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ARTICLE

Autologous CAR T-cell therapies supply chain: challenges and opportunities?

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Abstract Chimeric antigen receptor (CAR) T cells are considered a potentially disruptive cancer therapy, showing highly promising results. Their recent success and regulatory approval (both in the USA and Europe) are likely to generate a rapidly increasing demand and a need for the design of robust and scalable manufacturing and distribution models that will ensure timely and cost-effective delivery of the therapy to the patient. However, there are challenging tasks as these therapies are accompanied by a series of constraints and particularities that need to be taken into consideration in the decision-making process. Here, we present an overview of the current state of the art in the CAR T cell market and present novel concepts that can debottleneck key elements of the current supply chain model and, we believe, help this technology achieve its long-term potential.

Introduction

Chimeric antigen receptors (CARs) are recombinant receptors for antigens that can make T lymphocytes tumourspecific. Through genetic modification, T cells are engineered to express the CAR receptor that redirects their specificity and function, enabling them to recognize and destroy cancer cells [1]. This individualised, emerging immunotherapy has shown promising results particularly in the treatment of B-cell lymphoma [2–4] and has encouraged further clinical research. In August 2017, the U.S. Food and

Drug Administration (FDA) gave an historic approval of the first autologous, cell-based cancer therapy that has potentially changed the future of cancer therapies. Trisagenlecleucel is an autologous CAR T-cell therapy for B-cell acute lymphoblastic leukaemia (ALL) and is the first such therapy to other innovative cancer treatments. Following that, Axicabtagene ciloleucel was approved by the U.S. FDA in October 2017. The therapy is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma. Both of the CAR T cell therapies are showing promising results with remission rates significantly higher compared to chemotherapy. Recently, both therapies received approval from the European Medicines Agency (EMA) [5]. The therapies are available through restricted programs (Risk Evaluation and Mitigation Strategies (REMS) for the USA and PRIority MEdicines (PRIME) for Europe [5–7]. Given their high manufacturing, distribution and administration costs the two marketed therapies are offered at a relatively high list price (around $475,000 for trisagenlecleucel and $373,000 for axicabtagene ciloleucel). The promising results of the two marketed therapies have encouraged further research in the field resulting in numerous clinical trials (Fig. 1) on both autologous and allogeneic products. Currently, China and the United States act as the main hubs, hosting almost 80% of the 317 global CAR-T clinical trials. Despite the fact that haematological malignancies represent only a small fraction of human cancer [8], they are

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at the forefront of clinical research for the advancement of cancer treatment (currently 233 listed clinical trials, 7 of which are on related equipment/procedure). On the other hand, the complexity in the characterisation of solid tumours (anatomic location, histology, immunohistochemical strains) and the lack of a single, direct CAR target, pose additional challenges related to on-target off-tumour toxicity [9]. Nevertheless, the documented CAR trials for solid tumours are currently 94, while clinical interest in these therapies is gradually growing. Current research is also focusing on advances in the use of different target antigens, aiming to develop CAR T cell therapies for other malignancy types [2]. Table 1 summarizes the main target antigens currently in study, and the targeted cancer type. Despite their initial success, CAR T cell therapies face a series of challenges that need to be tackled to facilitate and ensure their smooth and stable establishment in the drug market. Such challenges are associated with various steps throughout the CAR T cell therapies manufacturing, supply and licensing process. The manufacturing process of CAR T cell therapies is highly complicated, as it comprises a large number of steps which are challenging to perform and coordinate. In addition, processing steps are currently

operated in batch mode—often in different locations—thus increasing the complexity. Moreover, the supply chain model currently followed by the CAR T cell industry is able to serve a finite number of patients that does not go beyond the order of hundreds per region/country annually. Therefore, as we move forward with the likely establishment of CAR T cell therapies as key therapeutic options in cancer treatment, the current models will prove to be challenging to scale up (autologous processes cannot be scaled up volumetrically) and thus require significant improvements. Furthermore, challenges arise from the regulation and reimbursement procedures associated with CAR T cell therapies, as the latter are characterised by a significantly high cost and a complex chain of custody. The aforementioned challenges will become more profound as patient numbers increase. Taking the UK as an example, currently a maximum of 1000 patients are receiving CAR T cell therapies across all active trials, available at specialised centres that do not exceed the order of 10. However, based on reports by the HMRN Haematological Malignancy Research Network [10] and forecasts on the population that we performed in this work (Appendix A), these figures are expected to increase, as the population

