of uncertainty around our estimates (particularly as it relates to CAR-T manufacturing costs for large-cap companies where there is often limited visibility), we'd expect other current commercial therapies to fall somewhere within or close to our range, other than at the tiny scales right at commercial launch (i.e., first quarter profit for Autolus after anticipated 4Q24 launch of obecabtagene autoleucel [obe-cel]).

Optimizing Overhead and QA/QC Represent Opportunities to Further Reduce CoGS

Reducing overhead costs through increasing scale is of particular importance for smaller/early-stage companies where the slope of the scale-to-cost curve is steepest (see Figure 6). At the current scale for our model (900 doses / year), overhead drives the greatest share of overall costs at $111K/dose (41% and 68% for base process and optimized process, respectively). As a process scales up (or out), overhead labor will comprise an increasingly smaller contribution to overall cost on a per dose basis at the facility. This concept brings us to our final cost scenario (Milestone 3) where we take our optimized process and scale it up from 900 to 2,300 doses / year (Figure 10), which our estimated volume for Kite in the US for FY2023.

Scaling up to this level brings meaningful benefit to the per dose cost, leading to a 68% reduction in overhead for labor and facility. This savings accounts for the fact that CapEx in the scaled-up case is 5-fold higher than the optimized process case (see Table 1), but increased dose production still produces a lower per dose facility cost. On the LST side, we'd expect better leverage as CAR-T supply chain infrastructure is better established (i.e., CryoPort's [CYRX, MP] bioservice facility network buildout) and / or supply chains are increasingly decentralized given the increasing development of allogeneic therapies (vs. autologous), with more upside if capacity shifts increasingly to CDMOs over time.

Figure 11. Comparison of Overhead Cost / Dose in Optimized (Milestone 2) vs. Scaled-Up Optimized Processes (Milestone 3)



Source: Leerink Partners estimates

QA/QC Represents a Major Cost and the Largest Opportunity for Innovation Among Tools Companies

QA/QC in process and in batch release are other cost components widely regarded as significant cost bottlenecks in CAR-T manufacturing. However, this is an area that has still yet to be addressed sufficiently in optimized processes today, with our cost model only contemplating solutions that exist currently as opposed to potential efficiencies to be gained from future innovation. Even so, **QA/QC represents the third most significant CoGS reduction** in our scenario analysis with a $15M delta between our base case and optimized scenarios. This difference is driven almost entirely from labor hour efficiencies gained from incremental automation in certain assays, with the assays and instruments themselves largely static across our two scenarios. Of our modeled assays, potency testing via ELISA or cytotoxicity is the most time/cost-intensive, both in-process and in batch release. In our base case, potency represents ~37% of batch release costs (before accounting for batch failure) and ~60% in the optimized case scenario. In our earlier FDD C&GT panel (link here), one KOL indicated that current standard assays are characterization tools typically used in research/academic labs, not fit-for-purpose in bioproduction process control.

APPENDIX

Model and Cost Assumptions

We contemplate a base case scenario (Milestone 1) and an "improved" case scenario (Milestone 2) to reflect process changes that could have a material impact on overall CoGS. These scenarios utilize a number of different key input assumptions, which we distinguish below:

- **Process/Turnaround time:** Turnaround time (time to complete manufacturing of one dose) plays a significant role in cost per dose and ultimately the ability to treat the patient before further disease progression. As part of our fixed cost calculation, we amortize total cost across total doses produced per year, which is influenced by process time length. To estimate labor costs, we apply a scale factor tied to our time assumption across each process step.

  In our base case scenario, we assume a 30-day manufacturing process, roughly in line with the current manufacturing paradigm. For our improved case scenario, we assume a ~16-day process time, in line with process time reported at Kite Pharma (GILD) as of 2023. In 2024, this process was upgraded to a 14-day turnaround time. According to KOL feedback and management commentary, process times range between 35 and 40 days on the high-end and as low as 7-10 days on the low-end for more aggressive processes.

- **Out-of-Spec (Batch Failure) Rate**: We use an assumption for out-of-spec batches, referring to the overall rate in which batches do not meet regulatory specifications/standards and are scrapped. We use separate out-of-spec assumptions for manually processed unit operations and automated/closed unit operations given that automated processing will typically reduce batch failure given the lower exposure to contamination in "open" manipulations. Our assumptions are blended based on the level of automation assumed and is amortized directly to raw cost estimates.

  In our base case scenario, we assume a 12.5% out-of-spec (batch failure) rate for manual processing, which accounts for various estimates for commercialized therapies, including ~18% for LEGN's Carvykti, ~3% for Novartis's Kymriah, 8% for BMS and 2seventy, and ~5% for Kite (part of GILD). In our improved case, we assume 5% failure, closer in line with Kite's current capability.

