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How single-use technology will be critical to the commercialization of cell and gene therapies

Scaling up cell & gene therapies from research and development to commercialization is creating a new set of challenges for manufacturers.

With the urgent demand of speeding up the market reach for these life-altering innovative therapies a high risk is inherent to implement inefficient workflow processes. This article will demonstrate, how adopting innovative single-use solutions for in-process sampling can have a tremendous effect in efficiency and effectiveness to the workflow. Single-use solutions continue to provide productive strategies in effectively scaling up these processes while reducing risks and costs.

Cell and gene therapies are an effective modality for treating and even curing complex diseases, with rapid advancements in therapy development that have resulted in significant regulatory approvals in recent years. The first CAR-T therapies, tisagenlecleucel (Kymriah® from Novartis) for pediatric acute lymphoblastic leukemia and onasemnogene abeparvovec-xioi (Zolgensma® from AveXis) for spinal muscular atrophy with children under the age of 2, are two examples of treatment and curative options that were not available with API drugs before[1] With more than 1,000 clinical trials in cell and gene therapy applications ongoing in this space, over the next few years a large number of these products are likely to come to market (see Fig. 1-2).[2]

When compared to the production and delivery of monoclonal antibodies (mAb) therapies, moving novel cell and gene therapies from process development and clinical stages to commercial, large scale manufacturing has introduced a host of new challenges. Bringing a new product to market will always present a multitude of challenges with logistics, infrastructure and finding highly skilled labor. Additionally, safety and efficacy of the therapy are always going to be a concern for the manufacturer, but the challenges facing these manufactures is resulting in new solutions having to be developed and designed to overcome these new obstacles to commercialization.

These obstacles are becoming increasingly complex, due to the nature in which cell and gene therapies are produced and delivered to patients. Dr. Scott Gottlieb, M.D., former commissioner of the U.S. Food and Drug Administration (FDA), spoke about this issue in 2019, saying: "In contrast to traditional drug review, some of the more challenging questions when it comes to gene therapy relate to drug manufacturing and quality."[3] Autologous therapies indeed present a greater challenge during production scale-up due to the personalization of these medicines – that is, one batch for each patient. Each manufacturing lot is unique and every therapy starts with material from the patient that is then processed through the manufacturing workflow and transported back to that patient for administration.

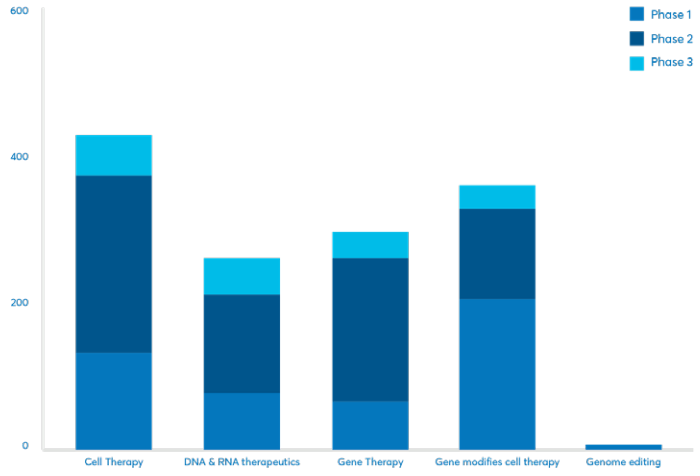

Figure 1. Clinical activity for cell and gene therapies in terms of trial phase.[2]

There are a multitude of issues to be concerned with when scaling a drug manufacturing process normally, and the life-altering potential of these therapies has only created more momentum.[4] The demand for reducing the time that a therapy reaches the market is pushing manufacturers to implement rudimentary, lab scale processes into commercialization level that are neither efficient nor effective in the long run. In the case of an autologous cell therapy and some gene therapy process, the batch sizes (working volumes) can be quite small with poor yield. Understanding this early in process development can be critical in how the processes are scaled in a production setting (for example, identifying manual operations that are being performed inside a biological safety cabinet.) Designing new fluid pathways to move liquid from unit operations while still maintaining sterility and integrity will be critical to scale-up success.

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IMPLEMENTING SINGLE-USE SAMPLING METHODS IN CELL AND GENE MANUFACTURING

Personalized therapies are unique in that the entire manufacturing process and each of its inputs are the product itself – as it is often said, "the process is the product." Many of these processes cannot be sterile filtered prior to formulation and fill finish, so all inputs into that process are the product that will be administered. In a low yield process, being mindful of areas of loss can improve overall yield and controlling the amount of fluid sampled for in-process measurements can have a dramatic effect on final yield.

