Bridging the Gap

The pressure is on apheresis centres to introduce stronger quality management systems to truly take advantage of apheresis capabilities, thus paving the way for new therapies with increased potential.

Regenerative medicine (the art of repairing or replacing damaged tissues and organs through cellular engineering) has seen remarkable advances in the past decade. Positive clinical trial results, particularly in cancer immunotherapy, have prompted a surge in the number of cell-based therapies progressing toward commercialisation. Apheresis and cell collection centres must quickly adapt to handle the increased demand for cell therapy starting materials. Concerns over upholding quality oversight, particularly for Good Manufacturing Practice (GMP)-qualified starting materials, should also be addressed.

Apheresis collection centres interact closely with both donors and the pharmaceutical companies developing cellular therapies and are, therefore, in an ideal position to devise solutions to these challenges. This article will focus on how apheresis facilities aim to adapt collection centre infrastructure to support higher demand while streamlining downstream processing and ensuring quality oversight. The authors will examine specific quality control challenges posed by cryopreserved GMP products and the related need to adapt and standardise cold chain protocols. Bridging the gap from donor collection to successful therapeutic relies on the ability to collect high-quality starting material and assure that the finest quality and efficacy of the final cell-based product can be achieved.

Starting Point

Regenerative medicine and cellular therapy are relatively new technologies, both based on the use of biomaterials to treat or cure human disease. While there is a good deal of overlap between the two industries, the most obvious distinction is that cellular therapies always use living human cells as the starting point for manufactured medicines.

As clinical trials for these therapies advance and multiply, it has become clear that starting material variability and availability pose a challenge to the fledgling industry. Now that cellular therapeutics are entering the commercial development stage, the need for apheresis-derived human primary cells for both autologous and allogeneic therapies is rapidly expanding (1). Meeting that need is going to be difficult since it is still unclear how the industry plans to manufacture and commercialise a consistent, high-quality product derived from living cells that are both intrinsically variable and a limited resource. This article focusses on ongoing efforts by apheresis and cell collection centres to bridge the gap between apheresis donations and cell therapy starting material that support the manufacture of consistent, high-quality therapeutics.

Donor Networks

Apheresis and cell collection centres are already feeling the burden of increased demand for cell therapy starting materials. Collecting apheresis material starts with donors. Apheresis donation is more complicated and time-consuming than standard blood donation. Specialised training is needed to work with donors and handle apheresis equipment, and complex protocols and instrumentation are needed to separate and isolate blood components.

Proactive maintenance of a robust donor network is a critical requirement for collecting high-quality starting materials (2-3). The variability of donor material is cited as the most critical factor impinging on cell therapy manufacture (4). This variability must be counterbalanced by a diverse network of reliable, recallable donors and optimised cell collection protocols. Starting material from patient donors is impacted by the severity of their disease, significantly lowering the number of healthy target cells that can be isolated from a given blood volume. The quality of cellular starting material is very important because factors like cell number, viability, biological activity, and purity all directly impact downstream manufacturing and potency of the therapeutic product (5):

Identifying healthy donors for allogeneic products is, in some ways, more straightforward, in that donation volume and target cell numbers are not as big a concern. Nevertheless, a large donor network is essential, since pharma developers often ask that donors meet stringent inclusion and exclusion criteria to align with project parameters (7). The opportunity to recall valuable donors is important to maintaining a reliable, consistent product, and a good apheresis centre is careful to sustain a strong, positive relationship with donors.

“The quality of precursor material is absolutely essential since it will determine the quality of the downstream product. You need to have high-quality material going in because it will affect a lot of other parameters downstream.” – Head of T Cell Processing, Global Pharmaceutical Company (6)
Improving Infrastructure

To deal with increased demand for cell therapy starting materials, the industry must first address availability by improving cell collection and apheresis centre infrastructure. Current apheresis centre infrastructure is already showing strain in the struggle to support the burgeoning need for apheresis (8). More apheresis specialists are needed, as well as expanded workspace capacity and expanded donor recruitment. Dealing with multiple site assessment requirements and collection protocols are also placing growing time demands on apheresis centre staff (9).

