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Are You Ready for a Tech Transfer?

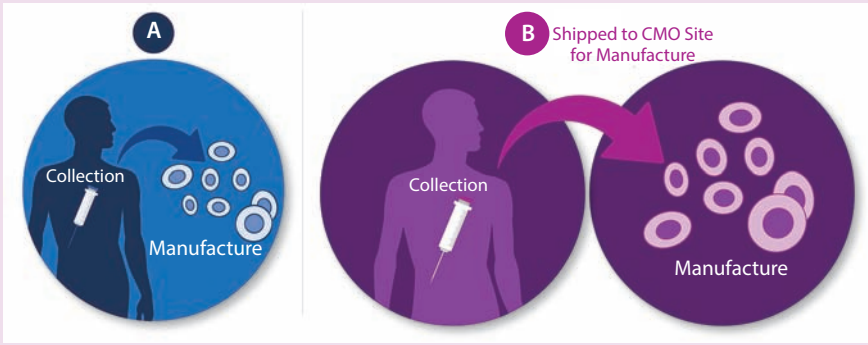
Part 1: Challenges and Critical Factors for Success in Cell Therapy Development

by Catherine McIntyre and Cenk Sumen

Cell therapies offer enormous promise for treatment of a range of conditions by replacing damaged tissue or leveraging the body's own resources to heal itself. Not surprisingly, the cell therapy industry is growing rapidly and is poised to have a major impact on healthcare and disease treatment. The Alliance for Regenerative Medicine (ARM) has reported on the robust state of the industry, noting that revenue from cell-derived products grew from US$460 million in 2010 to $1.3 billion in 2013 (1).

A critical aspect of cell therapy development is transfer of knowledge from a development organization to a manufacturing organization. The development organization (product sponsor) is generally the transferring site. A contract manufacturing or contract development and manufacturing organization (CMO or CDMO, respectively) often is the receiving site. In general, technology transfer to a CDMO is advised when a sponsor company requires the resources, capacity, facilities, and/or expertise directly relevant to cell therapy to meet industrial and regulatory requirements needed to advance a therapeutic product toward commercialization. So it is essential for a sponsor company to evaluate the strategy, timelines, and infrastructure necessary for a successful and streamlined technology transfer. In one sense, a rapid transition to good manufacturing practice (GMP) manufacturing at the receiving site may seem like an obvious goal. But in practice, such reckless speed can lead to an

Figure 1: Technology transfer moves a process into a different environment and as a result, the product should be properly defined before the transfer is initiated. Before technology transfer, raw biological material collection (e.g., bone marrow, apheresis) and manufacture may be colocated, typically at a clinical site (A). Following technology transfer, clinical and manufacturing sites are no longer in close proximity (B).



incomplete transfer or an unstable process and/or analytical methods. Consequently, that can lead to unnecessary deviations and additional time and resources required to overcome them.

Key factors in technology transfer include having a dedicated and multidisciplinary team, an attention to detail, a focus on timeline and cost, and the experience to recognize risks and mitigate them as appropriate when they appear during the transition. In some cases, the transferring site might be different from that of the originator of the process. The process may have been licensed from a hospital, an academic institution, or another company. Alternatively, the process may require transfer from one CDMO to another. The experience and knowledge of the process originator is fundamental and foundational to success and should be leveraged during a transition.

Transfer of patient-specific therapies can be complicated by the variable nature of starting raw materials. Unlike off-the-shelf processes (in which a master cell bank serves as a consistent and well-defined starting material with patient-specific therapies), starting materials can vary dramatically from patient to patient depending on severity and/or type of illness, age, and differences in cell population percentages. Furthermore, in many situations, material from healthy individuals is used for process development as well as training, engineering, and qualification runs. That material may not represent the variability seen in the affected patient population.