Single-use technology (SUT) are offering a more flexible, cost-effective and safer approach to sterile fluid handling in cell and gene therapy manufacturing when compared to traditional methods in place today. While sterile and efficient sampling at each stage of the process is one of the more critical steps in every biopharma manufacturing workflow, cell and gene manufacturing requires small batch sampling under aseptic conditions to preserve the limited material from and for the intended patient – all while complying to regulatory standards and facilitating scientifically sound and representative results. Single-use solutions are one of the most efficient strategies in effectively scaling up these therapies by improving workflows and reducing system risks and costs.

SYSTEM-RELEVANT RISK REDUCTION: OPEN VS. CLOSED SYSTEMS

Many current cell and gene manufacturing processes are manual and labor intensive, particularly around fluid management and sampling, with an estimate of three-times more hands-on operations than for traditional biologic manufacturing.[5] Many operations are performed in an open-system workflow that is inherited from the clinical stage and carried into the commercialization stage, or adapted from traditional methods of sampling. The conical tube, for example, is a staple product found in virtually every laboratory and production setting, used in a traditional way by removing the cap it is commonly used for taking open samples from a process.

Open, manual (and therefore, variable) manipulations are often conducted in biologic safety cabinets within a Class 10,000/Grade B cleanroom, an isolator or glove box. These methods share a

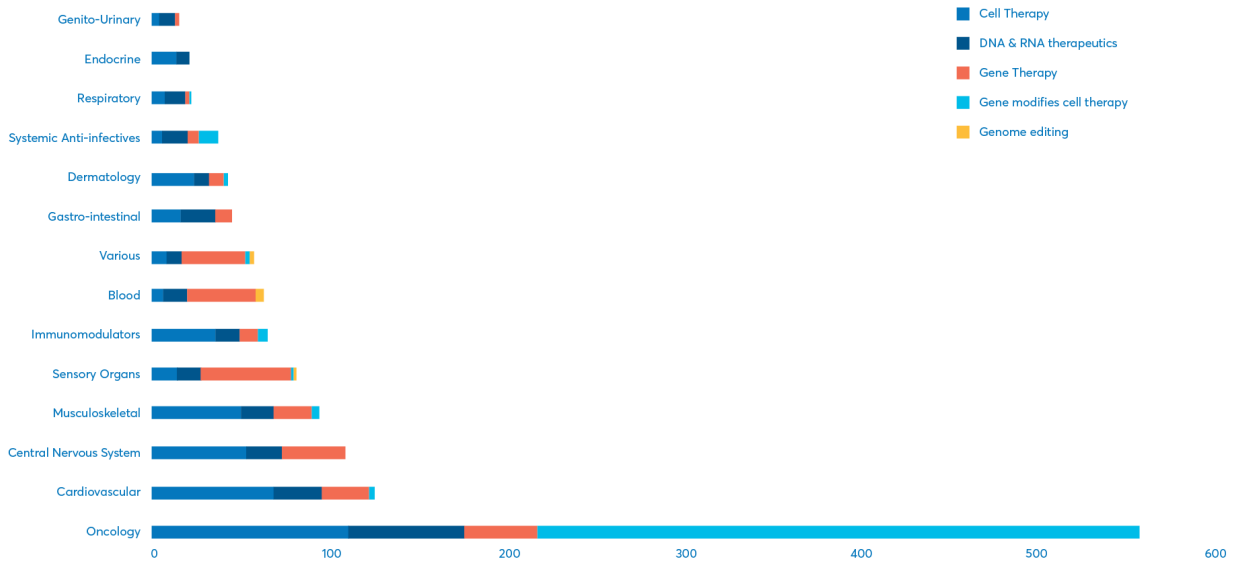

Figure 2. Clinical activity for cell and gene therapies in terms of trial phase.[2]

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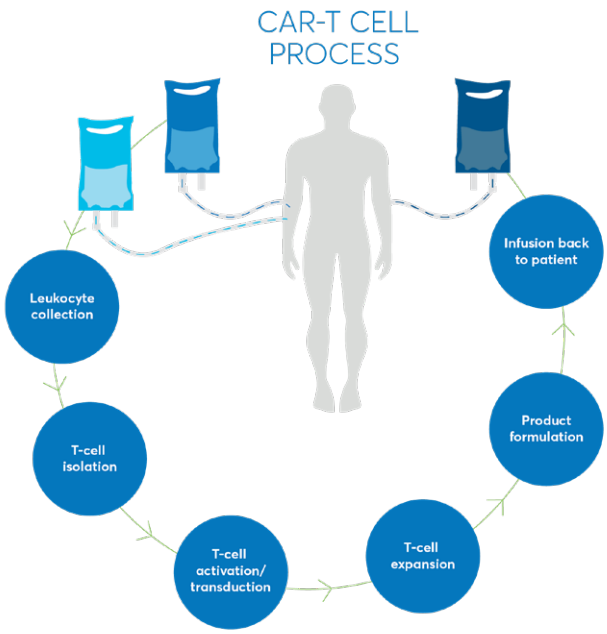