Fig. 1 Map of clinical trials1 currently on chimeric antigen receptor T cell therapies (Source: ClinicalTrials.gov). The results were generated using “CHIMERIC OR CAR OR CAR T OR B-cell OR T-cell OR NHL OR FL OR HL OR HODGKIN OR SOLID AND CAR T-CELL” as search terms.

is growing, and CAR T cell therapies are likely to become available for other cancer types, potentially reaching 40,000 people by year 2031 (Appendix A). Furthermore, in an effort to maximise the success of the therapy with respect to the administration, the UK government awarded £21M through the Industrial Strategy Challenge Fund, with the creation of a UK-wide network Advanced Therapies Treatment Centres (ATTCs). ATTCs will be responsible for the supply, maintenance and delivery of those medicines in the NHS (Fig. 2). Each of the ATTCs are themselves formed of several

organisations (hospitals, research centres, industrial manufacturers), serving an extended geographical region (Fig. 2). Each ATTC is depicted using bubble size to illustrate the different number of collaborating hospitals in each ATTC. Despite the large number of total collaborating hospitals (approximately 29), there are areas that are underrepresented, such as London and South East England, as well as Northern Ireland. The emerging ATTCs strategy is a centralised model, where fewer, large ATTCs are established, each to serve multiple geographical locations. This may imply a necessary transition in the future, in order to create a scalable, decentralised delivery network, ensuring adequate supply for the rapidly increasing patient population. In this paper we identify and discuss challenges in CAR T cell therapy manufacturing and supply chain arising from: (a) the increasing demand, (b) the nature of the process and/ or product and (c) the increasingly complex logistics.

Autologous CAR T cells lifecycle: the current state-of-the-art

In order to understand fully the complexity of the supply chain and associated logistics in autologous CAR T cell therapies, it is important to map out the lifecycle of the therapy from collection to delivery (vein-to-vein). A typical lifecycle in autologous CAR T cell therapies comprises three main steps: (a) leukapheresis (cell collection), (b) therapy manufacturing and (c) therapy administration [11, 12]. The successful operation of such a supply chain model requires the orchestration of multiple components [13]. In a typical supply chain model in the pharmaceutical industry

there are typically established warehouses/distribution centres in place, responsible for the storage and distribution of the manufactured drug to the retailers. By contrast, in the case of CAR T cells, cells are transported directly from the clinical site to the manufacturing locations and back to the hospital, thus imposing additional constraints with respect to storage, activity coordination and sample tracking.

Manufacturing

CAR T cell therapy manufacturing is the lengthiest and most important step of the lifecycle (Fig. 3). Following the collection, the sample is transferred to the manufacturing site, where it undergoes a series of processing steps, to express successfully the CAR receptor. Once the product is formulated, it is assessed through Quality Control (QC) for the identification of the Critical Quality Attributes (CQAs) to ensure drug efficacy, potency and safety [12, 14]. Following Qualified Person (QP) release, the product is transferred to the clinical site, where it is administered to the patient. The end-to-end process for the two leading market products are reported to have target median turnaround times of 17 and 22 days for axicabtagene ciloleucel and trisagenlecleucel respectively [15–18]. Here we give an overview of the procedures followed in: (a) the leukapheresis clinical site, (b) the manufacturing site and (c) the administration clinical site.

Clinical site for collection

The leukapheresis (Fig. 3) procedure takes place at a specialized clinical site. Patient blood is extracted and the leucocytes are separated, while the remainder of the blood is returned to the patient's circulation [12]. Following that, the sample is transferred to the manufacturing site for further processing. The sample can be transferred either frozen (−80 oC) or cryopreserved (−180oC). This is a choice that depends on the manufacturer and the procedure that has received regulatory authorisation. In general, cryopreservation is preferred in terms of shelf-life as it allows a more flexible transport/treatment window, compared to the fresh product that has a strict 24-h upper storage limit. Specifically, cryo transport systems can maintain temperature and quality for 10–14 days.