- **Process Automation:** Cell therapy manufacturing remains highly manual, lacking fit-for-purpose tools and closed systems that enable automated production. Some bioprocessing suppliers and CDMOs are developing instruments that meet these needs, opening the door to near-term automation. In addition to estimating

automated instrument costs, our model estimates a reduction in labor hours and batch failure rates to capture the effect of automation, as referenced earlier. In our base case scenario, we are assuming a fully manual process and in our improved case scenario, we are only assuming automation applied to downstream unit operations (separation, expansion, formulation, QC).

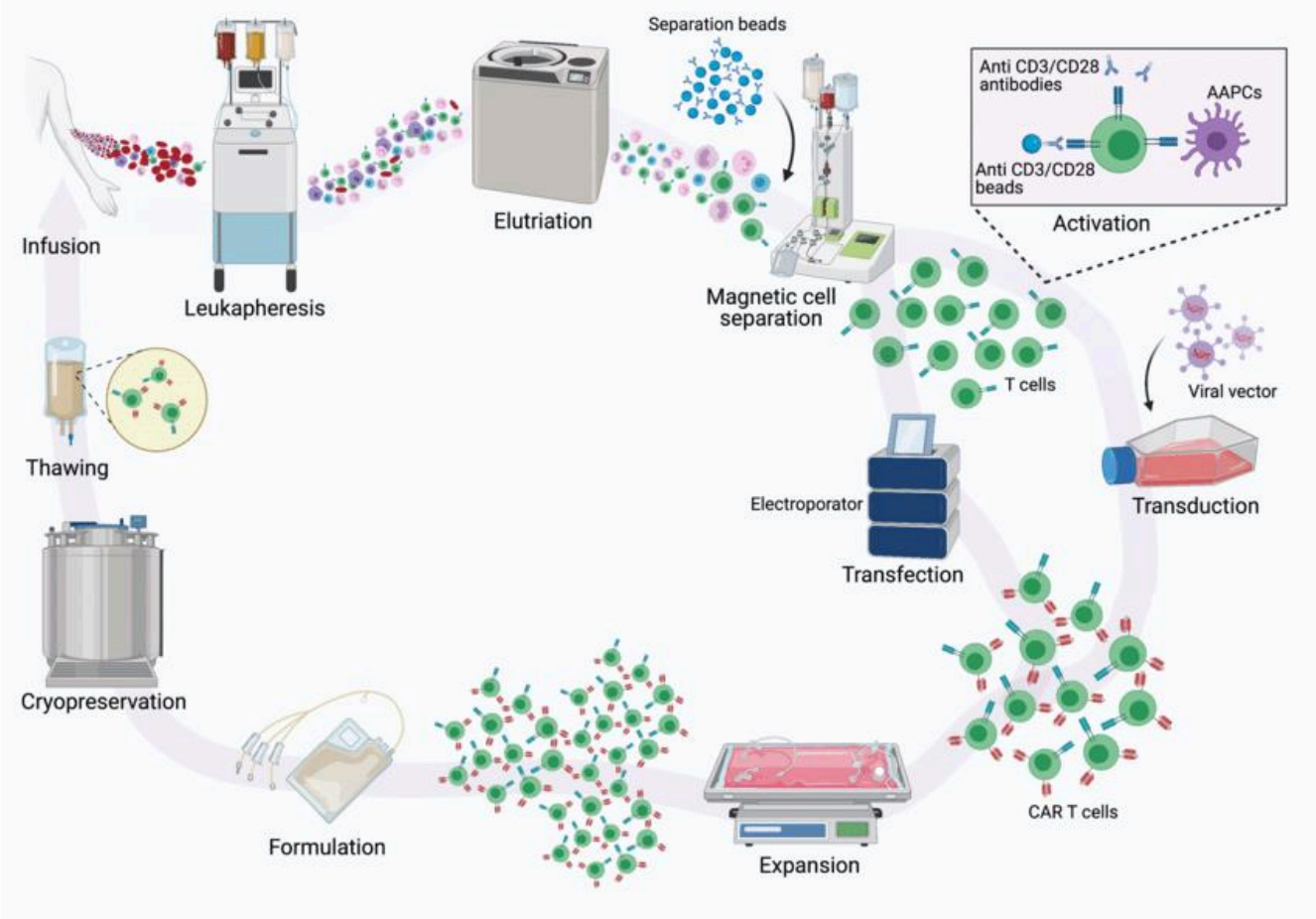
Note, our cost estimates are based on closed/automated solutions that exist today and do not contemplate potential efficiencies to be gained from future innovation. For instance, our "automated" QC and batch release estimates are relatively more innovative but still based on highly manual processes. Closed systems on the market today are generally siloed to specific unit operations, and there is no current end-to-end closed loop solution or suite of products that currently exists.

