# SUPPORTING THE TECH TRANSFER CONTINUUM FOR CELL & GENE THERAPIES

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As growing numbers of biopharmaceutical companies experience clinical success with new cell and gene therapies, they are satisfying their development and manufacturing needs in collaboration with contract service providers. Those organizations that can support the continuum of tech transfer projects from preclinical to commercial manufacturing will be best positioned to meet the expanding needs of the marketplace.

## TECH TRANSFER CONTINUUM

Technology transfer of cell- and gene-therapy production processes is a complex undertaking that can occur at different stages of development. The reasons for transferring a process vary significantly and often correlate with the maturity of the process.

When companies initiate development programs for next-generation therapies, they often rely on assistance from university laboratories or other academic institutions for production of the small quantities of material required for early studies. They may find, however, that those organizations are unable or unwilling to license cell lines and other reagents used in manufacturing at later stages. Additionally, the cell lines may not be very well characterized or the pedigree is unknown, information that is necessary for an FDA biologics license application (BLA) filing and commercial production.

In these cases, the company must turn to a contract development and manufacturing organization (CDMO) that can help identify appropriate cell line platforms, create master cell banks, identify and source raw materials and design production and purification strategies to generate products that meet purity and safety standards and other desired quality attribute specifications. In some cases, both raw material and product specifications must be established. Processes and analytical methods must be developed and qualified using reliable standards and controls. Batch and test records also need to be drafted.

Companies further along in the development cycle may need a horizontal transfer of information to switch service providers in order to gain access to larger-scale production capabilities. There are currently a limited number of CDMOs that can provide support for the commercialization of these advanced therapies. Most projects, therefore, require the transfer from one outsourcing partner to another as they advance to Phase III and beyond.

Clients who are in the midst of Phase I/II studies often produce clinical material using less-than-optimal processes. Typically the process controls and methods need to be optimized to establish a process and analytics suitable for Phase III trials. There are consequently opportunities in vertical transfer of information to incorporate improvements, not only in the processes themselves but also the analytical methods that support them.

Mature projects that are moving from Phase III into commercial production can present challenges of their own. Difficulties may arise when client processes are not as characterized or controlled as would be expected based on client descriptions. It is essential that sponsor firms transferring next generation technologies to CDMOs be fully aware of the actual state of their processes and accurately describe them to their outsourcing partners prior to project initiation.

## THE REGULATORY PERSPECTIVE

Pharmaceutical technology transfer as defined by the Parenteral Drug Association (PDA) "consists of planned and controlled actions that are based on well-defined acceptance criteria to convey a manufacturing process, analytical method, packaging component, or any other step or process along the pharmaceutical drug lifecycle from an originator site, known as a sending unit (SU), to a new site, the receiving unit (RU)."[1]

The goal of tech transfer as outlined in ICH Q10 is to "transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization." This knowledge "forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement."[2]

Controls for transfer of processes, documentation and professional expertise are essential, according to the World Health Organization, which states that "Technology transfer embodies both the transfer of documentation and the demonstrated ability of the RU to effectively perform the critical elements of the transferred technology to the satisfaction of all parties and any applicable regulatory bodies."[3]

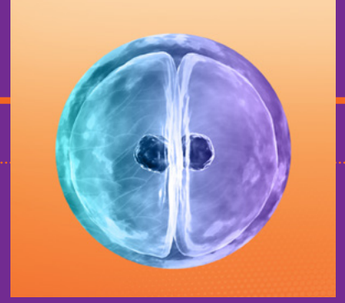
Overall, technology transfer should be pursued using a science and risk-based approach that achieves a balance between risk minimization and cost-effectiveness while aligning with applicable regulatory expectations.[4]

## HIGHLY STRUCTURED APPROACH

Inefficiencies during technology transfer can have significant, negative time and cost consequences and may also lead to the need for additional process development work.[5] Personalized medicines such as cell and gene therapies in fact have the potential to suffer from greater manufacturing variability due to the increased influence of the underlying biology, which can lead to inefficiencies in technology transfer.[6]

Regardless of the maturation stage of a next-generation therapy project or the type of technology transfer to a CDMO, technology transfer should follow a highly structured approach[7], starting with robust information exchange through provision of a comprehensive technology transfer document package or technology transfer package that contains the process description, process parameters, process performance, and a process development report.[5] Any available information on the analytical requirements and processes should also be provided.[7] Other aspects of an effective technology transfer program include an agreed-upon, detailed project transfer strategy with clearly delineated acceptance criteria for all steps of the tech transfer process, including final GMP manufacture[8,9]; established project management procedures; small-scale runs to verify performance; and at least one pre-GMP engineering run.[7]

Technology transfer begins with sharing of all relevant information including safety aspects (e.g. safety profile, material safety data sheets, biosafety level concerns, etc.) and process (e.g. cell line, manufacturing reagents, process conditions, purification methodology etc.), and analytical (e.g. protocols, custom reagents, assay standards,



## Tech Transfer **at Brammer**

Brammer Bio was established in 2006 as a biologics CDMO focused on providing process development, clinical and commercial supply of autologous and allogeneic cell therapies, and viral vector products used for ex vivo and in vivo applications. With facilities for early -stage projects in Florida, and late-stage and commercial manufacturing projects in Massachusetts, the company can transfer in external projects all along the product development continuum as well as transfer projects internally as they progress from early to later stages.