Table 1 Antigen types currently under study and the targeted cancer type (list based on results on clinical trials currently in place).

Cancer type Antigen

B cell malignancies CD19, CD20, CD22, CD23, CD30, ROR1, kappa light chain, PD-1 AML CD28, CD128, CD33, CD44, CD44v6, NKG2D Hodgkin Lymphoma CD30 T cell malignancies CD5, CD30 Myeloma CD138, CS-1, CD38, NKG2D, CD44v6, BCMA, CD19 Solid tumours anti-HER2/neu, EGFRvIII, GD-2, CEA, FAP, Glypican 3, Mesothelin, IL13Ra2

Autologous CAR T-cell therapies supply chain: challenges and opportunities?

Manufacturing site

At the manufacturing site, cells undergo a series of modifications (enrichment, activation, genetic modification,

expansion, formulation, and cryopreservation) until the final product is ready to be shipped to the hospital for administration. Most of the manufacturing steps are based on the supply of commonly available raw materials, such as

Fig. 2 Visual representation of the advanced therapies treatment centres in the UK. Bubble sizes refer to the different number of hospitals in each region.

Fig. 3 Current CAR T-cell process/distribution steps along with key bottlenecks and challenges.

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medium, cell washing accessory sets and selection reagents. One of the key steps in the manufacturing of CAR T cell therapies is that of the genetic modification (Fig. 3, Point 2). This processing step is responsible for the transduction of the patient T cells with the CAR receptor. This can be performed using either viral or non-viral gene transfer systems, with the former being the current standard practice. Following the successful completion of those steps, the final product is then assessed through Quality Control/Assurance, cryopreserved and transferred to the administration site. It should be underlined that QC/QA can be performed either in the manufacturer's facilities or outsourced to a third party.

Clinical site for administration

Following successful release of the therapy, the product is shipped to the hospital, where it is thawed and administered to the patient (Fig. 3). This step is usually coordinated with the progress of the patient's medical condition as it requires approximately 1 week of pre-conditioning, prior to the administration of the therapy.

Materials management

A complete vein-to-vein procedure requires the availability of various input materials for the successful execution of each process step (Table 2). As product demand scales up, management of the input material supply chain will become more important. Special focus should be given to the step of "genetic modification", performed using viral vectors. The latter are complex products, characterised by lengthy

manufacturing procedures (approximately two weeks) and a separate supply chain model. Thus, it is imperative to estimate the demand, in order to ensure that raw material shortage will not become a bottleneck.

Storage and transportation

Similar to the QC/QA, depending on the business model adopted by the manufacturer, storage facilities are either owned by the manufacturer or rented from a third party. Due to the short product shelf-life (i.e. 24 h for fresh product), long storage times are not advised. Based on the process stage and the condition (fresh or cryopreserved), samples/therapies are transferred in dry shippers in order to ensure that temperature conditions are maintained at required levels. Transportation from one site to another can be by road or air. The choice of the most suitable transportation mode is often based on: (a) location of sites, (b) time restrictions and (c) weather conditions. Given the criticality of the condition of patients treated with CAR T cells, it is imperative that the therapy turnaround time is minimised. Therefore, improvements both in storage and transportation that can decrease waiting times can maintain the efficacy of the therapeutic treatment.

Autologous CAR T cells lifecycle: risks and challenges

Given the product nature and complex supply chain model, CAR T cell therapy commercialisation is currently a challenging task. Issues may arise from different aspects, such as: (1) manufacturing, (2) supply chain, (3) business models, (4) reimbursement and (5) clinical adoption. Here we focus on challenges arising from the current supply chain/ business model and we present an overview of risks associated with the rest of the factors. Aiming to understand better the various design and manufacturing decisions, as well as the process and other steps followed today in CAR T cell therapy manufacturing, we formulate a Resource Task Network (RTN) [19] (Fig. 4). The network depicts all key processes in place in CAR T cell therapy manufacturing, along with the chosen technology/procedure, intermediate products, as well as required raw materials. The complexity of the process in terms of task coordination and material supply is evident. Moreover, key decisions need to be made with respect to the condition of the leukapheresis sample. The latter can be transferred from the clinical to the manufacturing site either cryopreserved or frozen. The two alternatives imply significant differences in the supply chain model and the required processing times.