- **Non-transduction Capacity Utilization Rate:** We view transduction as the major bottleneck in cell therapy manufacturing today, likely leading to under-utilization in other processing steps (63% in both scenarios).
- **Manufacturing Scale:** Manufacturing scale drives our estimate of overhead costs, which accounts for an outsized 40%+ of total CoGS in our base case of 900 dose annual capacity. In the improved case, we assume capacity for 2300 doses/year.
- **Viral Vector Assumptions:**
    - **Multiplicity of infection (MOI):** MOI reflects the impact transduction efficiency has on overall costs. Both of our scenarios assume an MOI of 6, which means a manufacturer needs 5x as many viral vectors as cells to be transduced in order to get enough gene-edited cells.
    - **Vector Manufacturing Type (Adherent vs. Suspension):** As a base assumption, we take adherent vector manufacturing as it is the current standard. We acknowledge that this may change in the mid-term as manufacturers transition to suspension. Despite such potential transitions, it is not clear which commercial products would benefit from suspension vector as FDA may require equivalence testing when making process changes.
    - **Vector Quality / Procurement:** Vector procurement, even within a single product story can be a mix of in-house and CDMO product. We keep our assumption as in-house.
- **Facility Capex and Fixed Cost Useful Life:** In both scenarios, we amortize all equipment fixed costs over a 10-year average useful life. For the profit pool analysis, we assume a 5-year average useful life for the 2029 process based on GILD's 2023 10-K, where they state a useful life of 4-10 years. As discussed earlier, fixed costs are also calculated on a per dose basis given estimates for doses per year (and process time). Separately, we assume capex costs incurred to build the

manufacturing facility of $40M and $200M in our base and improved case scenarios, respectively (both amortized over a 20-year useful life).

The Process: Equipment and Consumables Used in the Cell Therapy Manufacturing Process

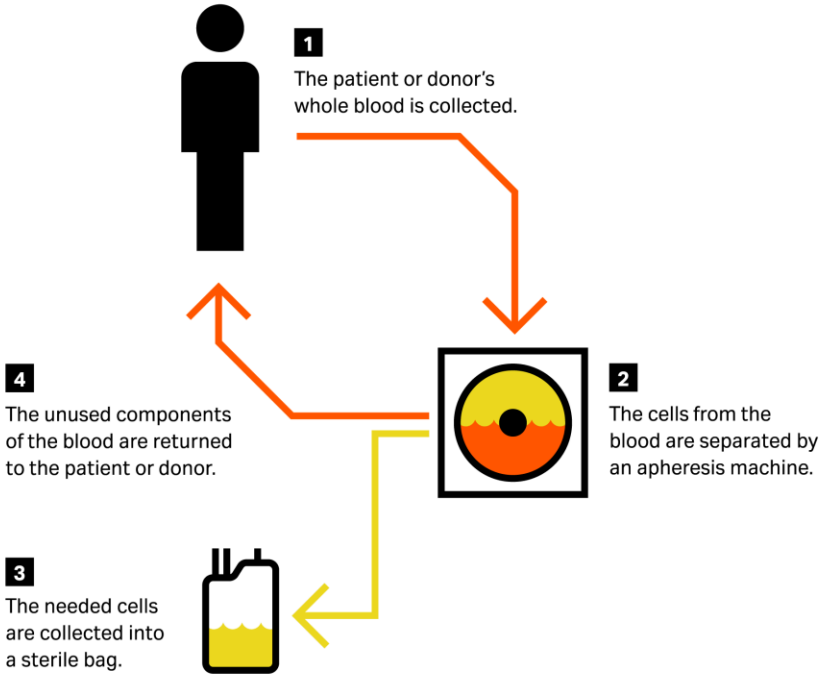
Figure 12. CAR T Manufacturing Workflow



Source: Blood Cancer Discovery – AACR Journals, Leerink Partners

Our cost analysis for autologous cell therapy manufacturing utilizes a bottoms-up approach and includes individual cost estimates for specific instruments, consumables, and labor costs across each process step, roughly outlined below.