Adding to that complexity is the fact that transfer of patient-specific therapies separates the clinical site (and patients) from the manufacturing site. Consider the scenario outlined in Figure 1, in which a therapeutic product is developed at an academic medical center. Before technology transfer, collection of biological raw material through apheresis, for example, and manufacturing of the therapeutic product takes place within close physical proximity. Once the process is transferred to a CDMO, collection of starting materials and manufacture of the therapeutic product are separated by time and distance. In such cases, it is critical to establish that starting materials (e.g., apheresis product) will retain key quality characteristics during shipment and will remain stable during shipment from collection site to manufacturing site.

Partnering with an experienced CDMO allows the transferring site to identify and overcome those and other challenges and use specific services and capacity as required by project timelines and fiscal and fundraising constraints. A CDMO also can facilitate process integration and execute seamless transitions through technology transfer stage checkpoints as well as incorporate key analytical method-development goals.

Application of a systematic approach during such a critical transition can help ensure timely progress toward — and achievement of — milestones. Once the decision has been made to execute a technology transfer, a number of factors can combine to determine the success of the engagement.

Table 1: Four stages of training at the transferring and receiving sites

Stage	Description
1	Receiving-site personnel undergo paper training to ensure familiarity with all existing process documentation.
2	Transferring-site personnel participate in physical observation of, and hands-on training with the process at the transferring site.
3	Receiving-site personnel perform the process under observation of transferring site subject matter experts.
4	Receiving-site personnel execute several "dress rehearsals" (engineering runs) of the process in a cleanroom environment, evaluating changes to the master batch record as well as analytical protocols after each engineering run.

Table 2: Types of batches prepared during the technology transfer process

Technology Transfer Batch Type	Purpose
Training	Provide process familiarity, incorporate analytical protocols
Engineering	Perform process in the cleanroom, create the master batch record (MBR), and ensure that all materials and equipment have been specified and detailed for the process
GMP (PQ/PV)	Qualify or validate process; run process under finalized specifications under the finalized MBR

Set the Strategy

The first step toward a successful technology transfer must be a clear, well-defined strategy that addresses scope, timeline, and resources at both the transferring and receiving site. It should be agreed upon by all stakeholders and defined consistently with the clinical development plan.

Describe the processes that will be transferred: They will include (but are not limited to) the receipt and accession of the starting material at the receiving site, manufacture of the cell therapy product, in-process and final product testing using analytical methods, product release and shipment of final product to the clinical site, and other ancillary processes that are required to successfully complete the clinical manufacturing process. Include a detailed description of processes being transferred for specific technologies, and define process

parameters and set expectations for those processes. The process description also should describe possible process or equipment adaptations of the receiving site compared with the transferring site.

Describe the analytical methods being transferred: These can include (but are not limited to) tests performed on incoming product raw material (e.g., apheresis) in-process samples, identity and potency assays, and final product testing (e.g., cell counts, viability determination, phenotype, endotoxin, sterility, and mycoplasma testing). Include a description of the analytical methods that are for specific testing technologies.

Documentation: In your transfer strategy, include a gap analysis and risk assessment of the process and analytical methods being transferred. Also include a quality agreement to align the expectations for quality assurance between the organizations. The agreement should detail the requirements for qualification studies and the process for handling process deviations. In addition, assess the need for a comparability study using material generated during the technology transfer, before or during process qualification (PQ) runs.

Other Aspects: The transfer strategy should also detail

- onsite training of receiving-site personnel first at the transferring site before transfer and again at the receiving site (Table 1), with mutually agreed-upon criteria to assess the effectiveness of the training
- practice runs performed by trained staff at the receiving site to assess the technology transfer and compare it to the original success criteria determined at project onset
- the number of technical transfer batches that will be produced and at what scale (Table 2)
- analytical methods qualification and acceptance criteria
- the number of engineering runs and acceptance criteria.

Your engineering run definition should include processes performed at full-scale in a cleanroom. That allows for completion of a master batch record (MBR), verification of analytic methods, and completion of all raw material and supply logistics (including shipment of the final product and assessment of the technology transfer against predefined acceptance criteria). The engineering run definition may or may not include full quality review and release.