Figure 3. Generic workflow for CAR-T therapy.

common increased risk of contamination and batch loss as they are all exposed to the production environment with the potential for human variability and error. This is especially critical in cell and gene therapy manufacturing as many sampling steps are needed, final filtration/sterilization steps cannot be used as the cells are not able to withstand terminal sterilization methods and – most importantly – there is no back-up if the process is contaminated. Moreover, open processes not only can have the potential for inaccurate results about a process and its parameters, but an operator relying on this data may then make misinformed choices about the batch in production, further putting the process at risk.

Closed-system solutions enabled by single-use technology provide an aseptic alternative to these otherwise open processes. Sampling platforms like the Avantor OmniTop Sample Tubes® system offer a new alternative choice to help ensure accuracy in these sampling process steps when using conical tubes. The OmniTop Sample Tubes® system provides a means to draw liquid into the conical tube without removing the cap, ensuring a closed system solution for sampling in both monoclonal antibody and vaccine production, where sampling volumes are not limited by the overall volume of the process. By reducing the risk of contamination by removing exposure to the production environment, the sampling process becomes more secure and efficient, with benefits that include improved material robustness and reproducibility, sterility assurance, easier pathway for introducing sampling automation.

INCREASING YIELD: EXACT VOLUME SAMPLING

Cell and gene therapy manufacturing is divided in autologous (therapy that relies on cells from the patient) and allogenic (therapy that relies on a single source of cells to treat many different patients). Immunotherapy approaches, such as CAR-T technology, are autologous and thus supply chains and manufacturing are driven batch-to-batch by a small starting volume and a high number of sampling requirements. Because sampling is a net negative process, any volume removed will have a negative effect of the overall yield.

A method to remove an exact sampling volume necessary for analytical testing can reduce the amount of any excess volume removed, thereby increasing the overall product yield. Systems such as the Avantor Omnitop Sample Tubes® sampling platform with an adjustable volume sampling system (AVSS) are especially beneficial in critical small sampling scenarios like cell and gene manufacturing for the precision and control that they offer in drawing the sample. The Omnitop Sample Tubes® AVSS enables manufacturers to collect the exact volume sample required for testing while eliminating volume loss typically associated with sampling due to line losses or pre-flush requirements. The system is driven by two pre-attached syringes that are sterilized with the sample collection vessel, allowing for simple manipulation of fluid flow. An adjustment tool allows users to move the adjustable dip tube within the Omnitop Sample Tubes® system to the collection volume needed, to as little as 0.5 mL.

CONCLUSION

Cell and gene therapies are providing unprecedented methods of treatment and curative medicines, however working with living cells is much more complex than other protein-based therapeutics, such as monoclonal antibodies (mAbs). Autologous cells as the starting material mean a significant batch-to-batch variation, adding complexity to the process. It is therefore critical that the sampling methodology is consistent and does not provide any additional process variation.

The Omnitop Sample Tubes® AVSS enables manufacturers to collect the exact volume sample required for testing while eliminating volume loss typically associated with sampling due to line losses or pre-flush requirements.

Cell and gene manufacturers are benefitting from collaborating with suppliers to tailor single-use systems and technology to the individual manufacturing requirements in the sampling process, giving way to custom-designed pathways with a wide variety of components and available connections that allow efficiency and process security in these workflows. With the precision and security of single-use sampling solutions, some of the main challenges in cell and gene manufacturing can be improved with the implementation of closed-system processing using ready-to-use sterilized solutions to mitigate contamination risk and enable automation, and low-volume sample management systems that help to increase product yields by reducing over-volume sampling and line losses.

Continuous investment in innovation and collaboration is required and suppliers to the industry can make valuable contributions to cell and gene therapy production based on their existing expertise, technology capabilities and commitment to providing solutions. This is the fundamental goal of scalability and, with a continuous commitment to innovation and collaboration across the industry, the life-changing, life-saving potential of cell and gene therapy can be realized.

Figure 4. The Avantor Omnitop Sample Tubes® AVSS Adjustable Volume Sampling System, designed to pull exact volume samples and eliminate fluid line losses, for the most critical applications.

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Tim has 20+ years of experience as an engineer and business development with VWR, PAW BioScience Products, and Biopure Corporation where he has designed single-use products, components, and systems that are used by the global drug and vaccine manufacturing industry.

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