Figure 13. Apheresis Workflow



Source: Cytiva, Leerink Partners

1. Apheresis/Leukapheresis:

Blood is collected from the patient (or a donor in allogeneic therapies), usually conducted at a hospital or blood transfusion centers/clinics. Generally, the process involves drawing blood from the patient, routing the blood to a centrifuge where leukocytes called PBMC's (peripheral blood mononuclear cells, ~70% of which include T-cells) are isolated from the blood. The PBMCs are collected in a sterile bag called a leukopak, while the remaining red blood cells and plasma is sent back to the donor. The entire leukapheresis process is typically done simultaneously. There is also usually an in-process QC (quality control) step required, where initial cell counts are taken using a cell counter; cell viability assays may also be required such as flow cytometry or Trypan Blue (see section on QC). Where manual and automated methods differ most significantly in this step is in fixed costs; in an automated process, fit-for-purpose apheresis platforms such as the Kabi LOVO or Terumo Spectra Optia system can be used whereas if done manually, more traditional density gradient centrifuges can be utilized at a lower initial capital cost but with lower throughput. Variable costs include minor reagent and consumables including blood collection tubing, sterile leukopak bags, leukoreduction filters, density gradient centrifugation media, centrifuge tubes, pipetting, and buffer/wash reagents, which can be sourced from a number of lab equipment suppliers

including TMO, DHR, MilliporeSigma, Corning (GLW, Not Rated), BD (BDX, Not Rated), among several others. Because apheresis is usually done outside of the manufacturing facility, we do not include labor in our analysis.

- **Instruments:** Fresenius Kabi (FSNUY, Not Rated) LOVO**,** Terumo (TRUMY, Not Rated) Spectra Optia
- **Consumables:** Fresenius Kabi LOVO Leukopak

2. Cryopreservation

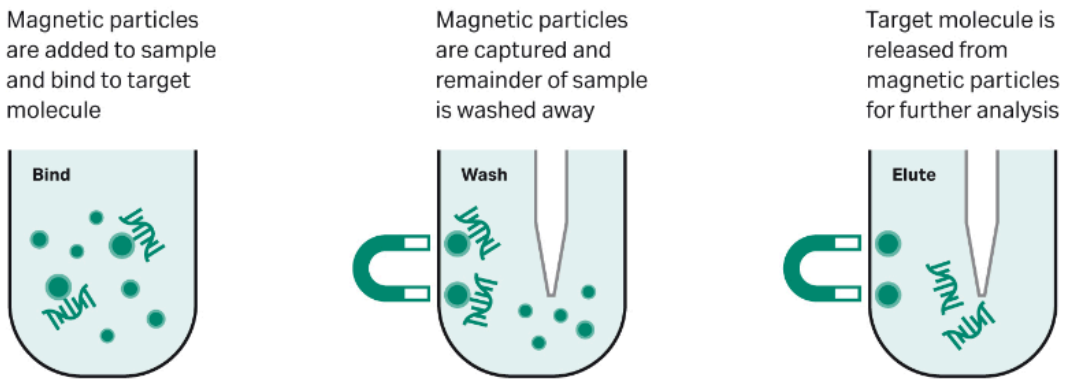
Before processing, cells need to be cryopreserved to maintain sample stability during shipment to the manufacturing facility. Note, this is different from cryogenic shipping post manufacturing (which is done by CYRX). The patient sample is cryopreserved and frozen in a controlled matter, usually using a lab freezer (i.e., products from TMO, AVTR (Not Rated) or Cytiva), and preserved using freeze media (cryoprotective agents that reduce cooling rates) which can be sourced from media suppliers such as CryoStor BioLife (BLFS , NR), IntegriCell (CYRX, MP) and others. Shippers (i.e., transport vessels) can be supplied from cell therapy supply chain services such as CYRX's Elite or Advanced Therapies shipper (ATS) or logistics services from UPS (Not Rated) Marken. This step is generally similar for most processes and is also done outside of the actual manufacturing facility.

- **Instruments:** Cytiva VIA Freezer, TMO CryoMed,
- **Consumables:** BLFS (Not Rated) CryoStor (for cryopreservation) and media
- **Services:** CYRX IntegriCell

3. Cell Purification

Cell therapies need to be manufactured with a homogenous population of a specific subtype of T-cell (i.e., CD3, CD62L, CD8, CD4, etc.), so heterogenous populations (PBMCs collected from patients have a mix of different T-cells and other leukocytes) need to be further purified to isolate/select for the desired subtype. After receiving the leukopaks from the apheresis facility, the bags containing the cells must be thawed and washed. Done manually, lab techs can thaw and wash leukopaks in a hot water bath (supplied by most lab providers) with varying levels of precision. Afterwards, the cells are spun down and washed, typically in a benchtop centrifuge, manually reconstituted in buffer media. Alternatively, automated thawing, washing, and cell processing/separation devices are available from Miltenyi and Cytiva, where the lab tech simply transfers the cells to the device and sets the appropriate protocol. Variable costs include buffers and wash solutions/media, as well as centrifuge tubes and other minor consumables for the manual method. Fixed costs for the manual and automated processes are somewhat comparable; however, the process between thawing and washing is somewhat closed whereas manual processes are exposed to open manipulations, with potential for contamination or human error.