Finally, the transfer strategy should describe the number of PQ or verification runs and acceptance criteria. Processes must be performed under full current good manufacturing practice (CGMP), with the finalized and approved MBR and ancillary standard operating procedures (SOPs) in the clinical manufacturing facility. Conduct full testing using qualified analytical methods and regulatory-compliant final product release and shipment.

Time the Transfer

Technology transfer relocates a process into a different environment. As a result, the transfer process should be properly defined before a move is initiated. The time is right for a technology transfer when ranges for quality, final product, and in-process parameters are well understood and robust.

The transfer must include information about parameters before and after individual unit operations as well as ranges for expected recoveries and/or yields across unit operations. Critical process parameters (CPPs) must be evaluated on the basis of historical data, and CPPs with potentially high impact on critical quality attributes (CQAs) must be identified. Technical operations experts on the transferring team evaluate CPPs and CQAs, so information from processes that failed or did not proceed as expected during development can provide extremely useful information. The transferring company also must define acceptance criteria for incoming raw materials (e.g., apheresis), other biological materials used in a process, and critical process steps. The final cell-therapy product should be defined and ranges established based on data collected during process development and maturation.

Identify Milestones

The transferring site should identify key development and clinical milestones and come to agreement with the receiving site on necessary and practical timelines. Technology transfer must be built into the overall timeline for product development and commercialization. Often, external deadlines — such as a desired investigational new drug (IND) submission date or funding milestones — can drive the timelines of technology transfer, but care must be taken to allow both parties sufficient time to successfully proceed through transfer stages. Technology transfer is a marathon, not a sprint.

Sharing Information

Open and honest sharing of information from sponsor to CDMO is critical for success. Process descriptions, protocols, SOPs, work instructions (WIs), and MBR (if already developed by the transferring site) all contain useful information for performing a given process. However, technology transfer teams should not underestimate the criticality of unspoken and unwritten information inherent to scientists, operators, and technicians at a CDMO. The originating facility, if different from the transferring site, should

be involved to ensure capture of the full history of a process.

To develop a technical understanding of the technology to be transferred, a combined team (with members from both sponsor and CDMO) should review all available scientific and technical data and documentation. Those materials should include process development reports, a process description, SOPs, material and equipment specifications, acceptance criteria, logistics, and clinical considerations.

The CDMO also must understand biological material and final product variability, process consistency and robustness, and failure rates. The CDMO should leverage experience gained through previous technology transfers to preempt and mitigate potential risks to the success of the project.

Once the receiving site has reviewed all provided information, additional development activities might be required. Such activities should be performed after technology transfer and under strict change control.

Program Kickoff and Charter

After agreements have been made to move forward with a collaborative project, a project initiation meeting is the first major milestone in technology transfer. During that meeting, expert team members from both the transferring and receiving sites meet, transfer technical and logistic information, and lay the groundwork for a program charter. Next comes a program kickoff meeting at the CDMO site to detail the basic science, manufacturing process, analytical and testing procedures, storage, shipping, and all other technical issues specific to the project.

A program charter is a high-level document developed and agreed upon by all team members. It lays the groundwork for a program and captures all important elements in a format that is readily understandable by all members of the team implementing the program. This provides a central point of reference and formal agreement of program scope, deliverables, and constraints. Specifically, a program charter should identify the following:

- Stakeholders (roles, responsibilities, communication plan)
- Technology transfer strategy (the transfer activities, need for process development or improvements once transfer has been completed, training, process implementation, and process qualification)
- Timeline
- Assumptions
- Risk assessments and gap analyses.

Define Roles and Responsibilities, and Set Up Communication Paths

Upon establishing a collaborative sponsor–CDMO team, it is crucial to set expectations for open communication between both parties. A communication plan compiled jointly will identify the roles and responsibilities of team members at the sponsor and/or transferring site and the CDMO, summarize expectations, and provide an up-to-date and comprehensive list of contact information available to the team. This document should be revisited and updated regularly as a project moves between stages.

