CELL & GENE THERAPY INSIGHTS

STRATEGIES FOR SCALE-UP & SCALE-OUT

SPOTLIGHT

EXPERT INSIGHT

The long road to affordability: a cost of goods analysis for an autologous CAR-T process

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With the 2017 FDA approvals and launches of the first gene-modified cell and pure-play gene therapy products to gain licensure in the United States, increasing attention has been paid to the high cost of this emerging class of therapies. Although currently approved therapies are for orphan indications, prices similar to those charged today will be unaffordable for products marketed for larger indications. Using public information, we constructed a cost of goods model for an autologous gene-modified cell therapy product, evaluated the relationship of estimated manufacturing costs to list prices of CAR-T products, and investigated the potential impact of various factors on manufacturing costs. Our findings highlight in particular the importance of maximizing employee productivity, leveraging automation and technology, and accurately forecasting capacity needs to achieve the manufacturing cost improvements that will likely be required to drive broad adoption of autologous gene-modified cell therapies.

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INTRODUCTION

After decades of development in which Cell and Gene Therapy (C&GT) products struggled to demonstrate clinically compelling efficacy, fund development efforts, and bring new products to market, the field appears to have passed an inflection point. Compelling demonstrations of efficacy by multiple products have ushered in a new era in the field, led by the first FDA approvals for gene-modified cell therapies (Kymriah®, Yescarta®) and a pure-play gene therapy (Luxturna™)

product in 2017. (Throughout this article, we refer to products delivering a gene therapy directly to patients by way of a viral vector as 'pure-play gene therapies', and those using genetic modification of cells as 'gene-modified cell therapies'. We recognize this language differs from the current FDA convention, however we find it a useful framework for describing the unique manufacturing considerations of these two very distinct classes of therapies). Among other comparable deals, the $11.9 billion acquisition of Kite by Gilead, and the $9 billion acquisition of Juno by Celgene have caught the attention of investors, triggering an unprecedented level of financial investment in the cell and gene therapy space. According to the Alliance for Regenerative Medicine, at least $7.9B in funding was raised by Regenerative Medicine companies during the first 6 months of 2018, and 977 Regenerative Medicine clinical trials were ongoing worldwide as of June 2018 [1].

However, despite palpable excitement for the tremendous clinical advances that have been made in recent years, there has been increasing controversy over the high prices of approved therapies. Each of the three products approved in 2017 command US list prices of between $373,000 and $850,000. In the UK, Novartis's Kymriah® was approved by the National Institute for Health and Care Excellence (NICE; the national arbiter of reimbursement decisions based on analysis of cost effectiveness) for its pediatric ALL indication, but at a price steeply discounted from its $475,000 US list price [2]. Both Kymriah® and Kite/Gilead's Yescarta® were originally rejected by NICE for the larger adult lymphoma indication, although Kite/Gilead later struck a deal with NICE to enable discounted Yescarta® access through the Cancer Drugs Fund. In the USA, the Institute for Clinical and Economic Review (ICER) issued a report suggesting that the $850,000 Luxturna™ list price was as much as 2- to 4-fold above cost–effectiveness standards [3]. Beyond the impact of high list prices for these products, the costs of such therapies are further increased by high ancillary costs associated with product administration (e.g., need for delivery under hospital admission, monitoring for and control of side effects such as cytokine release syndrome, etc.).

We aimed to investigate the relationship of manufacturing costs to high prices for gene-modified cell products, and to determine the highest value routes for potential investment in cost reductions. To this end, we constructed a cost of goods sold (COGS) model for a hypothetical chimeric antigen receptor T-cell (CAR-T) product using publicly available information about the manufacturing process for Yescarta® as our guide.

METHODS: COGS MODEL

Using a published patent application [4] and journal article [5], LinkedIn profiles of employees, and published articles on Kite's El Segundo manufacturing facility, we constructed a process flow diagram (PFD) describing the unit operations, materials and equipment utilized in a Yescarta®-like manufacturing process (Figure 1).