Figure 14. Purification Bead Mechanism



Source: Cytiva, Company filings

Once thawed, the sample is purified for the desired cell type by selecting for specific cell surface markers, in this case the desired T-cell receptor protein (CD3, CD4, etc.). This is typically achieved using magnetic beads conjugated (tagged/labeled) with antibodies specific to the marker (i.e., anti-CD3, etc.). In this process, the sample is mixed with the beads in a vessel (such as a column), and the magnetic beads bind to the selected marker. A magnet is then externally applied to immobilize the beads (and the selected cells) while the remainder of the sample is washed away using an elution buffer. The bead labels then need to be removed, which can be done using an elution reagent and/or another magnet. Afterwards, another in-process QC step can be conducted (cell count, viability) using similar methods as mentioned above. Potential variable costs include the beads (i.e., TMO Dynabeads), magnetic columns, and buffer reagents. Fixed costs involve the magnets (i.e., DynaMag-15, Miltenyi Prodigy) but this step can also be automated via a closed device such as from Miltenyi and Cytiva. Note, the process is only closed within the specific unit operation, but still needs to be manually transferred in between steps.

- **Instruments:** Miltenyi Biotec (Private) CliniMACS Prodigy**,** TMO CTS Rotea or Attune Flow Cytometer**,** Terumo Elutra**,** Cytiva (part of DHR) Sepax C-Pro
- **Consumables:** Miltenyi Biotec AutoMACS**,** TMO CTS Rotea kits and media**,** TMO Dynabeads**,** Stemcell Technologies (Private) EasySep

4. Activation

For T-cells to function and grow in humans, their receptors need to be activated by 2 key signals— one from an antigen fragment, usually on antigen-presenting cells (APCs), as well as a non-specific co-stimulatory signal expressed by the APC and TCR (commonly acting as immune checkpoints in nature). When harvesting T-cells for cell therapy following purification, additional activation beads conjugated to artificial antigen and co-stimulatory signals (i.e.,

antibodies) are applied in a process similar to purification beads above; note that sometimes the process of purification and activation are combined. Once the cells are activated, they are then expanded initially to prepare for the following critical transduction step; this is done by transferring the purified/activated cells to a reaction vessel such as Wilson Wolf's disposable vessel G-Rex (TECH) or other benchtop bioreactors, incubated with growth media (i.e., nutrients/vitamins and growth factors such as IL-2 cytokines).

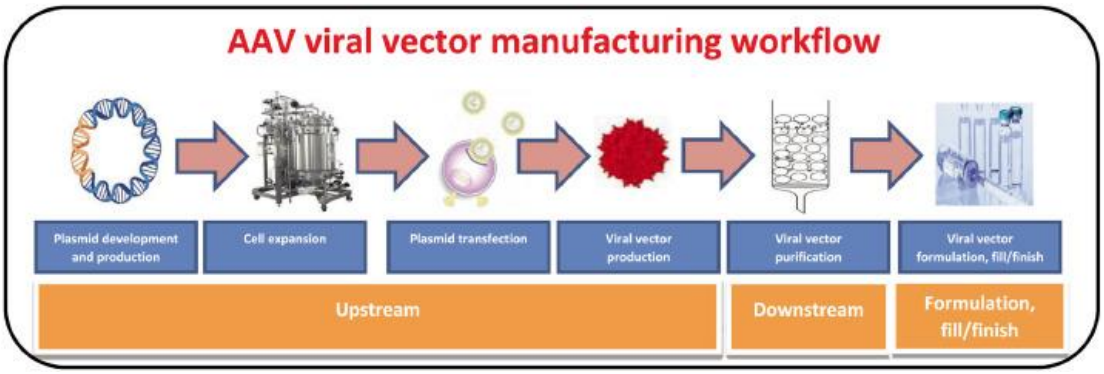
In a primarily manual process, the acts of transferring the cells, adding media, and other manipulations are usually done in a biosafety cabinet or BSC (essentially an enclosed/ventilated lab workstation) and cell expansion occurs in a vessel, which in turn will usually be placed in an incubator (essentially a temperature-controlled box, like a heated fridge). In an automated process, liquid handling (i.e., sample manipulations) can be partially automated. Activation is also usually capped with an in-process control step (i.e., cell count). Possible variable costs include the beads, columns, growth media, disposable activation/expansion vessels, and other consumables/reagents. Fixed costs include the automated closed equipment for activation (i.e., Miltenyi Prodigy, Cytiva), as well as biosafety cabinets and incubators which can be sourced from any number of lab suppliers.