The emphasis at Brammer Bio is on communication and transparency. We listen intently to our clients and work hard to ensure that our client team is aligned on all aspects of a project. Brammer's technology transfer teams include experienced scientists from all areas relevant to each individual project (e.g. process development, analytical development, manufacturing, quality, etc.) and are facilitated by a dedicated project manager. Each team member has clearly defined responsibilities and each interacts with their counterpart on the client or internal project team to ensure close, frequent and transparent interactions.

At Brammer Bio's Florida facility, we provide process development support as well as the production of GMP material for Phase I/II studies. In Massachusetts, we have the capability to support both large- and small-volume late-stage and commercial manufacturing, including formulation development and fill/finish services. In both locations, we also provide analytics development and testing. To facilitate tech transfer between Brammer's Florida and Massachusetts sites, we have an SU team in Florida and a RU team in Massachusetts with extensive experience managing the internal transfer of projects. Brammer's tech transfer teams accept projects from clients directly into Florida for early phase support and into Massachusetts for late phase support. The Florida tech transfer team's experience, together with input from the Massachusetts team, allows them to develop controlled processes and analytics with a perspective for large scale manufacturing, even at an early stage. The Florida SU together with the Massachusetts RU facilitates the seamless transfer of technology for late stage manufacturing, thereby streamlining and accelerating the lifecycle of a product to market.

Clients that transfer projects to Brammer Bio benefit from the collective learning and depth of knowledge regarding process development and the identification of optimal solutions gained by the company during the completion of over 100 client projects and the delivery of over 150 clinical lots for human trials. This high level of both process and analytical development, and clinical supply and commercial manufacturing expertise makes Brammer Bio a comprehensive, integrated outsourcing partner for pharmaceutical companies requiring assistance with their next-generation therapy projects.

etc.) details. In essence, the client must provide all of the available information that will enable the CDMO to design, develop, optimize or implement processes resource efficient manner depending on their level of maturity.

The CDMO must also ensure that its technology transfer team is closely aligned with the client's team with regard to all facets of the project, including the development program, manufacturing requirements, and product release requirements. Close collaboration with transparent, two-way communication facilitates a successful technology transfer and successful project completion. Direct communication between scientists and engineers at the SU and RU is essential to success.[7] In addition to alignment of the SU and RU, alignment of the information technology and quality systems, culture, and project management and problem solving approaches is equally important.[10]

## VIRAL VECTOR TECHNOLOGY TRANSFER SOLUTIONS

As mentioned above, the range of support required during the transfer of projects focused on next-generation therapies varies from project to project, and along the product lifecycle.

One of the most common issues is raw material sourcing. Many clients bring processes to CDMOs that use raw materials that are not appropriate for GMP manufacturing, such as uncharacterized animal-derived materials or chemicals of a lower grade than is suitable. CDMOs must have the capability to identify appropriate alternatives and perform the necessary comparability studies to show that they achieve similar process yields and similar product quality attributes.

It is also not unusual to have processes transferred to CDMOs that are not practical at larger scale. For instance, the upstream cell-culture configuration may be inappropriate for the scales needed at later stages; early processes conducted on flat stock often do not scale easily to the lot sizes needed for later-stage clinical studies, and thus the process may need to be redesigned. One primary downstream processing example is centrifugation, where a CDMO will develop a filtration or chromatographic purification method as an alternative. Some clients require assistance with formulation development as well, such as determining the appropriate concentration, packaging (e.g. which vial to use) and fill volume to ensure delivery of the correct dose with minimal product loss.

With respect to analytical methods, protocols often need to be developed to support manufacturing processes. In many cases, characterized references standards for the analytical methods also need to be established. The assays need to be qualified and then fully validated to support release of the product at different stages of development. P

## ABOUT THE AUTHORS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**Dr. Tate** has over 10 years experience purifying various biologics, including viruses, and has been integral in developing the technology transfer procedures at Brammer Bio. Dr. Tate received her Doctoral degree in biology from The State University of New York at Buffalo, where she also received a B.S and. BA in chemistry and biology respectively.