Labor hours associated with each processing step were estimated based on previous Dark Horse Consulting (DHC) experience

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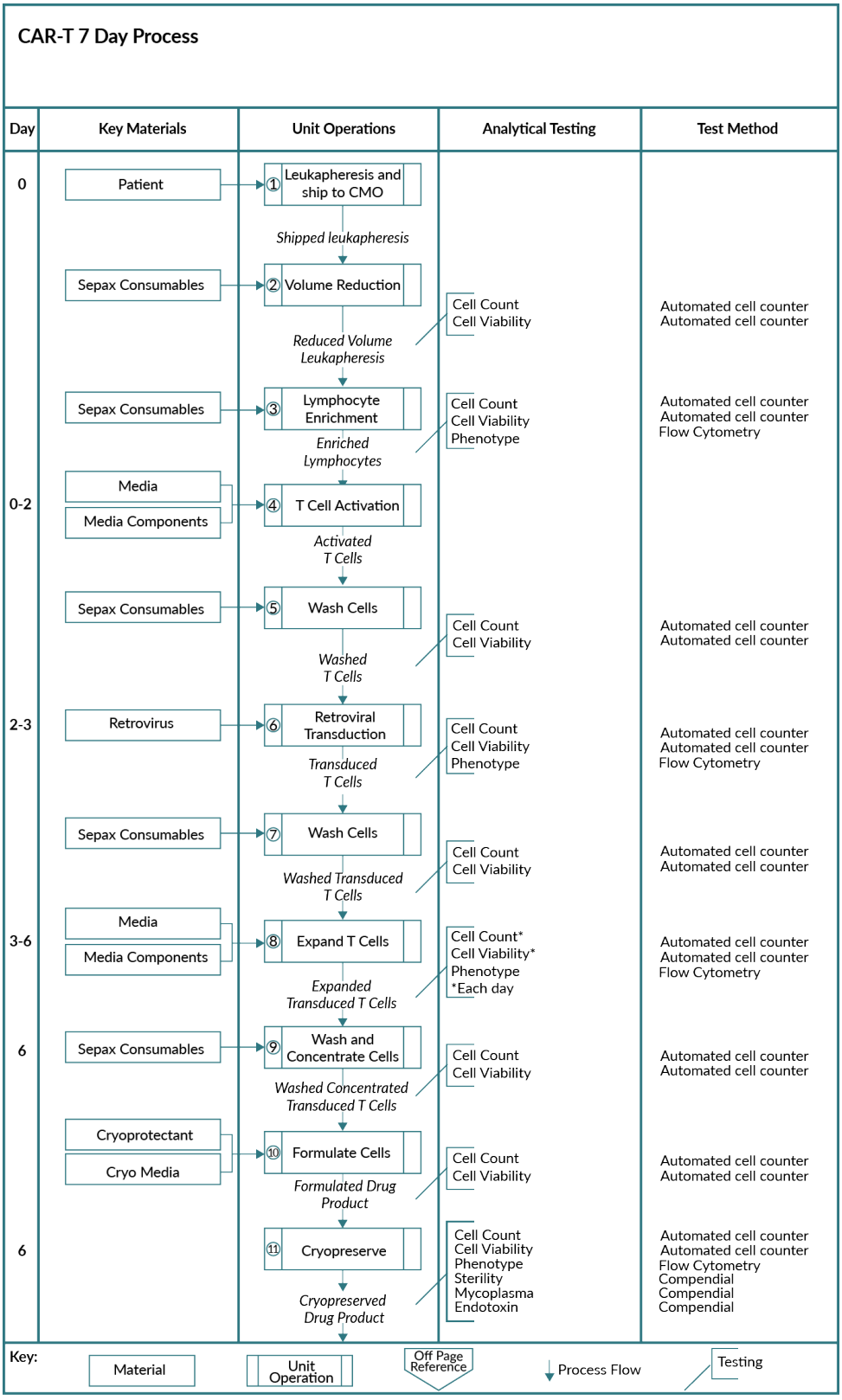
FIGURE 1

Process flow diagram for a CAR-T manufacturing process.



with the conduct of similar unit operations in a GMP environment and used to calculate projected employee numbers and labor costs for in-house manufacturing of a similar product. For the purposes of this analysis, it was assumed that all in process and release testing was performed in house. Based on these methods, we estimated just over 200 labor hours per lot, inclusive of manufacturing, QA, QC and logistics/supply chain management. Departmental management overhead was estimated at 20% of operating hours, and headcount-driven support functions (facilities, IT, HR, etc) at 10%. Estimated employee numbers based on these calculations (~400 FTE required for 1500 lots per year) were benchmarked against publicly available information (LinkedIn) for current employees and open job requisitions at Kite's El Segundo manufacturing facility (332 employees and 49 open requisitions as of March 2018). Good agreement was seen between both methods.