- **Instruments:** Miltenyi Biotec CliniMACS Prodigy**,** TMO CTS Rotea**,** Cytiva Xuri Cell Expansion
- **Consumables:** WilsonWolf (20% TECH ownership) G-Rex (single-use bioreactor)**,** TMO Dynabeads**,** Miltenyi Biotec CliniMACS**,** Cytiva Xuri Cellbag and reagents**,** CellGenix (part of SRT3-DE) GMP reagents**,** TECH GMP reagents and media

5. Transduction

In this critical next step, the activated T cells need to be modified to express the desired receptor for the target antigen. In most cell therapies, the genetic payload is transduced (i.e., delivered) via a viral vector (most commonly lentivirus LV or adeno-associated virus AAV), which are either manufactured in-house or outsourced to a CDMO such as OXBDF (Not Rated). Companies are also exploring non-viral vector means to introduce genes, such as liquid nanoparticles (LNP) and exosomes. The vector drives a meaningful share of CoGS because it itself is the product of a complicated process, which we detail in the appendix. Viruses are effective vectors (delivery mechanisms) because they have evolved molecular mechanisms that efficiently transport their genomes into the cells they infect. Viral particles (virions) consist of DNA/RNA enclosed in a protein shell called a capsid; in nature, this DNA codes for additional capsid proteins, but manufactured viral vectors code for a transgene that expresses a protein targeting the desired antigen.

Figure 15. AAV Viral Vector Manufacturing Workflow



Source: J Pharm Sci, Leerink Partners

At a high level, viral vectors are manufactured by producing a cell line for the capsid protein and transfecting it with the transgene in the form of a plasmid — independent DNA molecules that are well suited for individual gene transfers.

Plasmids are the largest individual cost component of viral vector manufacturing because they must be custom designed (to include the gene of interest) by companies such as Aldevron (DHR) via a highly manual process, i.e., stitching gene segments together in the desired sequence before being cloned. Transduction efficiency, which is driven by factors like full/empty capsid mix (i.e., was the gene expressed correctly?), has significant downstream impact of yield and process time.

Once the viral vector is in hand, the actual activation step on the cell therapy manufacturing side begins with prepping the cells and vector for transduction. Activated cells are spun down and resuspended in media and stock viral vector is diluted down to the specified working concentration. Cell and vector working solutions are then mixed and incubated in a flask or disposable vessel (including G-Rex) over the course of approximately 48 hours. Cell media will be a key variable cost here in addition to consumables, and once mixed, this task is relatively hands-off aside from 1-2 media exchanges. As with prior steps, an in-line process control step can be included (cell count).

- **Viral Vector Suppliers:** Oxford Biomedica**,** Brammer Bio (part of TMO)

6. Cell Separation

The cell solution is separated to enrich for the transduced cells. The process uses CAR expression to identify the desired cells, similar to the cell purification performed upstream. This step is essentially analogous to the upstream purification/separation steps.

- Same as the Cell Purification step

7. Expansion/Maintenance

Transduced cells incubate and clonally expand over the course of multiple days to produce a cell count sufficient for therapeutic effect. This step is somewhat analogous to a longer version of the initial upstream expansion step before activation, with transduced cells cultured with growth media (nutrients, growth factors) in bioreactor vessels. Expansion occurs over the course of 3-6 days, with regular media exchanges/refreshes (media need to be periodically removed and replenished during incubation), usually over the course of a larger seed train (transferring the cell culture to progressively larger vessels), typically beginning with a smaller T-flask (itself in incubators) to a larger production reactor. Note, cell therapy volumes scale to max volumes that are a fraction of what is typical for mAbs; for example, Cytiva's Xuri Cell Expansion system scales up to 25L vs. 5KL+ for mAbs. For cell therapies, bioreactors are almost always single-use, meaning that cell expansion occurs in single-use disposable bags held by the bioreactor platform. Because of the lower volume, "rocking motion" bioreactors are commonly used (Cytiva/DHR Xuri cell expansion system or SRT3-DE's Biostat RM TX), which are reactors that move the cell culture bag back and forth in a rocking motion to stir the mixture as a less-invasive alternative to using a physical impeller (stirrer) typical in larger bioreactors. But TECH's G-Rex single patient bioreactors (see here) are also gaining ground and already incorporated in a commercial therapy. These bioreactors have a gas permeable membrane that allows for gas exchange and fluid lines to exchange the media and other nutrients during expansion.

