



Chimeric antigen receptor–T cell therapy manufacturing: modelling the effect of offshore production on aggregate cost of goods

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Abstract

Cell and gene therapies have demonstrated excellent clinical results across a range of indications with chimeric antigen receptor (CAR)–T cell therapies among the first to reach market. Although these therapies are currently manufactured using patient-derived cells, therapies using healthy donor cells are in development, potentially offering avenues toward process improvement and patient access. An allogeneic model could significantly reduce aggregate cost of goods (COGs), potentially improving market penetration of these life-saving treatments. Furthermore, the shift toward offshore production may help reduce manufacturing costs. In this article, we examine production costs of an allogeneic CAR–T cell process and the potential differential manufacturing costs between regions. Two offshore locations are compared with regions within the United States. The critical findings of this article identify the COGs challenges facing manufacturing of allogeneic CAR–T immunotherapies, how these may evolve as production is sent offshore and the wider implication this trend could have.

Key Words: cell therapy, chimeric antigen receptor, chimeric antigen receptor–T cells, manufacturing, offshoring, production management, logistics, supply chain

Introduction

The recent approval by the U.S. Food and Drug Administration (FDA) of the first chimeric antigen receptor (CAR)–T cell therapies [1,2] marks a significant step toward the emergence of a new paradigm in cancer treatment. Because these therapies have only recently made their way out of investigational clinical trials, overall production volumes remain small and many questions on reimbursement have yet to be resolved [2]. Nevertheless, the robust clinical pipeline of CAR–T cell therapies from a number of developers coupled with the promise of more approvals will create the need for scalable, robust and cost-effective manufacturing and supply chain models that do not compromise therapeutic efficacy or patient safety [3].

To date, CAR–T cell therapies have largely been developed and commercialized on the basis of an

autologous model, whereby a patient's own cells are extracted, manipulated *ex vivo* and then re-infused. Furthermore, CAR–T cell therapies have been manufactured in centralized facilities, with the patient's apheresis product being transported either fresh or cryopreserved from the clinical facility to a manufacturing facility and back. This mode of production has been associated with high per-unit manufacturing costs, leading many to seek ways of containing key cost drivers, including ancillary materials, transportation and logistics and skilled labor [4].

The primary aim of this article is to identify how trends in the production of CAR–T cell therapies, namely, the development of an allogeneic model reliant upon donor cells, the geographic dispersion of production and consumption and the decreasing cost of ancillary materials, are likely to affect overall cost of goods (COGs), thereby potentially facilitating

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greater market penetration of these new life-saving treatments. A process economics modelling and calculation tool is used to model how CAR-T cell therapy production costs change in light of these trends. The results of this study are significant beyond CAR-T cell therapies because therapies developed on the basis of other cell types will face similar challenges as they reach market and seek ways to reduce manufacturing costs.

Current Manufacturing Strategies for CAR-T Therapies

Today, cell and gene therapies follow one of two main modes of production, which differ in regard to the source of the cells used to manufacture these therapeutic products. Autologous therapies involve the extraction, manipulation and re-infusion or re-administration of a patient's own cells, whereas allogeneic therapies use previously extracted and banked donor cells, making them more akin to an off-the-shelf product. These two main modes of production are used for therapies involving various cell types, including T cells, natural killer (NK) cells and mesenchymal stromal cells.

This article focuses specifically on CAR-T cell therapies due to their new arrival in the market and acute need for a commercially sustainable manufacturing and supply chain model. Current manufacturing strategies for CAR-T therapies

involve harvesting T cells, which are subsequently genetically modified and expanded *ex vivo*. This expanded product is then re-infused back into the patient from whence the cells first came. Harvesting and re-infusion are currently carried out in a clinical environment whereas manufacturing is conducted in a specialized current Good Manufacturing Practices (cGMP) facility [5].

It has been suggested that, given the logistical challenges and shipping costs, decentralized manufacturing of these therapies within the clinic or hospital may be both feasible [4] and cost effective [6,7]. Indeed, this proposal is attractive given the role of the patients' own material in the production of these therapies. Nevertheless, commercial CAR-T cell therapies such as Gilead's Yescarta (axicabtagene ciloleucel) and Novartis's Kymriah (tisagenlecleucel) are manufactured in large facilities located in El Segundo, California (Yescarta) and in Morris Plains, New Jersey, with additional manufacturing capacity in Leipzig, Germany (Kymriah).