Facility construction costs were estimated based on the $26M in leasehold improvement costs reported in Kite's SEC filings from 2015 and 2016. These costs were compared to benchmark estimates of cost per square foot for GMP facility construction by ISO classification, and found to be broadly within agreement for both methods. Facility validation expense was estimated at 20% of construction costs, or just over $5 million. Facility construction and validation expense was amortized over an estimated 15-year useful life.

Rent was estimated at $1.6 million per year based on reported numbers for the El Segundo facility in Kite's SEC filings. Other ongoing operational expenses were estimated based on prior DHC experience.

Required equipment per manufacturing line were estimated based on DHC experience. Where appropriate based on frequency of use (e.g., cell counters, BSCs, controlled rate freezers) equipment was assumed to be shared between lines. Required equipment lists were used to calculate equipment costs to fully equip facility for a range of target lot numbers per year. Equipment IQ/OQ/PQ expenses were estimated based on previous DHC experience. Calculated equipment costs using these methods totaled $12 million, which was reasonably close to the $18 million in equipment expenses reported in Kite's 2015 & 2016 SEC filings when it is considered that equipment was likely also purchased for other purposes and facilities during this period. Equipment purchase and setup expenses were amortized over an estimated 5-year useful life.

Apheresis costs were estimated based on procedural costs plus costs of shipping using a cGMP compliant courier service. Materials costs for retroviral vector were estimated based on benchmarking of viral vector CMO production costs per lot, assuming production at the 200L scale, with sensitivity analyses testing upstream viral yields ranging from 6E5 to 1.5E7 IU/mL [6], downstream purification yields in the range of 25–75%, and an MOI of 3 [5].

Sensitivity testing was performed to test variability in COGS within the full extent of reasonable input assumptions for each variable. Except as described for the 'Compounded Effect' scenario below, sensitivities were tested using modification of a single variable at a time for simplicity.

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FINDINGS

Estimated cost of goods is in line with biopharmaceutical industry standards

Our base case estimate of COGS was $58,200 per dose, with an estimated range of between $48,000 and $106,000 per dose based on sensitivity analyses of key input assumptions (Figure 2). At 13 to 28% of the Yescarta® list price of $373,000, these estimated COGS are in line with biopharmaceutical industry standards in the range of 15–25% [7,8]. Therefore, we conclude that, in order to offer similar therapies at more affordable prices without disincentivizing biopharmaceutical and/or venture investment in C&GT products, it will be necessary to effect dramatic reductions in costs of manufacturing.

Labor Costs are the Largest Contributor to COGS

By far the greatest contributor to COGS was labor, at an estimated 71% of manufacturing costs (Figure 3). Just under half of labor costs (48%) were for manufacturing personnel, with the remainder divided between quality control (QC; 16%), quality assurance (QA; 16%), supply chain management (SCM; 11%) and other functions (project management, facilities, etc.; 9%).

Materials costs represented 18% of COGS, with the largest components coming from apheresis, disposables, and virus. Although manufacture of a large lot of virus can represent a significant upfront effort and expense, using published scalable methods to estimate vector production costs and yields, viral vector costs were estimated to represent

FIGURE 2

Cost of goods estimates – sensitivity testing.