Standardisation addresses a lot of these issues. Pharma client companies should be cognisant of the fact that apheresis centre staff are highly trained and well familiar with optimising instrumentation operation and cell collection procedures. Pharma companies, regulatory agencies, and apheresis collection centres must work together to identify those areas where standardisation is possible (4, 10). In many cases, client companies can choose to take advantage of existing audits and protocols, rather than introducing new ones. Taking steps to reduce the number of different protocols in operation will reduce strain on staff and help tackle the issue of starting material variability.

Workspace infrastructure improvements will also be necessary to optimise starting material production, and, to some degree, these improvements are already underway (3). Adding staff and operating hours works for some clinics where space is at a premium. For private apheresis networks, it makes more sense to expand donor bed capacity and recruitment efforts (11-12). Expanded capacity to collect donor material, as well as standardised audits and collection methods, will help take the strain off apheresis collection centres striving to meet increased demand for cell therapy starting material.

Quality Systems

Quality of starting material is just as important as availability in the quest to produce safe and effective cell therapies. Since all cell-based products are variable by nature, apheresis centres must manage those factors over which they do have control to assure a consistent product. This means establishing and maintaining robust quality management systems. Again, this process starts with donors. All apheresis donors should be screened for infectious diseases prior to collection, and apheresis centres should establish detailed records of medical history, demographics, and lifestyle characteristics (13). Additional donor screening and qualification can be carried out where necessary to meet project specifications. Collection protocols should focus on optimising therapeutic cell yield. For stem cell collection, this entails optimising factors such as mobilisation techniques and collection timing (14-15).

Quality oversight of the apheresis procedure itself is just part of the process. Training programmes, vendor qualification, equipment, supplies, documentation, and process control all fall under quality management systems. Collected cells need to be carefully tracked for patient safety and evaluated to ensure cells meet quality control standards established by regulatory agencies, as well as any additional quality standards specified by the client who will be receiving the apheresis product. Along with standard viability assays, apheresis material suppliers should be testing identity, purity, and cell-specific functional activity, since all of these parameters affect downstream safety and efficacy of the final cell therapy product (16-17).

“Apheresis is key. For example, if post-thaw viability is good, say greater than 90%, you know things are going to work out well. If post-thaw viability falls to, say, 80%, the cells just aren’t going to perform as well.” – Head of T Cell Processing, Global Pharmaceutical Company (6)
Along with improving availability, cell therapy starting materials must be guaranteed to be of the highest achievable quality. To produce consistent and effective therapies, the industry needs to surmount the difficulties of dealing with an inherently variable living product.

While all quality management systems must follow industry best practice guidelines, quality oversight will necessarily diverge based on the intended use of the product. High-quality research use only (RUO) apheresis products are intended for the support of early-stage drug discovery and preclinical work. Ideally, these products should be equal in quality and efficacy to GMP products and, if possible, collected using identical apheresis instrumentation, methodology, and reagents.

All successful preclinical candidates will need to abide by GMP practices and regulations prior to their translation to the clinic (18). For cell collection centres supplying cell therapy products, quality oversight will necessarily diverge based on the intended use of the product. High-quality GMP products, quality oversight is even more stringent than for RUO products in that it includes comprehensive documentation of all procedures and materials. Cell collection must take place in a GMP-compliant, FDA-registered donor centre, and any further processing steps must take place in a GMP-compliant clean room environment.