Successful technology transfer occurs when team members on all sides of the transfer develop an open and proactive relationship with their counterparts, enabling frequent and timely communication as matters arise. To eliminate redundancy and duplication of effort, important information, decisions, and discussion summaries must be circulated to the extended team.

Team members should be proactive, take ownership of individual roles, and maintain accountability. Internal team communications also should not be overlooked, because consistent messaging between the transferring and receiving site will reduce confusion and frustration for all. A central and secure location (such as the Microsoft SharePoint online hosting service) to house all project-related documentation is essential to ensure that everyone has access to the same information at any given time. Additionally, staff turnover happens at both the transferring and receiving sites. So a central point of reference and open team-wide sharing of information can help mitigate loss of information caused by such turnovers.

Part two of this article will discuss critical success factors, best practices, and key strategies that will facilitate the successful transfer of a cell therapy manufacturing process.

Reference

1 Mackay, G. *State of the Regenerative Medicine Industry.* Alliance for Regenerative Medicine Annual Meeting 2014, 13 January 2014; http://alliancerm.org/sites/default/files/ARM_SOTI_PPT_2014.pdf.

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Are You Ready for a Tech Transfer?

Part 2: Overcoming Obstacles and Implementing Best Practices for Cell Therapy Technology Transfer

by Catherine McIntyre and Cenk Sumen

In part 1 of this two-part series, we outlined common challenges of technology transfer that are unique to the cell therapy industry and discussed strategies for success (**1**). Here, we delve even further into best practices and highlight key strategies for technology transfer that should be considered along the path to success.Creating a strong foundation for technology transfer will streamline clinical manufacturing processes and help position therapeutic products for long-term success. Below are key criteria for success.

Confirm Transfer Acceptance Criteria

Creation of a program charter is a perfect place to start discussions about acceptance criteria for activities to be performed during the course of a project. Acceptance criteria help you ascertain whether an ongoing technology transfer is successful at a given time. An absence of clear acceptance criteria before an activity leads to misaligned expectations of success, resulting in frustration and disappointment on all sides.

Acceptance criteria should be based on known data (usually generated during product development at a transferring and/or receiving site) and aligned to the project stage. Time should be invested as early in the program as possible to define acceptance criteria and how they will be documented. That includes formal training and development reports used to document a transfer process as well as the process description and associated documentation.

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Process Development and/or Improvements

Status and robustness of transferred processes can vary extremely, from client to another and often correlate to clients' understanding of good manufacturing practices (GMPs) and what is appropriate for each phase of a planned clinical trial. Processes that have been adapted to work well in R&D and academic/hospital GMP facilities are not always directly transferable to a GMP manufacturing setting. Anticipated and unanticipated adaptations might be involved. Some examples follow.

Changes in Incoming Product Materials: Incoming product materials collected from healthy individuals might differ from those collected from patients undergoing treatment. This carries a risk of unanticipated effects on manufacturing processes and analytical methods.

Changes in Scale: For patient-specific products, subbatch processing (splitting a lot to compare processes at transfer and receiving sites) might not be feasible. For allogeneic products, relatively small changes in scale can have unanticipated effects on a process.

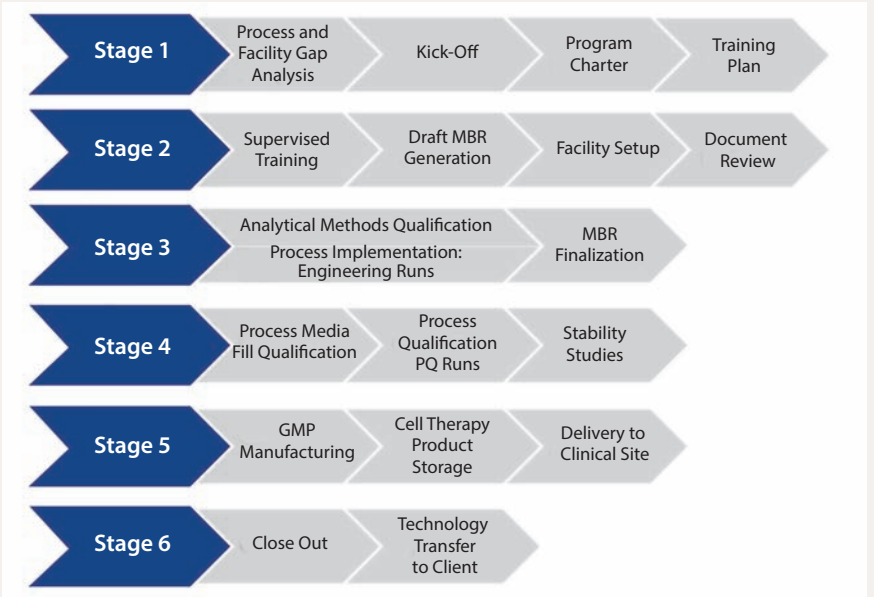
Changes in Procedure: Changing a bioreactor or expansion vessel type, for example, or transitioning from tissue culture flasks to culture bags is highly likely to affect a process.