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**Matt** has over thirty years of experience in biopharmaceutical development and operations. Prior to Brammer, he served as Director of Cell Culture Development at Gallus/Patheon Biologics where he was responsible for the development and/or tech transfer of over 20 phase I-III programs. Prior to joining Patheon, Matt worked as a Director of the Cell Sciences Development group for Sigma-Aldrich where he led a team of over 50 scientists and worked on over 30 different molecules or cell systems.

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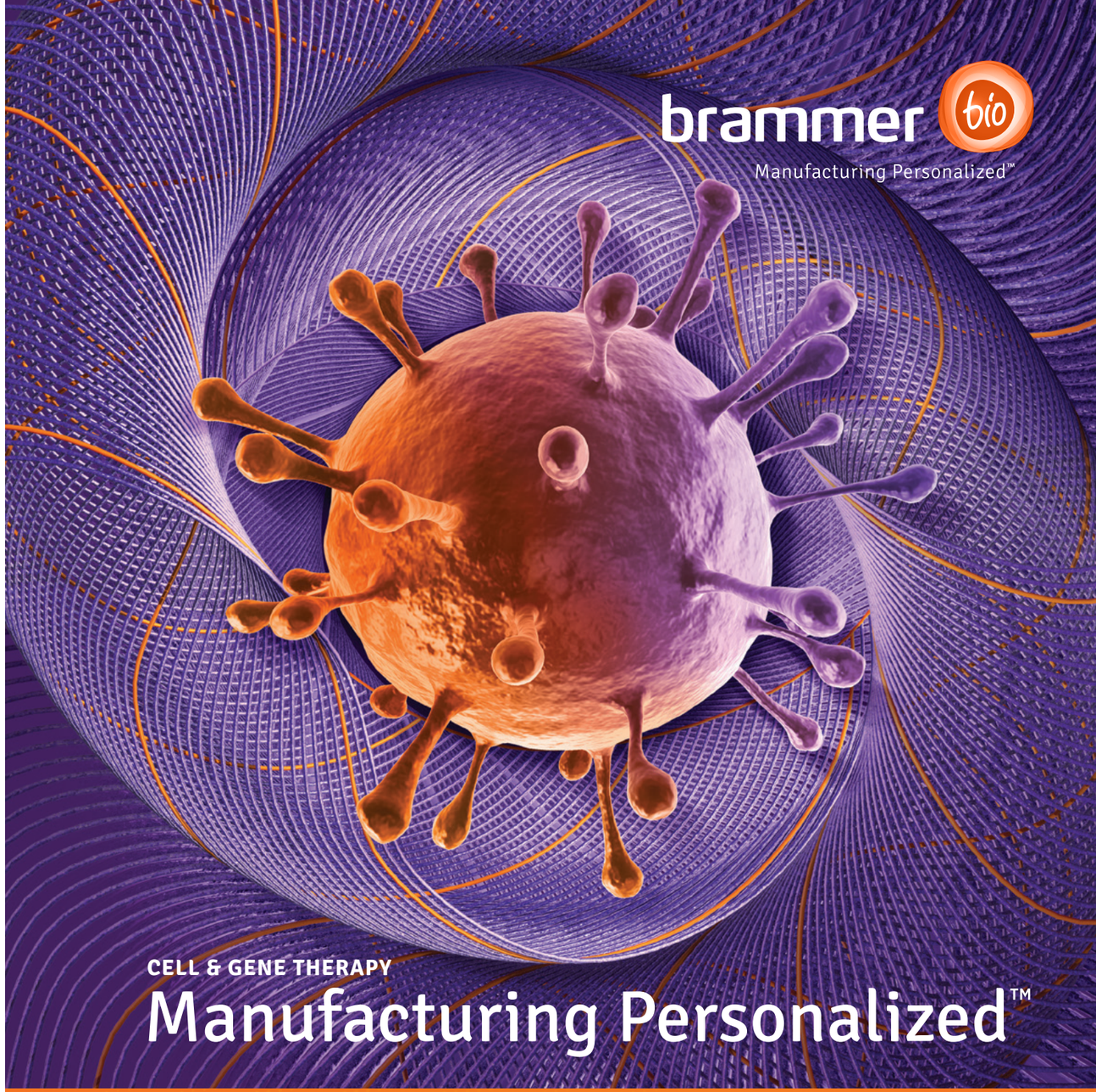


BEST-IN-CLASS CONTRACT MANUFACTURING

Brammer Bio is a CDMO focused on providing process development, clinical, and commercial supply of viral vector and cell and gene therapy products, enabling the delivery of novel medicines and improving patient health. We have a highly skilled team of scientists with the development, manufacturing and analytical expertise from 100 client projects that is required to tackle the challenges posed by these novel technologies and help accelerate their transition from the clinic to patients in need while focusing on meeting cGMP standards. Brammer Bio has the expertise to support your gene and cell therapy projects to Phase III and beyond.

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