Downstream Processing and Cold Chain Infrastructure

Maintaining the integrity of cell therapy starting material until it reaches the client is important. Because these are ‘living products’, they must be handled in a way that minimises loss of viability or functionality. In many cases, apheresis products are collected on-site and then shipped to a processing centre for further cell isolation and quality testing. Larger apheresis centres may have the flexibility to offer immediate on-site processing capabilities, such as isolation of peripheral blood mononuclear cells, stem cells, and primary cells, either shipping them to pharma clients as freshly isolated products or cryopreserving the cells to allow for on-hand availability and protection from extended shipping times or harmful temperature fluctuations.

Living cells are extremely vulnerable to fluctuations in temperature and can easily suffer loss of viability or therapeutic potency (19). For freshly isolated products, there is a fairly strict time limit of about 48 hours until the cells can no longer be used for their intended purpose. Cryopreservation, when done correctly, protects cell viability and integrity while giving the end user flexibility to store cells until they are needed (20). Cryopreservation is not always needed for small-scale pilot studies or autologous therapies where patient material is collected and administered on-site. However, logistics dictate that scale up to a commercialised product all but necessitates cryopreservation of cell therapy starting material to provide for shipping, storage, and manufacturing flexibility.

This can be problematic in regard to GMP-compliant materials. Currently, most cell therapy starting materials are sent off-site for GMP processing due to a lack of the necessary staff, space, equipment, and expertise needed to properly handle GMP products. These extra shipping and handling steps comprise an additional risk to the integrity of starting materials, even before they are shipped out to begin the manufacturing process. As the cell therapy industry continues to expand, it may make more sense to have GMP-compliant clean room facilities on-site at apheresis centres. This would essentially streamline production of GMP-compliant cells without the added risk of an additional step in the cold chain. It would also help standardise cell isolation, processing, and cryopreservation protocols between RUO and GMP apheresis products.
A Unique Perspective

The cell therapy landscape is evolving quickly, and the cell therapy starting material supply chain needs to evolve with it. Apheresis centres are at the forefront of cell therapy production. This gives them a unique perspective on the steps needed to ensure that the transition of cell therapy to mainstream medical practice goes smoothly. It seems clear that apheresis centres are already under strain due to the rapid increase of cell therapy applications. Hospitals and other collection sites need to increase both donor recruitment and collection centre capacity to handle increasing demand for starting materials. Added staff and workplace hours, plus additional facility space, equipment, and donor recruitment, are all needed to increase the availability of donated apheresis material.

Along with improving availability, cell therapy starting materials must be guaranteed to be of the highest achievable quality. To produce consistent and effective therapies, the industry needs to surmount the difficulties of dealing with an inherently variable living product. Standardising equipment, training, and collection protocols can go a long way toward achieving this goal. Additionally, apheresis centres need to implement strong quality management systems, starting with managing donor networks, as well as optimising apheresis procedures. Cell isolation, processing, and cryopreservation should also be optimised and monitored with the integrity of the final product in mind. Expanded apheresis capabilities and stringent quality management systems will help bridge the gap to a future in which medical science can reap the rewards of these promising new therapies.

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About the authors

Dominic Clarke PhD has over 15 years’ experience developing enabling solutions for cell therapy and bioprocessing applications. Dominic is the Global Head of Cell Therapy at HemaCare, where he is actively engaged with industry experts to ensure the highest quality materials are delivered. Previously, he held roles as the Global Product Manager for Charter Medical's cell therapy and bioprocessing disposables portfolio, focused on creating flexible closed-system solutions for early- and late-stage production, and as the Director of Research and Development at BioLife Solutions, developing novel biopreservation media and methods to support extended stability of cells and tissues. Email: dclarke@hemacare.com

Brad N Taylor PhD is the Senior Product Manager at HemaCare. Brad has over 13 years’ experience in the biotechnology industry, addressing multiple aspects of drug discovery and preclinical development. Previously, he held roles as Application Scientist and Product Manager in the in vivo imaging division of PerkinElmer, where he worked to bring innovative solutions to market to assist the research community in expanding and streamlining the process of preclinical drug discovery for cancer and other clinical applications in animal models of disease. Email: btaylor@hemacare.com