Centralized manufacturing is likely to persist in the near term, given the difficulty of implementing commercially compliant quality control (QC) and quality assurance in multiple locations, as well as the relative ease and efficacy with which the cells collected by apheresis and the final CAR-T cell product can be cryopreserved and thawed [8]. Even with allogeneic sourcing of cells, which may eliminate the need for time-sensitive logistics to the manufacturing

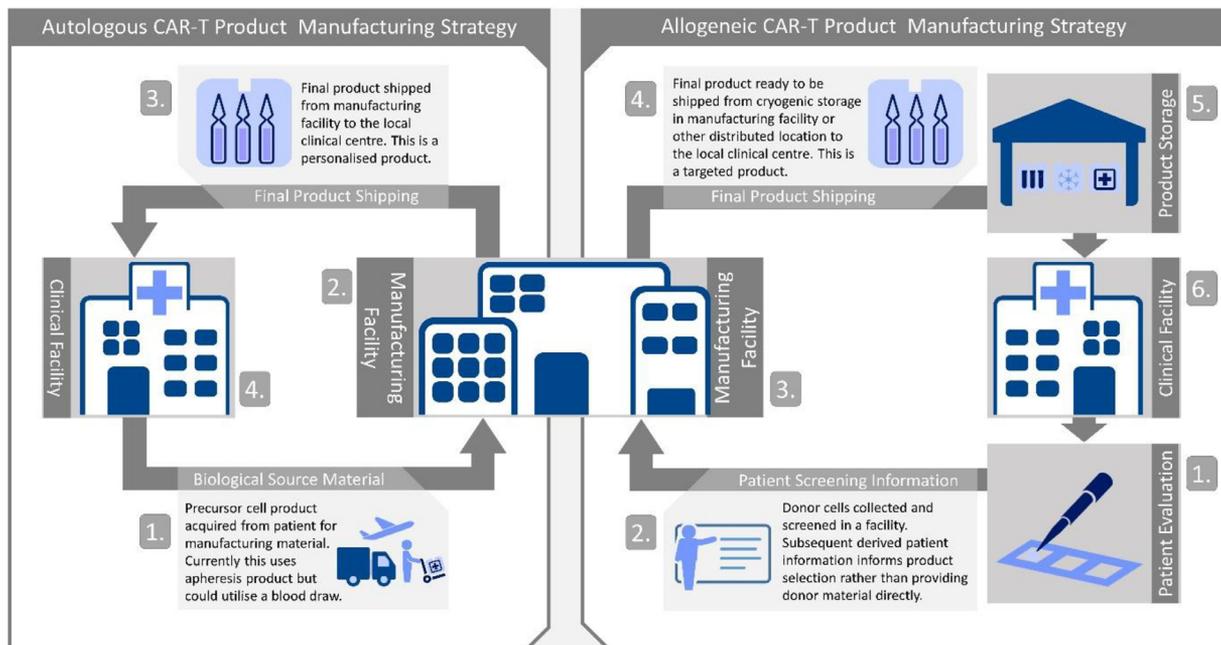


Figure 1. High-level process overview representation of autologous and allogeneic CAR-T therapies. Current developers are using apheresis products as manufacturing starting material. However, it may be possible to substitute this with a blood draw. For allogeneic manufacturing processes, patient material will be evaluated to inform product selection, which may be shipped from a storage facility directly rather than made-to-order. Manufacturing of product may take place at a centralized facility or a decentralized facility.

site where cells are harvested and banked, centralized manufacturing should be favored (Figure 1). Furthermore, the development of an allogeneic model enables the production of multiple doses from a single source, facilitating greater economies of scale, supporting production scale-up rather than scale-out.

Toward a Novel CAR-T Manufacturing Paradigm

Changes in the way that CAR-T cell therapies are produced and delivered will have an impact on the overall COG. With allogeneic production, many doses are produced from each donor, lowering unit costs considerably. Furthermore, we assume that the growth of the cell and gene therapy market will mean new entrants and greater competition, thereby lowering the cost associated with producing ancillary materials under cGMP, assuming no shortages (i.e., certain human-derived products).

The geography of production will continue to evolve as a result of the dynamic relationship between transportation and automation. On the one hand, the stable nature of cellular products that can be cryopreserved without significantly affecting potency and the high rate of recovery upon thawing provide a potential opportunity to relocate production ever further from the end user. This will enable manufacturers to explore alternative methods to control COGs – by relocating production to low-cost locations – without compromising quality. However, moving production further afield, although technically feasible, will likely lead to increased transportation costs and may introduce delays at border crossings.

Furthermore, the cost savings associated with shifting production offshore may be short-lived as an increasing proportion of the production process is automated. CAR-T cell therapy manufacturing has become decidedly more automated with the development and deployment of new equipment that encapsulates an increasingly diverse array of functions, such as Miltenyi Biotec's CliniMACS Prodigy System. By consolidating key processes, such as liquid handling and some in-process manipulations, COG values for academic dose production have been quoted as low as \$6000 [6] to \$20 000 [7]. These values do not, however, compare to similar costs incurred by approved products because they lack research and development costs, overheads, labor, facility costs, QC and analytics, FDA monitoring, licenses and royalties, clinical site onboarding, shipping and logistics as well as the profit margin.