Table 2 Materials as they are required for the completion of each process steps in the manufacturing of CAR T cells.

Process step Raw material

Leukapheresis • Selection accessory set • Components for selection medium • Selection reagents Activation and enrichment • Anti-CD3/anti-CD28 antibodies Genetic modification • Non-viral gene modification reagents (e.g. DNA plasmids, RNA) • Viral Vectors Expansion • Components for expansion medium (e.g. X-VIVO15, IL-2, other cytokines) Formulation (washing concentration) • Cell washing accessory sets • Components in cell washing medium (e.g. phosphate buffer saline) • Components in formulation medium Cryopreservation • Components used in cryopreservation medium (e.g. dimethyl sulfoxide)

Autologous CAR T-cell therapies supply chain: challenges and opportunities?

Supply chain and business model

The supply chain model currently followed in CAR T cell therapy manufacturing faces significant challenges related to scale-up/-out, timely delivery and cost. Moreover, aspects of primary importance in the design of an efficient supply chain network are: (1) sample tracking, (2) package & shipping, (3) storage & equipment validation and (4) chain-of-custody documentation. However, for a successful supply chain model, decisions on the aforementioned aspects need to be taken considering the particular product nature. In common with every other cell-based product, CAR T cells are easy to destroy due to mishandling, leading to contamination, loss of functionality or de-differentiation. Moreover, they are sensitive to temperature and stress, thus requiring experience in handling during transportation. Such risks are not always trivial, as mitigation strategies require trained personnel to be present along the journey of the sample/therapy, which may not always possible. Moreover, when designing the supply chain model, one needs also to consider the short product shelf-life that significantly restricts waiting/storage times. Furthermore, in autologous CAR T cell therapies, the patient becomes their own donor, which automatically makes the patient part of the supply chain. Patient scheduling is therefore necessary to ensure that times between collection and manufacturing, as well as product release and administration are minimized. Lastly, in autologous therapies any lost sample and/or

therapy cannot be replaced from stock, as each therapy is patient-specific and follows a one-to-one model. When designing the supply chain and business model of CAR T cells, one of the key limitations that we encounter is time. Due to their nature, those therapies are accompanied by tight shelf-life windows, imposing solutions where processing, storage and shipping times must be tightly controlled. Especially in cases where the product is transferred fresh (i.e. not frozen) from leukapheresis to manufacturing, laytime should not exceed the 24-h window. In addition to time restrictions, Table 3 illustrates five main risk factors that need to be considered during CAR T cell therapy manufacturing, release and administration. One of the most important characteristics in the supply chain model of CAR T cell therapies is sample tracking (sample and patient identification). Starting with sample identification, it is evident that each product (i.e. the sample) needs to be efficiently tracked throughout the process. The tracking required here is bi-directional as it must be ensured that the right therapy will be delivered to the right patient at the end of the product cycle. Due to their autologous nature, such products do not allow errors in tracking traceability and this factstressesthe need for cloud-based platforms and application programming interfaces. The latter will allow disparate systems and information provided by stakeholders to be connected seamlessly and shared, leadingto more efficient, low-risk sample tracking. As expected, patient identification is of high importance during cell harvesting, product release and treatment. During those

Fig. 4 Resource Task Network (RTN) for the CAR T cell therapy supply chain.