There are automated configurations that can be used; in a more manual process, liquid handling and media exchange are handled by techs in a biosafety cabinet—a highly manual and time-intensive step. Media exchange can be partially automated from bioreactor platforms from Cytiva and Sartorius, which support perfusion, and automated control and monitoring abilities (i.e., bags fitted with inline pH and DO sensors, control tower for the rocker). Media exchange can also be partially automated by liquid handling equipment, such as from Wilson Wolf. Following expansion, another cell count and potentially a cell viability assay is conducted (i.e., flow cytometry, Trypan Blue) before moving on to the next step, formulation. Automated methods are generally less invasive than sampling to take pH measurements. Bags, media, and reagents (i.e., cytokines, flow antibodies) are key variable inputs in this phase, while bioreactor platforms, BSCs, incubators, and flow cytometers are the primary fixed costs.

- **Instruments:** Same as Cell Activation step
- **Consumables:** TMO CTS OpTimizer, Cell SR, Cytiva Xuri Cellbag and reagents**,** TECH GMP reagents and media

8. Drug Product (DP) Formulation

Expanded cells are harvested and spun down before reconstituting cells in formulation buffer. This process is similar to other purification steps before the cells are re-constituted in the formulation reagents, including buffering agents, osmolytes, amino acids, protein supplements (e.g., human serum albumin), and cryoprotectants or cryoprotective agents (CPAs). Cells are then cryogenically frozen to maintain product stability. This process may make sure of a controlled-rate freezer, cryovials, and freezing medium such as liquid nitrogen.

- **Instruments:** Miltenyi ClinMacs Prodigy Formulation Instrument and kit; Cytiva Sefia S-2000;

9. Batch Release QA/QC:

Products undergo a series of QA/QC testing to ensure the product meets specific critical quality attributes (CQA) before shipping to the transfusion site. While CQA's have yet to be standardized, common CQA's include cell viability, potency, and sterility. In addition to batch release QA/QC, several steps include QA/QC in-process typically after every major unit operation, particularly for cell counting and cell viability. Cell counts (i.e., is there enough of the drug) and viability (i.e., are the cells alive/dead) assays are performed using traditional characterization tools, including automated cell counters and/or flow cytometers (sourced from TMO, DHR, etc.). Flow cytometers are capable of performing both cell count and viability assays simultaneously by targeting fluorescent-based markers that can distinguish between live and dead cells, but is relatively complicated to use (requires an operator and takes a day to complete), so is better reserved for batch-release QA/QC or other critical steps (such as after expansion), as opposed to running flow after every unit operation. Alternatively, automated cell counters and Trypan Blue assays (live cell membranes exclude certain dyes) are easier to use for in-process cell counts and viability, respectively.

Other QC assays are usually only in the batch release stage (before and after formulation) and include potency (i.e., does the therapy work) assays and sterility assays (are there contaminants) detecting for common contaminants including mycoplasma, endotoxin, and residual viral vector. Potency assays can vary by therapy but will generally involve targeting markers for T-cell activation; for instance IFNy is a cytokine released by activated T-cells and is a reliable marker for anti-tumor activity and transduced autologous T-cells. For sterility, methods usually include PCR, ELISA, or flow targeting the aforementioned contaminants.

- **Instruments:** TMO Invitrogen Cell Counters**,** Attune Flow Cytometer, and QuantStudio, CRL (Not Rated) EndoSafe, Axion (Private) Maestro, Agilent xCelligence; Accellix (private)
- **Consumables:** TMO PreQuant, MycoSeq, ViraSeq, TECH flow cytometry antibodies.

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Disclosures Appendix

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Analyst Certification

I, Puneet Souda, certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

I, Daina M. Graybosch, Ph.D., certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

Distribution of Ratings/Investment Banking Services (IB) as of 12/31/23

			IB Serv./Past 12 Mos.	
Rating	Count	Percent	Count	Percent
BUY [OP]	185	73.7	71	38.4
HOLD [MP]	63	25.1	7	11.1
SELL [UP]	3	1.2	0	0

Explanation of Ratings

Outperform (Buy): We expect this stock to outperform its benchmark over the next 12 months.

Market Perform (Hold/Neutral): We expect this stock to perform in line with its benchmark over the next 12 months.

Underperform (Sell): We expect this stock to underperform its benchmark over the next 12 months.

The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.