Despite advances in process automation, critical steps in commercial cell therapy manufacturing, including QC, quality assurance and analytical

testing, still depend on human labor [9,10]. Furthermore, activities, such as research and development, regulatory affairs, ongoing FDA-mandated monitoring of gene-modified products (15 years), intellectual property management, clinical site onboarding and management and shipping and logistics, among others, are difficult to automate.

The bespoke nature as well as the high cost and complexity associated with the current manufacturing model may limit market penetration and long-term sustainability. For this reason, there are efforts underway to address the most significant cost and risk drivers in the production of CAR-T cell therapies: single dosing associated with the autologous model, the production of qualified ancillary materials [11], transporting cryopreserved materials across large geographic distances [12] and hiring and retaining skilled labor. These efforts affect each other and the overall COGs associated with CAR-T cell therapy manufacturing in complex ways, as the tradeoff between offshore production and automation demonstrates.

Modelling a New CAR-T Manufacturing Paradigm

This article models how changes to the traditional CAR-T cell therapy manufacturing paradigm are likely to affect COGs. It considers how the development of an allogeneic production model, the potential relocation of production to lower cost domestic locations and offshore to other countries, as well as the reduced cost of critical ancillary materials interact with one another and, more broadly, shape COGs as a whole.

The analysis uses a process economics modelling and calculation tool developed to examine COGs for production of advanced therapies [12,13]. The eligible patient market was calculated for the USA by examining the number of patients with blood cancer per year (171,000) [14], assuming that allogeneic CAR-T therapies could capture 30% of this market and further assuming that a new therapeutic provider could capture 35% of this market. These values were then applied proportionate to the population for all of the countries in the modelling exercise with the exception of China where a new therapeutic provider was assumed to capture 5% of the domestic market. A further breakdown of numbers can be located in the supplementary information. Manufacturing capacity required is calculated based on producing approximately 18 000 to 60 000 doses/annum to meet these patient numbers.

Labor calculations and employee numbers were estimated following personal communications with contract manufacturers. Facility and equipment are

amortized over 10 years as suggested by the World-wide Capital and Fixed Assets Guide [22]. Labor and equipment have a 25%+/- margin for error on idle capacity and use at any given time period over the projected roll out period. Loan agreements are assumed at 10 years, with 5% interest. An investment discount factor is not applied. Staffing costs are calculated per salaried full-time individual at a given band within the company. Administrative costs are captured solely in the employment of administrative staff and associated training, not through any other costs or multipliers. Research and development costs, licensing, royalties and sales costs are not captured by this model. A further breakdown of costs is located in the supplementary information.

The manufacturing process examined here involves the production of an allogeneic CAR-T cell therapy manufactured in a central manufacturing facility using healthy donor-derived material. The benefit of choosing a healthy donor to a multiple-patient therapeutic model rather than a patient-specific one is to study the simpler case before turning in due course to the complexity of autologous supply with increased costs [15,16].

Scalable cell-processing technologies have been identified as a key factor in driving down the manufacturing costs for cell therapies [17,18]. For autologous CAR-T cell products, these platforms are likely to be smaller scale and modular with isolated product streams to separate out the batches and to allow efficient line-clearance procedures [19]. For allogeneic second-generation CAR-T products, the number of patients able to receive the product is higher and consequently the production scale will be similarly larger.

While there are few regulatory hurdles associated with moving production to lower cost locations domestically, there are several challenges associated with offshoring production. The movement of living cells and tissues across borders is subject to scrutiny on the part of national regulatory bodies such as the FDA in the United States and requires international harmonization of regulatory requirements to ensure the fluid movement of intermediate and final goods. Recent efforts by the International Standards Organization (ISO) to codify standards for cell transportation are likely to enable greater integration across countries moving forward.

Similarly, a recent position paper by the FDA has outlined alternative development pathways for advanced therapies [20], permitting multiple manufacturers to produce biologics under the same protocol and then treat patients enrolled in clinical trials at their individual sites. In this case, safety and efficacy data are pooled from all sites, and submitted as part of the biologics application for each individual site.

This direction of travel highlights the recognition by stakeholders that advanced therapies differ from traditional pharmaceuticals and thus require their own set of flexible regulatory, oversight and control mechanisms.

To study the efficacy of offshore CAR-T cell therapy manufacturing, we model the manufacturing process in four distinct geographies: Cambridge, Massachusetts (USA), Manchester, New Hampshire (USA), Monterrey, Nuevo León (Mexico) and Buenos Aires, Buenos Aires (Argentina). These geographies are selected to create variation in key variables, such as labor cost, transportation cost and facility cost, allowing us to understand how much of a cost driver these factors are in cell therapy manufacturing. These locations are not selected as final markets, but as manufacturing locations for therapies to be commercialized in the US market. They do not necessarily represent existing cell therapy manufacturing hubs, but their characteristics enable variance along dimensions that support the article's approach.