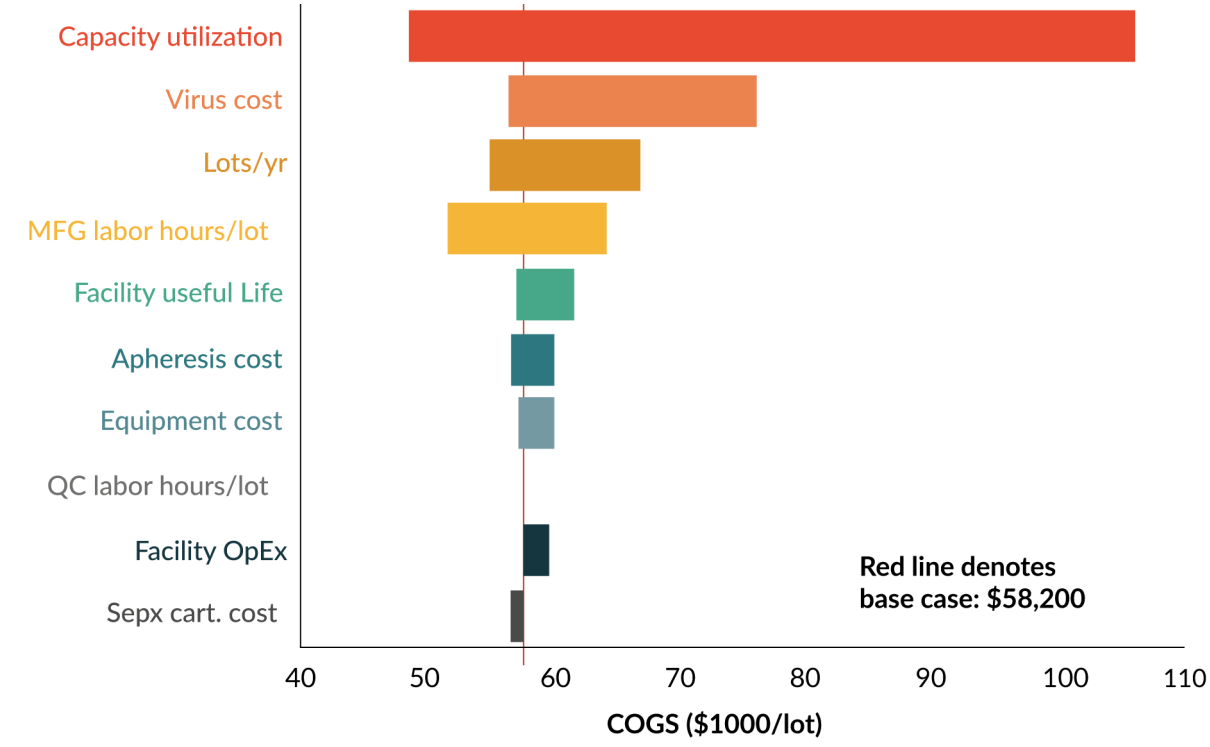
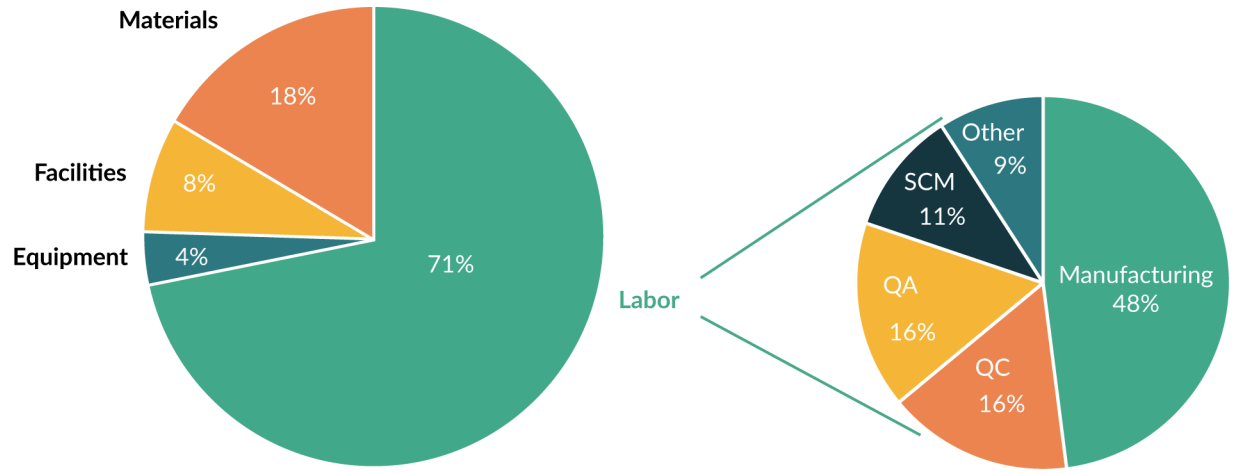


FIGURE 3

Breakdown of cost of goods by component.



only 3–4% of COGS in our base case scenario. However, the model was fairly sensitive to assumptions of less scalable methods and/or poor viral vector process yields (Figure 2), with virus costs reaching as much as 26% of COGS under 'worst case' assumptions for viral titer and purification yields, emphasizing that employing scalable viral production is a critical step in establishing a commercially viable COGS.

Facilities and equipment expense represented significant upfront investments for construction, equipment procurement, and validation, however they were a relatively minor component of per lot cost of goods at just 8% and 4%, respectively, when amortized across their estimated useful lives.

