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Immuno-Gene Therapy Mini-Series on Supporting Externally Manufactured Cell and Gene Therapies

Delivering externally manufactured cell and gene therapy products to patients: perspectives from the academic center experience

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Introduction

Cellular immunotherapy is the application of immune cells that are collected, and often modified ex vivo, to improve immune responses for a patient's treatment. The Foundation for the Accreditation of Cellular Therapy (FACT) defines immune effector cells (IECs) as cells designed to modulate immune responses for therapeutic purposes and includes cells such as T cells, B cells, natural killer (NK) cells and dendritic cells [1]. Many of these types of cells may be genetically modified to further enhance their cellular function. For example, T cells may be transduced with a chimeric antigen receptor (CAR), which is designed to bypass the co-stimulatory requirements for T cell activation upon antigen binding. With the commercialization of cell therapy products like axicabtagene ciloleucel, brexucabtagene autoleucel, tisagenlecleucel, lisocabtagene maraleucel, and idecabtagene vicleucel, with many more in the pipeline, this is an exciting time for the cell therapy community. The number of investigational products is expanding rapidly as well. Although most of the current investigational products used in early phase clinical trials are CAR-T cells, CAR technologies and other gene modifications of NK cells; macrophages; and $CD34^+$ hematopoietic progenitor cells appear to be rapidly developing in the pipeline. Reflecting the importance of ensuring institutional readiness for managing such therapies, there have been significant discussions on proposed recommendations for developing an institutional multidisciplinary immune effector cell program [2–4].

Most IEC products are derived from cells collected via leukapheresis either from the patient for autologous use or from healthy donors for allogeneic use. Because many of these cell therapy products are manufactured outside of the institution by industry developers, they must be properly shipped to the manufacturing facility. When manufacturing is completed, the cell product is shipped back to the institution for administration to the patient. Consequently, owing to the nature of using live cells as a therapeutic option, both commercially available and investigational cellular products require an additional level of scrutiny of the planning and logistics for successful implementation and delivery to patients. Figure 1 demonstrates a high-level overview of the various processes involved in the transport of cells to and from the manufacturer. Autologous or allogeneic leukapheresis collections are shipped fresh or frozen to the manufacturer. The manufactured product is sent back to the treating center and delivered to the patient. Cell therapy products that are manufactured as an "off-the-shelf" therapy from allogeneic sources are typically shipped to the institution and stored on site until the patient is ready for infusion. Each of these scenarios requires its own set of protocols and procedures to properly manage the process.

The cell processing facility (CPF) plays a critical role to ensure proper handling and safety of the product as it is transported from the academic center to the manufacturer and back to the patient for infusion. As such, the laboratory responsibilities for managing externally manufactured products are significant; many are listed in Table 1. For each clinical trial, significant effort is needed to review the laboratory manuals and assess the requirements for the processing laboratory and to put forth comprehensive logistics and staffing planning to ensure the successful execution of the trial. It is clear that the rapid expansion of industry-sponsored clinical trials using investigational cell therapy products has had a significant impact on the workflow of many CPFs, and there is a need to streamline processes to reduce the burden resulting from diverse requirements for handling externally manufactured products.

As a response to these challenges and to promote the dissemination of improved practices, the Immuno-Gene Therapy Committee (IGT) of the International Society for Cell and Gene Therapy (ISCT) invited several groups from CPFs within academic centers and hospitals to share their experiences, how they have incorporated workflows into their normal work routine, and how they organized their programs to accommodate these products. In addition, the mini-series includes the results of a survey, conducted on behalf of the IGT Committee of ISCT, that aimed to capture current practices of CPFs for handling of externally manufactured cell or cell-based gene therapy products (CGT). It is understood that all team members of an institutional immune effector program are important, but the main focus of this mini-series is finding solutions for the laboratory's role in handling the cellular product. Therefore, the intended audience of this mini-series includes CPFs or internal current good manufacturing processes (cGMP) manufacturing facilities that already handle commercial cell therapy products or investigational products in early/mid-phase clinical trials, those laboratories just beginning, and partners in industry interested in reducing the burden