stages, the patient needs to be identified and linked to the sample, in order: (a) for the sample to receive the patientspecific identity that is required (cell harvesting) and (b) to ensure that the patient-specific identity will be maintained, and the right therapy will return to the right patient (product release & treatment). Moreover, packaging & shipping as well as storage & equipment validation are identified as key risk factors associated with product quality and timely delivery. As mentioned above, the product of interest is of a sensitive nature, thus requiring special handling. In order to minimize risks of product loss, it is of the utmost importance to ensure that the desired conditions are met and maintained during storage and transportation. Table 3 lists both temperature and time excursions as two of the most important risk factors that need to be considered during the design of novel supply chain solutions. Evidently, there is pre-eminent need for the design of shipping solutions for: (a) temperature maintenance and (b) optimal duration that

can de-risk environmental and handling extremes. Similarly, the equipment used for product storage needs to be validated in order to ensure that both the desired conditions, as well as product integrity are maintained. Lastly, chain-of-custody documentation is currently challenging to address as it is required to record: (a)location,(b) security and (c) temperature, while involving various facilities, people and organizations. Lately we have seen the emergence of digital tools and software platforms ("cell orchestration platforms") from several companies (e.g. TrakCel) [20, 21], designed to synchronise the various activities involved. Moreover, such tools assist with sample tracking, while keeping the patient identity and data private. Nevertheless, digitalisation is often perceived as a threat that will lead to automated solutions and consequently loss of jobs. However, automation is likely to replace repetitive, error-prone tasks in human activities, allowing the operators to have more time to be creative, redesign and optimize procedures and of course be in charge of the automated operating system [22, 23].

Other associated risks

As mentioned earlier, challenges also arise from: (1) manufacturing, (2) reimbursement and (3) clinical adoption of these therapies. The manufacturing process consists of

several complex steps that need to be coordinated and performed for the successful delivery of the therapy. Given the speedy turnaround required, manufacturing times need to be optimised and therefore, raw material availability is of high importance, particularly in the case of viral vectors that may have significant lead times. This is, however, a challenging task as resources are currently limited and the demand is unknown. Most of the decisions related to the manufacturing process need to be made prior to filing for regulatory approval, as they are considered fundamental for the therapy quality and efficacy and therefore cannot vary. Such matters refer to: (a) condition in which the therapy is transferred (fresh or cryopreserved), (b) choice of vector (lenti- or retro- vector) and (c) design of the process. Moreover, decisions on outsourcing and/or in-house processing for parts of the manufacturing line (e.g. quality control, storage) are required to be made well in advance and have a direct effect on the business and supply chain model. Unlike other (bio-) pharmaceutical products, the patient-specific character of CAR T cell manufacturing does not allow volumetric scale-up, posing additional challenges to the roadmap towards commercialisation. Currently, the commercially available therapies are offered at a significantly high cost, challenging the establishment of reimbursement procedures. Discussions are currently in place on how these therapies should be evaluated and reimbursed. There is a series of fundamental questions that need to be addressed, such as: (a) value of cure with focus on societal preferences, (b) choice of appropriate criteria for the evaluation of curative therapies, (c) appropriate characterisation of uncertainty and (d) application of appropriate discount rates [24]. Lastly, a wider clinical adoption of CAR T cell therapies will depend treatment efficiency and minimisation side effects. Other critical issues include chain-of-custody, as well as clinical responsibility.

Autologous CAR T cells value chain: opportunities

Up to this point we have mainly discussed the challenges and risks encountered throughout the manufacturing and

Table 3 Risk factors during CAR T-cell manufacturing (adapted from Griffiths & Lakelin [35]).

Harvesting starting material

Starting material logistics

Manufacturing Product release Therapy logistics Treatment

Patient identification High High Low High Low High Sample identification High High Low High High High Temperature excursions Low High Medium Low High Medium Time excursions Medium High Medium Low Medium Medium Resource allocations High High High Medium Medium High

Autologous CAR T-cell therapies supply chain: challenges and opportunities?

market establishment of CAR T cell therapies. The supply chain model that is currently in place can handle a finite and relatively low number of therapies and would require significant modifications to accommodate a larger patient population. Here we discuss the concept of a “dynamic” supply chain model that is designed to be adaptable based on the market needs.