Duration of T-cell Expansion Post-Activation Significantly Impacts COGS

Our base case model assumes a process of 7 days in duration, including 3 days of T-cell expansion post-activation (Figure 1). However, published process descriptions allow for an optional additional 3 days of T-cell expansion if necessary. To explore the impact of process duration on COGS, we modeled this longer process as well. The impact of an extended process was not insignificant. As a result of increased labor hours and longer facility and equipment cycle times, cost of goods increased by 16% to $67,600. This change was driven by both increased labor costs and reduced facility and equipment cycle times associated with the longer process duration.

Autologous Nature of Product & High Labor Costs Limits Benefits from Economies of Scale

Although the high list prices of Kymriah®, Yescarta® and Luxturna™ have attracted much attention, the fact that these products are currently approved only for a small handful of orphan and ultra-orphan indications make a near term affordability crisis unlikely. The prices of the one-time treatments Kymriah® and

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Yescarta® are similar to the annual costs for many enzyme replacement therapies for orphan conditions (e.g., Shire's Elaprase, BioMarin's Naglazyme and Sanofi Genzyme's Myozyme) [9]. Furthermore, even if these products achieved 100% market penetrance of their approved indications at list price (highly unlikely, even for products addressing orphan conditions with few treatment alternatives), the total combined cost to the system for purchase of these three products (not including ancillary care costs) would equate to $3 billion annually, which is less than 1% of annual prescription drug spend, and less than 0.1% of annual healthcare spend in the USA [10].

However, with many similar therapies in development for more and larger indications, it is easy to see the near-term potential for the availability of highly effective C&GT products to rapidly eclipse society's ability to pay for them. According to the Alliance for Regenerative Medicine, there were 314 clinical trials ongoing for gene-modified cell therapies during Q2 2018, including 166 Phase 2 and 14 Phase 3 trials [1]. Among C&GT products in clinical development are many products for far more common indications such as breast and lung cancer, stroke and heart failure. Unless these therapies can achieve manufacturing costs that enable prices well below those of any C&GT product currently on the market, an affordability crisis seems inevitable. As shown in Table 1, adoption of a new therapy priced at $350,000 by just 10% of incident cases for these four common conditions would amount to an additional $72.6 billion in annual drug spend. This equates to 22% of the total 2016 US prescription drug spend across all product classes and disease indications (Table 1). Although some of the additive costs would likely be offset by reduced costs in other categories of healthcare spend, it is clear that any such savings would be inadequate to fully offset the additive drug costs. For example, the annual cost of $213 billion for adoption by 10% of incident stroke cases is is approaching the estimated total annual cost of stroke care in the US ($34 billion) [11].

We investigated the potential impact of economies of scale on cost of goods by modeling COGs at annual production volumes ranging from 500 to 5,000 lots per year. Not surprisingly, given the autologous nature of the product and the high contribution of labor costs, economies of scale were limited, with only a 22% reduction in cost of goods anticipated from a 10-fold increase in production volume. We conclude that further cost reduction levers will be critical to enabling broad adoption of C&GT therapies in prevalent diseases.

TABLE 1

Annual prescription drug spend for $350,000 product adopted by 10% of incident patients.

Indication	US annual incidence	Annual cost at 10% adoption (US$ billions)	% of 2016 US prescription drug spend [10]
Stroke	610,000 [11]	21.3	6.5%
Heart failure	1,000,000 [11]	35.0	10.6%
Breast cancer	266,000 [12]	9.3	2.8%
NSCLC	199,000 [12]	7.0	2.1%

Challenge of Accurately Estimating Product Demand Introduces Significant Risk to COGS

In contrast to the relatively modest impact of economies of scale, we found that efficient use of established capacity was a critical factor influencing cost of goods. Given the long lead times necessary to hire and train qualified staff, build and validate a manufacturing facility, and purchase and validate equipment, it is necessary to predict capacity needs well in advance of the date that capacity needs to be online. Once the decision is made to target capacity to manufacture a given number of lots per year, expenses such as personnel, equipment and facilities become fixed costs that cannot be easily adjusted for changes in anticipated demand. Reimbursement uncertainties and lack of clear precedents to follow in modeling commercial adoption of these therapies make such capacity planning particularly challenging in the case of novel cell and gene therapy products. Therefore, we wanted to model the impact of overly optimistic commercial assumptions on per lot COGS.