Changes in Raw Materials: A conversion from research-grade to CGMP-compliant in-process materials can have unanticipated effects on a process.

Changes in Timing Before and After Processing: As mentioned in part 1, for example, a change in proximity of raw material collection and manufacturing site can have a significant impact.

Manufacturing timing can change in a cleanroom environment because of CGMP constraints. For example, movement in and out of a biosafety cabinet (BSC), extra time needed for documentation, and a need for real-time process verification by an independent operator all can add time. In-process monitoring of process parameters (e.g., cell counts) normally

Figure 1: Streamlining technology transfer



performed by an operator in an R&D laboratory often takes longer when samples must be sent out of a controlled-environment room (CER) to a quality control (QC) associate in another laboratory. So hold steps relying on a cell count can be significantly increased.

Changes in Product Storage and Shipment: Cell therapy products often are developed to be manufactured and shipped at a controlled temperature to a clinical site. But they have a limited shelf life as a result, which creates supply chain risks and potential product failure. Shipping and stability (including cryopreservation) studies typically are used in Stage 4 (Figure 1) to direct implementation of beneficial changes.

Changes in Analytical Assays: Development of more robust analytical methods (typically involving new equipment and protocols) can be evaluated and integrated into a technology transfer strategy.

Development requires process change, although such changes are best avoided during technology transfer. Process changes can seriously affect a program, and they are ideally implemented once transfer is complete under change control. A sponsor should understand that a contract development and manufacturing organization's (CDMO's) facility and operations do not need to be an exact replica of its own. Instead, the collective team should ensure that

- a process being transferred is robust and well-understood, with data-driven acceptance criteria
- the CDMO's facility, material flow, and environmental controls meet set process requirements
- equipment meets process-specific specifications
- QC testing and analytical procedures meet established product and assay parameters
- the CDMO's quality systems provide the relevant controls needed for implementation
- change control and quality by design (QbD) principles are stringently applied to unit operation (UO) inputs and outputs to demonstrate comparability through reliable assays.

Training

The training process should be documented in a training plan with predefined acceptance criteria used to measure success. It should be compiled by collaboration among the sponsor, transferring site (if different), and CDMO. For example, before being assigned to a given program, PCT team members will have undergone comprehensive training that includes but is not limited to an understanding of GMP requirements, cleanroom operations, use of common equipment, and aseptic techniques (assessed using media fill qualification). QC associates have complementary training in common QC assays and associated equipment.

At the start of a program, paper training (reading client-supplied materials) should provide the first exposure to the new process, and training should continue to develop throughout the program. Hands-on training performed by transferring-site staff allows a CDMO to capture practices, experience, and knowledge not included or difficult to define in standard operating procedures (SOPs). It is also an opportunity for a CDMO to audit the process before transfer. Setting prospective acceptance criteria and expectations will help guide and measure training success.

Follow-up training at a CDMO's facility allows a sponsor (or transferring site) to observe CDMO staff and provide additional technical feedback that will be essential for successful process implementation. Such training also allows a sponsor to develop trust and confidence in a CDMO's technical proficiency. The CDMO staff will continue to develop their knowledge further as SOPs, work instructions (WIs), and master batch records (MBRs) are compiled and processes implemented. The outcome of all training activities should be documented in a training report and the success of those activities evaluated and agreed upon before moving to process implementation.