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EQUITY RESEARCH TEAM

LEERINK PARTNERS

Research Management

Jim Kelly
Director of Equity Research
(212) 277-6096
jim.kelly@leerink.com

Julia Belladonna
Associate Director of Research
(212) 404-4524
julia.belladonna@leerink.com

Diversified Biopharmaceuticals

David Risinger, CFA
(212) 404-4539
david.risinger@leerink.com

Bryan R. Dollinger, Ph.D.
(212) 404-4537
bryan.dollinger@leerink.com

Jason Zhuang
(212) 404-4552
Jason.zhuang@leerink.com

Targeted Oncology

Andrew Berens, M.D.
(212) 277-6108
andrew.berens@leerink.com

Kenneth Shields
(212) 277-6190
ken.shields@leerink.com

Amanda Acosta-Ruiz, Ph.D.
(212) 404-4591
amanda.acostaruiz@leerink.com

Emily Shutman
(212) 404-4599
emily.shutman@leerink.com

Immuno-Oncology

Daina M. Graybosch, Ph.D.
(212) 277-6128
daina.graybosch@leerink.com

Jeffrey La Rosa
(212) 277-6103
jeffrey.larosa@leerink.com

Rabib S. Chaudhury, Ph.D.
(212) 277-6268
rabib.chaudhury@leerink.com

Emerging Oncology

Jonathan Chang, Ph.D., CFA
(617) 918-4015
jonathan.chang@leerink.com

Faisal A. Khurshid
(617) 918-4025
faisal.khurshid@leerink.com

Matthew Cowper, M.D.
(617) 918-4890
matthew.cowper@leerink.com

Dylan J. Drakes, Ph.D.
(617) 918-4712
dylan.drakes@leerink.com

Genetic Medicine

Mani Foroohar, M.D.
(212) 277-6089
mani.foroohar@leerink.com

Ryan McElroy
(212) 277-6175
ryan.mcelroy@leerink.com

Lili Nsongo, Ph.D.
(212) 277-6229
lili.nsongo@leerink.com

CJ Yeh, M.D.
(212) 404-4552
christopher.yeh@leerink.com

Immunology & Metabolism

Thomas J. Smith
(212) 277-6069
thomas.smith@leerink.com

Nat Charoensook, Ph.D., CFA
(212) 277-6264
nat.charoensook@leerink.com

Brian M. Conley, Ph.D.
(212) 277-6196
brian.conley@leerink.com

Will Humphrey
(212) 277-6255
william.humphrey@leerink.com

Neuroscience

Marc Goodman
(212) 277-6137
marc.goodman@leerink.com

Rudy Li, Ph.D., CFA
(212) 277-6127
rudy.li@leerink.com

Basma Radwan, Ph.D.
(212) 277-6151
basma.radwan@leerink.com

Madhu Yennawar, Ph.D.
(212) 277-6220
madhu.yennawar@leerink.com

Rare Disease

Joseph P. Schwartz
(617) 918-4575
joseph.schwartz@leerink.com

Jenny L. Gonzalez-Armenta, Ph.D.
(212) 277-6221
jenny.gonzalezarmenta@leerink.com

Joori Park, Ph.D.
(617) 918-4098
joori.park@leerink.com

Will Soghikian
(617) 918-4552
will.soghikian@leerink.com

Infectious Disease, Endocrine & Cardiovascular Disorders

Roanna Ruiz, Ph.D.
(212) 277-6144
roanna.ruiz@leerink.com

Rosa Chen, Ph.D.
(212) 404-4522
rosa.chen@leerink.com

Nik Gasic, Pharm.D.
(212) 277-6147
nik.gasic@leerink.com

Life Science Tools & Diagnostics

Puneet Souda
(212) 277-6091
puneet.souda@leerink.com

Isabella Prugue
(212) 277-6126
isabella.prugue@leerink.com

Philip S. Song
(212) 404-4587
philip.song@leerink.com

Michael Sonntag
(212) 277-6048
michael.sonntag@leerink.com

Medical Devices and Technology

Mike Kratky, CFA
(212) 277-6111
mike.kratky@leerink.com

Brett Gasaway
(212) 404-4588
brett.gasaway@leerink.com

Healthcare Technology and Distribution

Michael Cherny
(212) 277-6189
michael.cherny@leerink.com

Daniel Clark
(212) 277-6233
daniel.clark@leerink.com

Ahmed Muhammad
(212) 277-4570
ahmed.muhammad@leerink.com

Healthcare Providers and Managed Care

Whit Mayo
(629) 802-2560
whit.mayo@leerink.com

John French
(212) 277-6225
john.french@leerink.com

Alberta Massey
(212) 277-6263
alberta.massey@leerink.com

Morgan T. McCarthy
(212) 277-6224
morgan.mccarthy@leerink.com

Editorial

SR. EDITOR/SUPERVISORY ANALYST

Thomas A. Marsilio
(212) 277-6040
thomas.marsilio@leerink.com

SUPERVISORY ANALYSTS

Robert Egan
bob.egan@leerink.com

Mike He
mike.he@leerink.com

Emily Singletary
(212) 277-6115
emily.singletary@leerink.com

Jose Yordan
(212) 404-7236
jose.yordan@leerink.com