To do this, we modeled the COGS per lot for a facility constructed, equipped and staffed to deliver 1500 lots/year (our base case model assumption) if operated at 100%, 80%, 60%, or 40% of capacity (Figure 4). Given the significant fraction of costs that cannot be adjusted quickly for changing demand, the impact of capacity underutilization on cost of goods was highly dramatic – COGS per lot at 40% capacity utilization was $106,000, or nearly twice that of our base case scenario.

The need to predict capacity requirements well in advance to optimize cost of goods creates a difficult challenge for the field. On the one hand, overestimation of commercial adoption clearly has major, adverse consequences to COGS. On the other hand, given the 'on demand' nature of manufacturing of these products, it is critical to ensure adequate capacity is on hand to address demand. Given the high potential for rapid progression of the patient populations currently treated by these types of products, one could argue the need to even plan for some surge capacity to avoid delays in product turnaround due to peaks and valleys in demand. This assumption was built into our base case model, which assumed an average of 80% capacity utilization to allow for some variation in weekly demand.

The implications of this finding are that, while our estimate of steady state COGS is in the range of typical biopharmaceutical COGS as a percent of list price, the level of risk associated with COGS is substantially higher for autologous cell therapy products than for traditional biopharmaceuticals. For this reason, it will be critical for companies to invest in developing thoughtful and realistic commercial models that appropriately factor in considerations like adoption curves, potential reimbursement challenges, and the impact of competition. Products targeting conditions where rapid turnaround is less critical may be able to better manage their capacity through use of incoming frozen apheresis products and/or building in process hold steps to allow for optimized process scheduling across the 'peaks and valleys' of demand. The clear rationale for developing therapies for very serious conditions should also be balanced against the

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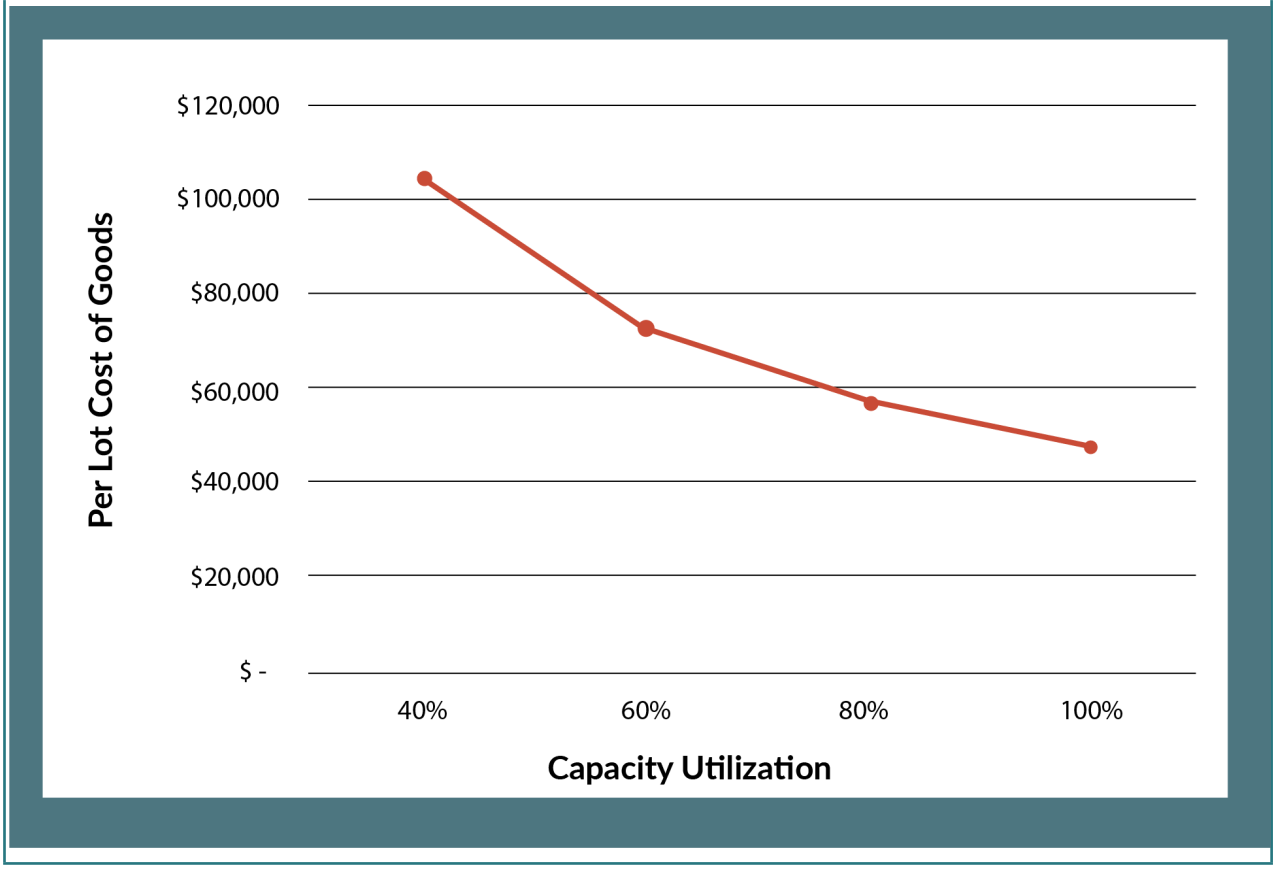
FIGURE 4