The concept of a “dynamic and flexible” supply chain

The current supply chain model (small-scale v1) (Fig. 5a) suggests that samples are transferred from the clinical site directly to the manufacturing facility and then they are shipped back to the hospital for administration. Nevertheless, the leukapheresis and administration procedures may happen at the same or different locations as presented in the small-scale v2 model (Fig. 5b). Both models are currently used and are sustainable for the current patient numbers. Despite their good performance, these operational models entail a series of risks that will arise as patient numbers increase. Here we mention some of these risks:

● Cryopreservation/freezing and thawing: Based on expert opinion, these procedures are considered to be part of the manufacturing process and should be performed under the control and supervision of the manufacturer, in order to avoid complications with chain of custody. With a limited number of samples, these processes can be easily performed under a controlled environment at a clinical site, however, as patient numbers increase, it is likely that all or part of these

procedures will need to take place at the manufacturing site or at a specialist 3rd party site, under the manufacturer’s control. ● Manufacturing capacity: Today, current facilities are able to handle the samples received from the leukapheresis centres. However, as the therapy becomes available to larger patient groups the need to process more therapies simultaneously (scale out) will become critical and therefore manufacturers will have to design a robust scheduling strategy and seek expansion opportunities (noting that volumetric scaling is not possible) in order to ensure that all samples are processed. Such an example is Kite Pharma’s new facility [25]. ● Hospital capacity: At the final point, where the therapy is delivered at the hospital, it may need to wait until patient conditioning has been completed. Current facilities offer limited storage space and may not be equipped with liquid nitrogen storage units, challenging the scale up even more.

The forecasted market growth indicates that therapy demand will increase rapidly in the next few years, implying that manufacturers need to adapt their current manufacturing and/or distribution strategy in order to efficiently ensure adequate supply of therapies. Here we present for the first time the concept of a “dynamic” supply chain that is able to adapt to the demand, ensuring that all received samples are treated on time and therapies are delivered to the patient in a timely manner. As shown in Fig. 5c, the Extended v1 model, suggests that an intermediate site is established between the leukapheresis centre and the manufacturing facility (Intermediate Site 1). This could serve as a freezing and storage site that operates under the control of

Fig. 5 Representation of the “dynamic” supply chain concept, where the supply chain network changes with respect to the increasing demand. Cases (a) and (b) represent the current state-ofthe-art, where samples are collected from various hospitals and/or leukapheresis sites (respectively),

transferred to the manufacturing facility and finally shipped to the hospital for administration. In (c) the extended v1 model is presented, where an intermediate collection point

between the leukapheresis and the manufacturing site is established. Lastly, (d) presented the extended v2 model, where following the introduction of the intermediate collection point between the leukapheresis and the manufacturing site, we propose the introduction of a second intermediate point between the manufacturing facility and the hospital.

the manufacturer, responsible for the cryopreservation and storage of the therapies in processing. Being part of the manufacturer's infrastructure, these sites can be controlled independently, giving the manufacturer greater freedom to schedule the logistics and shipments independently of hospital capacity and maintain control over the cryopreservation process. Nevertheless, patient scheduling remains one of the primary time constraints of highest priority. Similarly, the Extended v2 model (Fig. 5d), proposes the introduction of a fifth location, to be established as an intermediate point between the manufacturing facility and the hospital, when the therapy is returned to the patient (Intermediate Site 2). The site could undertake storage and potentially thawing under a controlled environment, aiming to debottleneck capacity constraints at the hospital site and allow the manufacturer to have control over the thawing process. This could also be the same location as the Intermediate Site 1, simplifying the distribution network. The aforementioned models offer different levels of freedom to the manufacturer and are not mutually exclusive. As manufacturers prepare to respond to increased demand scenarios, they can start from the most centralised network (Fig. 5a) and expand to the other configurations as the patient numbers and locations served increase. Furthermore, based on the demand forecasts the number of the facilities in use may increase (e.g. decentralised manufacturing using multiple facilities).