Given its strong biotechnology innovation ecosystem and focus on biomanufacturing, Cambridge serves as a case study representing onshore production. Manchester serves as a lower cost location with a significant role in the regenerative medicine industry given the newly established Advanced Regenerative Manufacturing Institute (ARMI). Monterrey's strong industrial base and engineering talent, proximity to the US market and harmonization on trade make it a viable low-cost nearshoring destination. The final case study is Buenos Aires, which serves as a viable offshore location because of its biomanufacturing base and lower cost of labor. We make a series of critical assumptions in our modelling exercise: we assume that these four locations have sufficiently large pools of skilled labor that vary primarily in regard to average wages, and that they all have qualified space for biomanufacturing that vary only in regard to price. By selecting onshore, nearshore and offshore cases, we include a number of variables, including cost of labor, cost of qualified space and cost of transportation and logistics for inbound and outbound clinical products. A process flow diagram outlining the hypothetical manufacturing strategy described is presented in [Figure 2](#).

Results and Discussion

Manufacturing strategies for CAR-T cell therapies are still in their infancy and undergoing rapid change. Historically, cell-manufacturing platforms have been developed using technology adapted from biopharmaceutical production. Consequently, there has been significant room for further optimization and improvement, which are only beginning to be

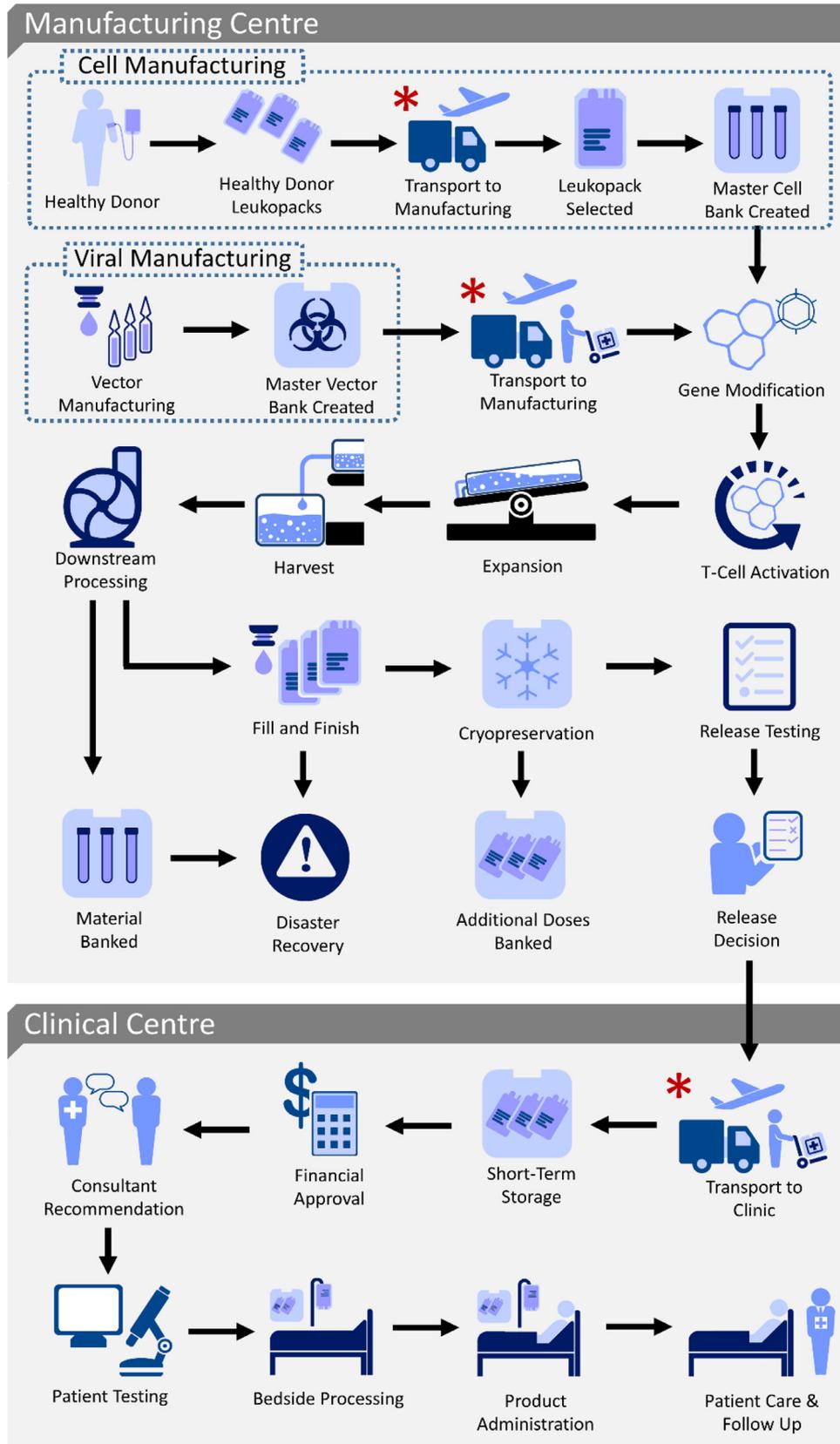


Figure 2. Process flow diagram for manufacturing of allogeneic CAR-T cellular therapies. Items in the dotted-line box are obtained from inventory rather than produced routinely as part of the process. Transport steps are highlighted (red asterisk); inbound clinical products are modelled as originating in the USA with outbound clinical products scheduled for delivery to clinical locations in each country.