Impact of capacity utilization on COGS (at target capacity of 1500 lots/year).



very obvious benefits of addressing conditions in which immediate product delivery is less critical to enable such scheduling advantages to be captured. The ability to share risk surrounding commercial adoption curves and demand peaks and valleys is also highly attractive in this context, and suggests that manufacturing consortia or CMOs offering flexible overflow capacity could be interesting models for further exploration.

Finally, the need to avoid carrying excess capacity highlights the value of developing expedited training programs and adopting process automation and other productivity improvements to enable more nimble adjustments with respect to the single largest cost component driving capacity risk (labor).

Improvements in Productivity Not Only Reduces COGS, but Also Risks Associated with Product Demand Uncertainty

Given the high contribution of labor costs to overall cost of goods, we next looked at the potential impact of a variety of productivity improvements on cost of goods. As significant fractions of labor costs came from each of manufacturing, QA, QC and supply chain, we evaluated potential mechanisms to increase productivity across each of these functions.

We first evaluated the potential to improve cost of goods through productivity improvements in the largest single component of labor costs, manufacturing labor. One study in

the literature reported potential labor savings of up to 72% from use of automation in manufacturing of a similar autologous T-cell product [13]. Case studies on use of Lean manufacturing strategies in pharmaceutical and medical device manufacturing have reported labor savings ranging from 20-50% [14,15]. Novartis scientists have reported reductions of up to 80% in flow cytometry sample preparation and analysis time through use of an automated flow cytometry analyzer [16], and case studies of Manufacturing Execution Systems (MES) report reductions in documentation issuance of 60–75% [17]. We further posited that use of electronic batch records and digital supply chain management systems could deliver similar efficiencies in materials release, batch record review, and supply chain management, and that process validation could be used to reduce skilled labor touchpoints as processes mature. We therefore modeled the COGS impact of labor productivity improvements of up to 70% across manufacturing, QC, QA and supply chain management functions through the combined impact of validation and automation improvements.

Not surprisingly given the significant contribution of labor costs, the impact of productivity improvements on COGS was substantial (Figure 5). For example, in our 'base case' assumption of 80% capacity utilization, a 50% increase in labor productivity across manufacturing, QC, QA and supply chain management functions led to a 35% decrease in overall product COGS from $58,200 to $37,600 per patient. Additionally, the reduction of labor costs had a compounding effect on COGS reduction, reducing both cost per lot and risk of COGS increases due to capacity underutilization (as shown by convergence of the lines at the right end of the chart in Figure 5).

Compounded Effect: A 'Best Case' COGS estimate

We next evaluated the compounded impact of multiple improvements to determine a 'best case' COGS estimate for a highly optimized process. For this analysis, we assumed: a target capacity of 5,000 lots per year; 100% capacity utilization; implementation of automation, lean manufacturing and digital technologies to achieve 70% productivity improvements across manufacturing, QA, QC and supply chain functions; a 50% drop in facility cost per lot due to more efficient facility utilization through automated manufacturing; and a 30% drop in materials costs due to economies of scale and negotiation of bulk purchasing discounts. The compounded effects of these many improvements brought COGS down to $21,400 – a substantial improvement, but still predictive of a price above $100,000 at typical biopharmaceutical gross margins. We conclude that, while significant improvements in COGS are feasible, ultimately more substantial changes such as transitioning to allogeneic platforms may be necessary to make C&GT products affordable for very large indications such as stroke, heart failure or diabetes.