Process Implementation

A sponsor and/or transferring site and the CDMO receiving site together should detail the process implementation method in an engineering run protocol, with predefined acceptance criteria used

to measure success. During this stage, analytical methods normally undergo qualification using samples generated during engineering runs as test articles.

The combined team should perform a phase-appropriate assessment of the qualification/validation level for the cleanroom, equipment, ancillary and manufacturing procedures, and analytical methods suitable for implementation before beginning engineering runs. That assessment should account for regulatory requirements while focusing on practical concerns in the context of the process being transferred (risk assessment). A CDMO's prior experience will be particularly valuable at this stage.

Performing an additional engineering run provides additional risk mitigation. During that run, a transferred process is performed in the cleanroom environment in Stage 3 before proceeding to PQ. The practice of executing a "dress rehearsal" also provides an opportunity to continue comparison with sponsor- and/or transferring site-manufactured product and process. Final adjustments to the process can be made at this point, along with adjustment of relevant documents and retraining deemed necessary.

During process implementation, acceptance criteria are normally narrower than those used during training runs and are again used to measure success. Data and observations from engineering runs should be captured in a report that will be jointly reviewed by both parties before making a decision to move on to PQ runs. Failure to make that assessment and jointly agree on a decision to move forward — based on timeline restrictions or other external factors — can result in failures down the line that are difficult to overcome.

Technology Transfer Case Studies

Critical Raw-Material Shortages
Example: Custom order for medium or supplement

Assumption: In-house stocks or secured lots will be sufficient should a manufacturer have a lot failure.

Risk of Failure: Medium probability, high impact

Mitigation: Secure lots with supplier

Mitigation Breakdown: Supplier had multiple successive lot failures.

PCT-Recommended Mitigation: Identify backup independent suppliers for critical materials.

Noncritical Raw-Material Shortage
Example: Normal saline

Assumption: A commonly used raw material will never be in short supply; multiple suppliers can be used should one supplier run out of material.

Risk of Failure: Low probability, high impact

Mitigation: Multiple suppliers manufacture and sell normal saline.

Mitigation Breakdown: A major US supplier reduced production that resulted in a severe shortage

PCT-Recommended Mitigation: Monitor supply chain of all materials carefully and increase in-house supplies and/or identify backup suppliers for noncritical raw materials.

Importance of Tribal Knowledge
Example: Trypan blue exclusion assay for the determination of viable-cell concentration and percent viability

Assumption: Standard procedures are performed in the same way in different laboratories.

Risk of Failure: Low probability, high impact

Mitigation: Staff at receiving site are highly trained in this assay and shown to have similar competency to each other by comparing similarity of cell counts and viability on the same samples.

Mitigation Breakdown: Transferring site had in-house modifications to the assay not transferred to the receiving site

PCT-Recommended Mitigations: Share data (ranges and variability) generated by a transferring site, and use this to assess data generated by the receiving site. Train receiving site staff at the transferring site facility.

Logistics and Product Stability
Example: Shipment of incoming raw material (e.g., apheresis) to manufacturing site or final product to clinical site

Assumption: Shipment will always be completed within 24 hours because shipping companies state that they can perform overnight shipment and delivery; 24-hour stability studies and shipping qualifications performed

Risk of Failure: Low probability, high impact

Mitigation: Careful monitoring of shipment in collaboration with shipping company will ensure delivery within a 24-hour window.

Mitigation Breakdown: During extreme weather events, shipments can be delayed while weather conditions improve. Shipping companies can lose track of shipments. Shipments can be held up in unexpected locations.

PCT-Recommended Mitigations: Do not underestimate the importance of good logistics management of shipments. Use a courier service (rather than a shipping company) to transport critical raw material and/or final product. Design and qualify shipping procedures for as long as possible (not <48 hours).