fully exploited. Looking forward, we are likely to witness significant improvements in reproducibility and replicability of manufacturing platforms as well as improvements in scale-up technologies for allogeneic products and scaled-down separate production streams for autologous. In this section, we present the results of the modelling exercise, and discuss implications of this work for cell therapies and regenerative medicine more broadly.

Autologous versus allogeneic

Autologous CAR-T therapy has several advantages over allogeneic in its mechanistic approach to treatment. Autologous products taken from the patient's own cells possess the ability to re-engraft within the host and persist long term, providing a durable response. Although this effect is likely to be absent from allogeneic approaches that use master banks of donor leukocytes, there are significant COG reduction advantages to be gained with deriving multiple therapeutic doses from a single manufactured batch (Figure 3). This COG reduction stems chiefly from the ability to spread the high initial cost of the donor materials and subsequent selection and enrichment, as well as the associated batch QC across a larger number of doses.

Staff and site costs

Two of the key cost drivers underlying operating expenses for manufacturing cell and gene therapies are staff and facility costs. Offshoring presents opportunities to reduce these operating expenses both through direct reductions in the workforce payroll, and also through reduced site costs from

cheaper office space and facilities management. Staff and site costs were modelled for the four regions (Figure 4). Significant reductions in staff costs were demonstrated for Monterrey, Mexico (4.34 million US\$ per year (M\$/y) and Buenos Aires, Argentina (4.57 M\$/y) versus the two USA-based regions Cambridge (17.53 M\$/y) and Manchester (12.26 M\$/y). Potential reductions on site costs were significantly less with Mexico (2.95 M\$/y) and Argentina (2.83 M\$/y) versus Cambridge (3.3 M\$/y) and Manchester (3.2 M\$/y).

Consumable costs

Although site and staff costs are significant monetary expenditures on aggregate, these costs are relatively minor contributors to the final headline figure dose cost. Indeed, under the manufacturing scenario examined, consumables account for a far higher proportion of dose cost than site and staff costs (Figure 5A). Indeed, the cost of consumables increases as a therapy makes its way through the clinical pipeline and regulators begin to demand that manufacturers shift from research-grade to cGMP consumables. It is yet unclear how the cost of consumables will change as the industry matures. While we may see economies of scale-driven cost reductions with increased approvals, they will likely not lead to lower prices without increased competition in the supply base.

The sensitivity analysis (Figure 5B) presents increasing and decreasing material COGs relative to current prices and highlights the significance of these potential reductions or increases in consumable COGs to the final unit price. Furthermore, these reductions would elevate the importance of staff

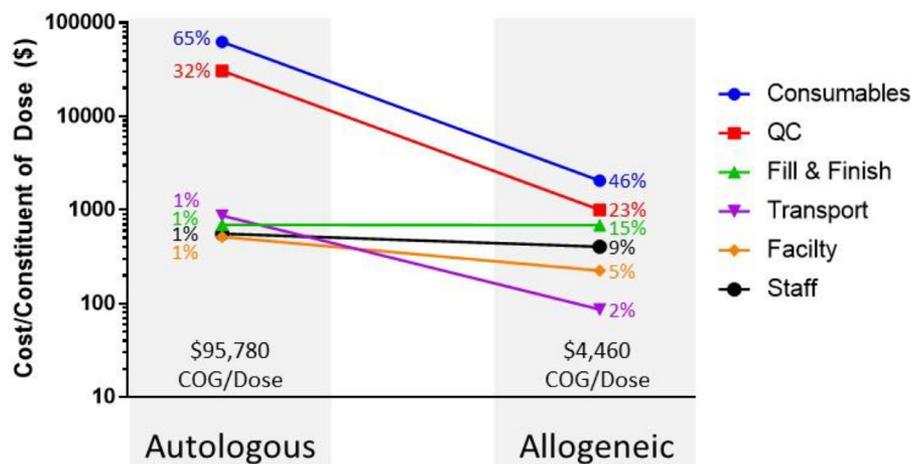


Figure 3. COGs between autologous and allogeneic CAR-T cell manufacturing processes. The process modelled used an 8- (auto) and 10- (allo) day manufacturing process with an identical facility structure and QC panel. Staffing levels were similar but additional operators were present for the autologous process. Percentages shown as portion of total production COGs.