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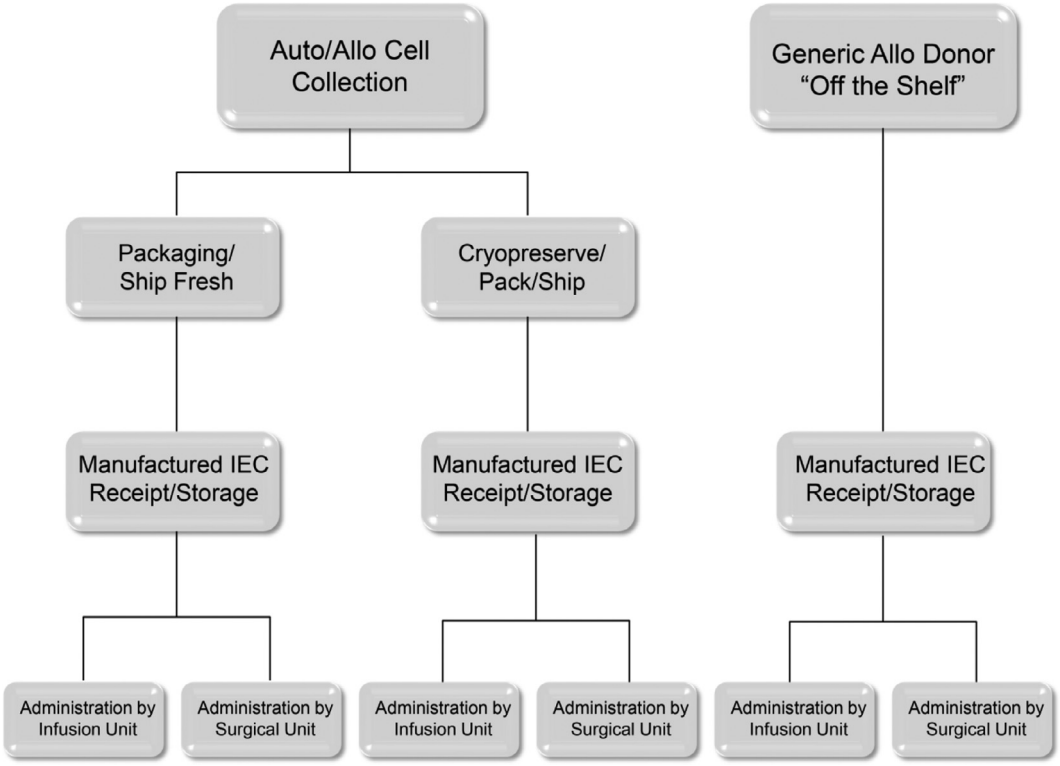

Figure 1. Various workflow scenarios that cell processing facilities may encounter when handling externally manufactured products.

of handling their products. The scope does not necessarily pertain to internally manufactured products or contract manufacturing for external companies, although certainly many principles would be shared with them. Although we focused on IECs for this mini-series, many of these concepts can be applied to industry-sponsored clinical trials using other cell therapy products such as mesenchymal stromal cells. Groups from the Immune, Progenitor and Cell Therapeutics (IMPACT) laboratory at the Mayo Clinic in Rochester, MN; the Immunologic Monitoring and Cell Products Laboratory (IMCPL) at the University of Pittsburgh Medical Center; the Cellular Therapy Laboratory (CPL) at the New York Presbyterian Columbia University Irving Medical Center; and the Cell & Molecular Therapies laboratory at the Royal Prince Alfred Hospital in Sydney, Australia, have provided their experience in the following articles.

Each of the institutions are unique and have developed processes and procedures that are tailored to their current environment. Still, there are some common themes that emerge from their perspectives. Because these CPFs were accredited by FACT and follow other state and federal regulations, the quality fundamentals for handling cellular therapy products were already in place. Proper documentation of activities was an important issue. As third-party sponsors/manufacturers began to introduce novel cell therapy products, their procedures for handling these products often were different from the laboratories' processes. The laboratories had to adjust to the incorporation or creation of new standard operating procedures (SOPs) and training documents. This led some to turn to digital solutions to manage and track documents. In response to mitigating these new risks into the laboratories, the groups had to re-evaluate processes and create new workflows. Additionally, workspace and laboratory layouts were modified to support these activities. In the case of the Mayo Clinic, they even created a new work unit.

Table 1
Aspects of laboratory responsibilities for handling externally manufactured products

Laboratory responsibilities	
• Facilities and equipment	• Safety
• Staffing and training	• Assessments
• Communication	• Budget
• Process control/improvement	• Regulatory interactions
• Quality assurance	• Documentation

Finally, efforts to prioritize communication between all the different participants involved in the process was an important part of successful implementation. Proactive communications in site initiation and qualification visits included various documents sent to the sponsors ahead of meetings with information regarding the facilities and high-level overview of selected laboratory processes. Internal communications between the CPF and clinical coordinators, protocol specialists, and physicians also appeared to help streamline the process and reduce the time from study initiation to patient enrollment. It was also clear that there were areas of product handling that were divergent. Documentation practices related to commercial products versus investigational products, the role of the CPF in making decisions for new trials and the nature of the laboratories themselves (cGMP facility versus a hematopoietic stem cell laboratory or combined laboratories) were some of the examples with noticeable differences. To be sure, these likely reflect the environment of the laboratory within the institution and thus may not be significant obstacles to defining best practices in the cell therapy community.

Taken together, the experiences from the academic centers can provide some consensus to improve efficiency without sacrificing quality for commercial and industry-sponsored clinical trials using IECs. Analyses from more specific aspects of cell therapy are providing additional insight as well. In a study comparing cell therapy infusion workflows, the study group found that inter-institutional variability in SOPs likely affected the efficiency of workflows [5]. This finding suggests that additional guidance and harmonization would accelerate the implementation of new cell therapy trials. It is anticipated that the lessons learned as presented in these articles will benefit both academic centers and industry partners to reduce efforts and resources to bring new cell therapy products to our patients.

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