Process Qualification

A sponsor and/or transferring site and CDMO receiving site together should detail the PQ processes in a PQ run protocol, with predefined acceptance criteria used to measure success. PQ runs are performed according to a prospectively determined set of criteria following an MBR. By contrast with engineering runs, PQ runs are "locked down" following process implementation. PQ runs follow the finalized process that will be used for clinical manufacturing and should be treated as such. These runs provide an opportunity to perform all finalized steps in sequence, from beginning to end (including QC testing). Whenever possible, they should simulate the clinical process from raw material collection and shipment through to final product release and shipment.

Just as with engineering runs, data and observations from PQ runs should be reviewed by both parties collaboratively before making a joint decision to move on to clinical manufacturing. Clients typically use information in PQ reports to support investigational new drug (IND) applications (or equivalent)

and comparability assessments based on prospectively set criteria.

Once PQ runs have been performed, a media-fill qualification of the process based on phase-appropriate risk assessment might be necessary. In such cases, the process (or parts of it) is replicated using tryptic soy broth (TSB) in lieu of medium and buffers used during clinical manufacturing. Samples are collected at regular intervals throughout this process and tested for sterility.

Clinical Manufacturing

A successful, streamlined program ultimately reaches GMP manufacturing (Stage 5, Figure 1) cost-effectively. It should consist of a firmly established, robust, and reliable qualified process with analytical assays, governed by an MBR and other controlled documents to allow production of tens to hundreds of GMP cell therapy batches at a CDMO site.

During implementation of a qualified process for the first few patients, a need often arises for ongoing troubleshooting and optimizing. That is based on the use of clinical sites for collection and dosing as well as the use of clinical material for the manufacturing process itself. In such cases, critical process parameters (CPPs) and unit operations can provide an ongoing and disciplined approach to maintaining process control.

As previously noted, before clinical manufacturing, technology transfer often is performed using raw material collected from healthy individuals by nonclinical collection facilities. However, materials from affected patients (clinical trial subjects) can vary considerably from those collected from healthy individuals. Such differences can result from the disease state of patients or from collection procedures implemented by clinical facilities. Either way, the result is a raw material that is different from what the CDMO had previously encountered during technology transfer. Such differences can affect the manufacturing process or the ability of a QC laboratory to reliably perform its assays.

Ongoing discussion and dialog among all parties is critical at this time. Tackling problems (if and when they arise) requires a calm and methodological approach. Once those issues have been ironed out, clinical manufacturing usually becomes routine.

However, a transferring site should nonetheless ensure that a process doesn't become "trapped" at the CDMO, developing barriers to the "transfer-out" of the process to another sponsor-designated facility. Stage 6 of Figure 1 incorporates a defined and structured strategy for successful process transfer out of a CMDO if and when required.

Risk Management

Gaps and risks should be evaluated regularly and consistently at the beginning of technology transfer and move forward consistently. Large and expected risks are proactively addressed usually at the start of technology transfer. Small or unforeseen risks that are not identified early can have unanticipated negative effects on a project and could even stop the project altogether. For example, single-vendor suppliers of common and critical materials are a well-known risk. A lot failure by a vendor or a company acquisition can result in a raw material becoming no longer available, and an alternative will need to be found or the process changed or adapted. That could lead to the need for comparability studies before continuing with patient accrual in a trial, resulting in unanticipated delays. The "Technology Transfer Case Studies" box describes other potential risks and mitigation strategies.

Strategy for Success

Cell-based therapeutics come with inherent variability and present unique challenges for technology transfer processes. Having a structured, strategic approach will minimize risk and enable transferring sites to generate greater value for process and product. A clear, long-term vision of the process and product — combined with CDMO expertise to navigate the technology transfer pathway — will help position a cell-based therapeutic for commercial success.

Reference

1 McIntyre C, Sumen C. Are You Ready for a Tech Transfer? Part 1: Challenges and Critical Factors for Success in Cell-Therapy Development. *BioProcess Int.* 13(4) 2015: S44–S47.

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