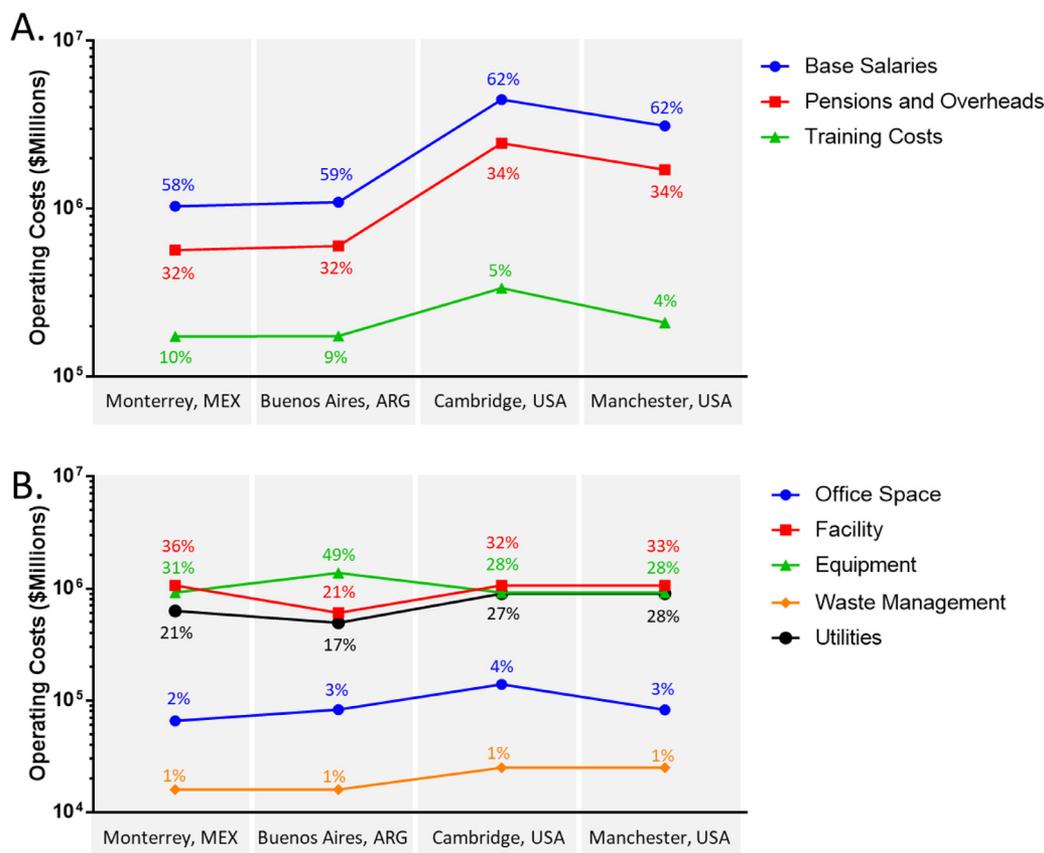


Figure 4. Staff (A) and site (B) costs between regions. Employment numbers remain constant between regions. Wage metrics were adjusted using local wage indexes. Percentages shown as portion of total operating costs per year.

costs (and to a lesser extent facility costs) as contributors to the final unit price. With reductions of 80–90% on consumable COGs, staff costs increase four-fold in their contribution to unit cost at ~20% of the total in Cambridge. This makes the potential cost savings to be obtained through offshoring dramatically more appealing, at least temporarily. The reduction in the weight of consumables on aggregate COGs and increased weight of staff and facility cost would strengthen the business case for greater automation in the production process while simultaneously eroding the business case for offshoring.

Ramping up production

A phased roll-out of an allogeneic CAR-T cell therapy is presented in Figure 6. This examines a theoretical cash flow, doses shipped and average COGs/dose over a 10-year duration. Notably, research and development costs as well as any licensing fees and royalty costs are excluded from the cash flow, which could significantly influence the upfront costs prior to “year 0”. As the roll-out progresses to new markets and doses shipped increases, there is a marginal but statistically significant decrease in COGs/dose.

More significantly, it is important to note that the COGs between sites converges as roll-out progresses (minimum/maximum Tukey plots). This suggests that, as the product landscape matures, the difference in production costs between regions will become less apparent.

Conclusions and Future Outlook

Despite the evident challenges associated with transferring even simple processes between multiple sites [21], standardized production facilities and associated quality systems have been established by both cell and gene therapy developers and contract manufacturing organizations across continents. Similarly, solutions such as ThermoFisher’s CryoHubs, World Courier’s Logistics Platform and the Trakcell and Vineti orchestration platforms are helping to establish robust supply chains to support the movement of goods. Investment has also taken place within the clinic itself, particularly in the UK with the establishing of Advanced Therapy Treatment Centers at distributed clinical locations to create seamless supply chains from harvest to release of cell products [4]. These key