Future considerations

Systematic decision making in autologous CAR T cell therapies

In the previous section, we presented two novel types of supply chain concepts that aim to debottleneck both manufacturing and storage capacity issues. Although moving towards the establishment of such solutions will bring a step change in the current state of the art, it will also be accompanied by significant increases in the capital and/or variable costs of the manufacturer. Moreover, decisions on the number and location of sites need to be taken prior to investment, ensuring that the model will be robust and result in an improved performance, while balancing the need to anticipate future demands and putting excessive capital at risk. Risk management and capacity optimisation in pharmaceutical supply chain models have been investigated by various research and industrial groups over the last few years. Some of the aspects of interest are: multi-product manufacturing [26], new product decisions/portfolio planning [27, 28], impact of innovative technologies on the supply chain [29], as well as capacity and long-term planning [30–33]. It is therefore evident that "systems" approaches have been employed for the improvement and/

or assistance of decision-making in the design of efficient distribution models of (bio)pharmaceuticals and will be relevant here. As we move towards more personalized medicines and particularly autologous therapies, the current supply chain models will have to adapt in order to meet both patient and provider expectations. Therefore, the pharmaceutical industry needs to re-think the one-type-fits-all model that is currently in place. In order to de-risk and smooth the transition, advanced mathematical modelling methods can be employed that can provide a low-cost test bed to run different configuration scenarios, such as the ones presented above. Constraints on

processing times, capacity, as well as regulatory implications can be considered in the model structure so that the generated solutions comply with all pre-defined specifications. The discussed models are usually validated using real-world data from previous case studies, thus ensuring their credibility. Such solutions may also provide evidence that can be included in the dossier for regulatory approval, strengthening the application. Further uses of such models could be to evaluate the benefits of alternative emerging technologies such as allogeneic therapies, continuous processing, non-viral gene editing systems etc.

Allogeneic CAR T cell therapies

While autologous CAR T cells have demonstrated remarkable results, efforts are made towards the successful development of allogeneic therapies, where the apheresis material is harvested from healthy donors. Future marketed allogeneic therapies have the potential to significantly challenge the market share of autologous products. From a manufacturing and supply chain perspective, allogeneic technologies can use a “cell-bank” model, where the starting material is readily available to be manufactured, therefore reducing waiting times upstream of the supply chain and facilitating volumetric scaling. The reducing waiting times and potentially increased scales could lead to faster responses to the demand and therefore shorter return times of the overall therapy.

Conclusions

Autologous therapies are expected to require new types of biopharmaceutical supply chain models as they stand today. Their patient-specific nature places patients as an integral part of the distribution network, thus challenging the design of generic supply chain models. Moreover, the uncertain market size and demand, as well as the limited supply of key raw materials, require the development of a detailed manufacturing and distribution plan that will be able to

mitigate risks of failure. Furthermore, increasing demand cannot be met by volumetric scaling. Aiming to make the CAR T cell therapies scalable, responsive and more cost-effective, we describe novel supply chain concepts based on the introduction of intermediate collection points, aiming to mitigate risks related with storage capacity at the manufacturing and hospital sites. There are still various challenges and decisions that need to be tackled and answered, such as location/number of sites. Such questions can be addressed through systems approaches that employ modelling and optimisation methods in order to design equally good solutions that respond to all, sometimes conflicting, objectives.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Appendix A

For the patient population forecast studies, we assume a constant average growth of approximately 0.4% [34] and constant incidence rates per 100,000 people ((HMRN (Haematological Malignancy Research Network), 2018)), as presented in Table A.1 in the supplementary information. Based on these assumptions, we present indicative projections (Table A.2, supplementary information) for the liquid cancer patient population in the UK for the next 15 years. In order to estimate the patient population, we only consider liquid cancer types as currently CAR T therapies are considered to be more advanced in that space. Furthermore, the types of liquid cancer here have been chosen based on data availability. Patient population numbers for types not present in the current set are either scarcely provided or not available. The three final rows of Table A.2 (please see supplementary information) represent: (1) the total number of patients with liquid cancer in theUK forthenext 15years, (2) a scenario where estimates are 20% lower and (3) a scenario where estimates are 20% higher. Figure A1 of the

supplementary information represents the ±20% case. Nevertheless, CAR T cell therapies will most probably not be the first line of therapy, therefore limiting the number of eligible patients. Figure A.1 (please see supplementary information) illustrates a potential scenario, where only 10% of the totalpatientpopulationwillbe eligible forCARTcelltherapy treatment. Despite this constraint, patient numbers are estimated to increase almost fivefold by 2031, thus challenging CART manufacturing and supply chain scale up.

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