CONCLUSIONS

Although the rare indications of currently marketed gene modified cell products make an immediate affordability crisis unlikely, it will be critical to bring down costs substantially

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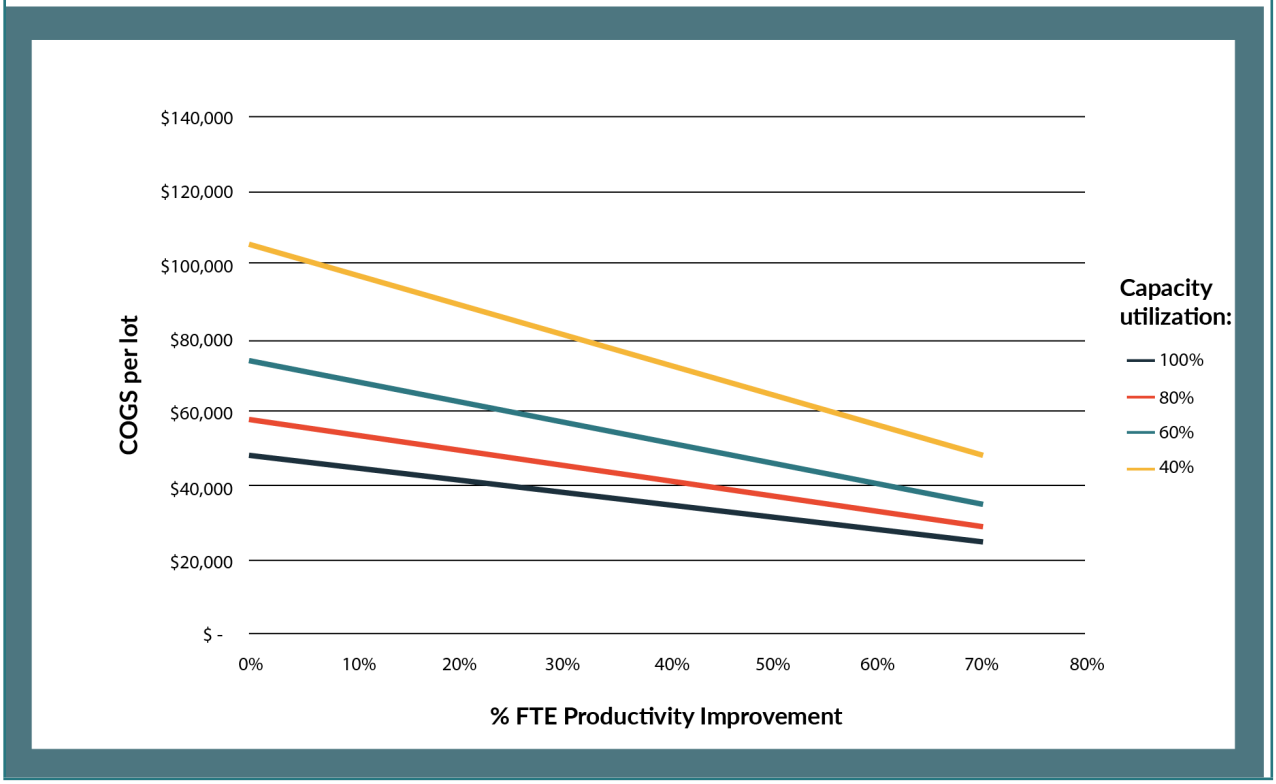
FIGURE 5

Cost of goods as a function of productivity improvement and capacity utilization (at target capacity of 1500 lots/year).



in order to affordably address more prevalent indications. By our calculations, current cost of goods for gene modified cell products leave little room for price reduction without disincentivizing investment in this important class of therapies. Furthermore, companies take on significant margin risk due to the need to build capacity well in advance of achieving clarity regarding commercial demand. Economies of scale are unlikely to deliver sufficient COGS improvements to enable affordable manufacturing of autologous gene modified cell products for larger indications. We predict that significant COGS improvements are achievable, but that innovation on multiple fronts will be required to achieve the level of dramatic COGS reduction required to make autologous gene modified cell therapies substantially more affordable than they are today. We propose that the keys to reducing both COGS and COGS associated risk are efficient capacity utilization, use of productivity enhancing technology solutions to reduce fixed labor costs, and establishment of rapid and efficient training programs to enable a more nimble response to evolving demand forecasts.

FINANCIAL & COMPETING INTERESTS DISCLOSURE

The authors are employed by Dark Horse Consulting, a provider of consulting services to the Cell and Gene Therapy field. No writing assistance was utilized in the production of this manuscript.

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