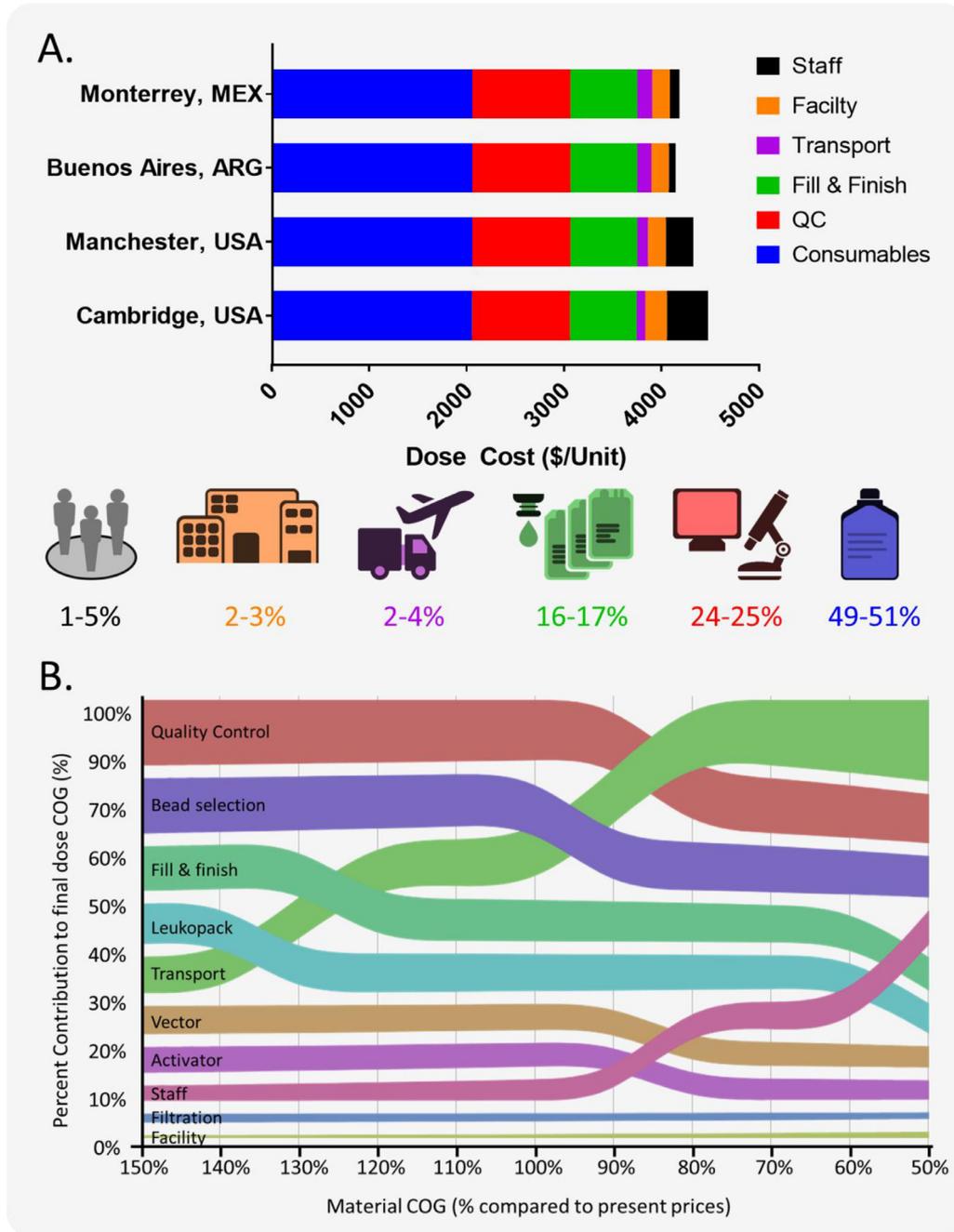


Figure 5. Breakdown of cost per dose shipped between regions (A) and a sensitivity analysis of changing consumable costs (B). The sensitivity analysis (B) examines percentage cost increases or reductions to material COGs. The X-axis examines progressive COGs reductions in all consumable materials used in the process from 100% (current prices) up to 150% (equivalent to a 50% increase on current prices) and down to 50% (equivalent to a 50% discount on current prices). At this 50% discount, transport becomes the largest contributor to cost of goods and staff moves from being 11% of dose cost to 25% (in Cambridge, Massachusetts), significantly increasing its relative percentage contribution to final dose price. These figures do not include any potential savings realized through increasing economies of scale as doses shipped across the advanced therapy industry increase. Unforeseen challenges such as customs barriers, which might affect inbound raw materials, including virus to offshore sites, are not captured. QC, patient qualification tests and release testing are not included in these costs. Percentages shown as portion of total production COGs per dose unit.

developments minimize variation and help ensure reproducibility across the value chain.

Although the systems are in place to facilitate offshoring, the burden of risk and associated unknowns

make the prospect unappealing at present given the small current potential savings in operating costs versus additional complexity in operations management. Furthermore, the trend toward greater process

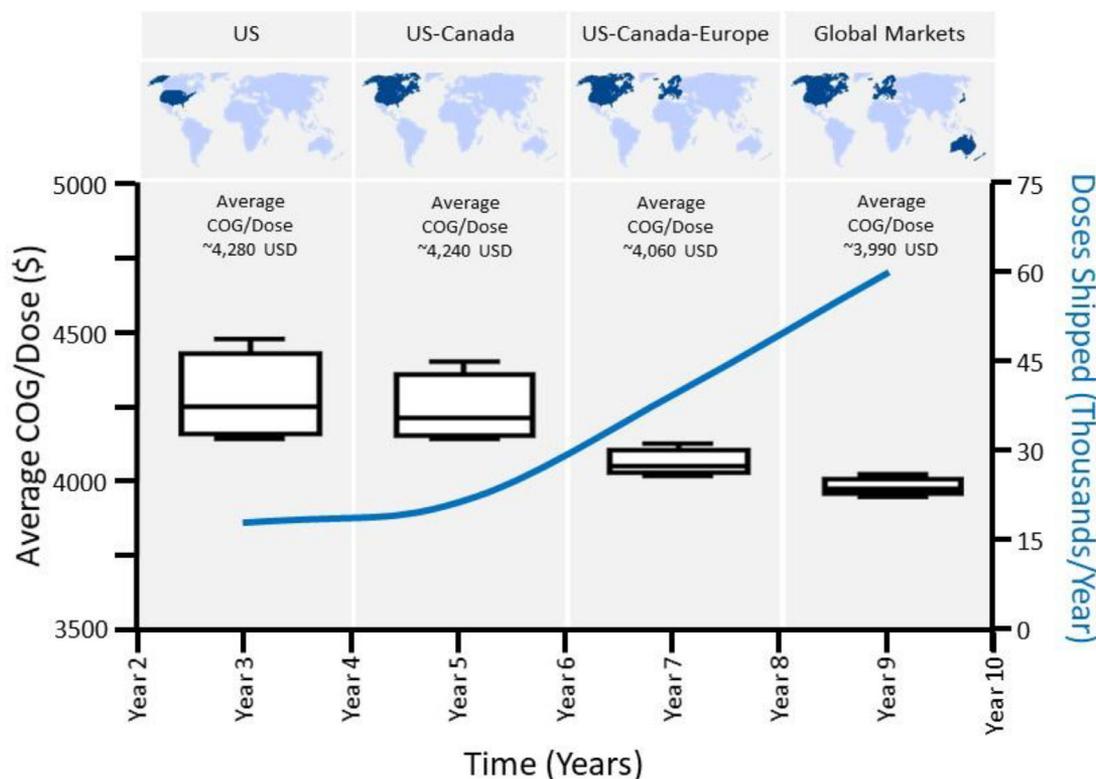


Figure 6. Examining the progressive global roll-out of an allogeneic CAR-T therapeutic. The COGs/dose is presented as an average of all four sites (Boston, USA, Manchester, USA, Monterrey, Mexico and Buenos Aires, Argentina). COGs ranges between \$4280 and \$3990 with a lower standard deviation between the costs of manufacturing site locations as roll-out progresses. No reductions in consumable costs or shipping costs over time are accounted for. Box plots are presented as minimum/maximum Tukey plots.

automation may eventually erode any marginal benefit associated with lower labor costs in offshore locations. Finally, the commercial manufacturing model for cell and gene therapies may require the creation of more contained production systems. In the automotive industry, the difficulty of transporting the final product encourages companies to assemble cars where they sell them, although many components and subsystems may still be imported.

Cell and gene therapy manufacturing may eventually adopt a similar model, albeit for different reasons. Here the cross-border movement of cells creates a series of regulatory and cost-related challenges. For example, clearing customs is a non-trivial task, especially when shipping personalized and perishable treatments. Finally, large and dynamic markets protected by strong industrial policy regimes may require domestic manufacturing to foster the development of a novel industry within their political economy.

This study has analyzed key forecasted trends in the production of CAR-T cell therapies, and how these trends are likely to shape production costs, thereby affecting the degree to which these therapies become commercial successes. Specifically, we have highlighted an allogeneic model

reliant upon donor cells, showing how the geographic dispersion of production and consumption and the decreasing cost of ancillary materials are likely to affect one another and further shape overall COGs. The modelling exercise and findings presented here have implications for other cell and gene therapies.

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Disclosure of interests: Richard Harrison conducted this work while working at Loughborough University and The University of Nottingham but has since moved to The Cell and Gene

Therapy Catapult. Ezequiel Zylberberg works with Akron Biotech, a manufacturer of ancillary materials used in the production of CAR-T cell therapies. Simon Ellison works for World Courier. Bruce Levine received consultancy fees from Brammer Bio and Incysus, has patents and royalties with and received research funding from Novartis Pharmaceuticals Corporation and holds equity ownership in and received research funding from Tmunity Therapeutics.

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Supplementary material

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