

EXPERT INSIGHT

Points to Consider for Cell Manufacturing Equipment and Components

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Advances in manufacturing technologies, as well as early development and adoption of industry-wide standards will contribute to a vibrant industry for cell-based therapeutic products (CTP). A critical aspect is manufacturing equipment that can address specific and unique challenges associated with CTP manufacturing. The move towards fully closed and automated systems heightens the need for integrated and standardized strategies to ensure the manufacturing of CTPs with controlled safety and quality profiles. This paper summarizes key points to consider for cell manufacturing equipment and components. In addition to enabling common baseline understanding for equipment requirements, it is meant to stimulate broader discussions for developing best practices and standards for CTP manufacturing equipment.

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Cell-based therapeutic products (CTP) have gained significant momentum with recent advances in biology that have led to clinical successes and increased investment and efforts toward commercialization. Yet a robust manufacturing ecosystem for this nascent industry is required to bring various CTPs to

the market [1,2]. A critical gap in the manufacturing ecosystem is the need for better cell manufacturing equipment [3].

Equipment systems used in various steps (or unit operations) of CTP manufacturing may include instruments for cell collection, cell isolation/selection, cell expansion,

cell washing and volume reduction, cell storage and transportation. The unit operations can vary immensely based on the manufacturing model (i.e., autologous vs allogenic), cell type, intended purpose, among other factors. In addition, cells are “living” entities highly sensitive to even the simplest manipulations (such



as differences in a cell transferring procedure). The role of cell manufacturing equipment cannot be understated.

Much of the cell manufacturing equipment in current use was originally designed for other purposes and has been adapted for use in CTP manufacturing. For example, CTP manufacturing has borrowed bioreactors originally designed for biologics manufacturing or cell collection equipment originally designed as medical devices (e.g., apheresis machine). While this makeshift equipment has helped to produce clinical material for use in clinical trials, more robust equipment addressing specific and unique CTP manufacturing challenges and critical quality attributes (CQAs) is required to build a vibrant industry.

Below we list specific needs for cell manufacturing equipment, including challenges associated with direct adoption of equipment or devices designed for other purposes. Firstly, there is an immediate need to develop fully closed systems to ensure the safety of the final product. As the field is moving toward automation to reduce manufacturing variabilities and increase throughput [4], proper connections will become critically important when integrating and repurposing existing equipment between upstream and downstream processes. Secondly, manufacturing processes for CTPs are inherently very different from biologics manufacturing. In contrast to biologics manufacturing that uses well-characterized clonal cell lines as the starting material, CTP, particularly autologous CTP, uses cells collected and isolated from patients (e.g., monocytes, lymphocytes) which can have significant variability; therefore, additional equipment is required to further

process cells to target sub-populations. In addition, the product of a biologics manufacturing can be isolated and purified, but the products of CTP manufacturing have fewer purification options. Intrinsically, any equipment component that comes into direct or indirect contact with cells could potentially introduce impurities and toxicities to the final cell product. Thirdly, some of the devices borrowed from the medical device industry are regulated differently and cannot appropriately meet the requirements for cell manufacturing. Lastly, CTPs represent a broad and complex class of products, each of which has its own set of critical quality attributes (CQA). Equipment must be designed and optimized to process cells with controlled safety and quality profiles for a given CTP. We believe manufacturing technology advancements as well as early development and adoption of industry-wide standards will be critical to accelerate innovation for the cell therapy industry.

At the moment, there are no standards specifically addressing unique requirements associated with CTP manufacturing equipment. On the other hand, many standards exist for more mature sectors, such as medical devices [5] and biopharmaceutical manufacturing [6]. In the absence of specific cell manufacturing standards, guidances and guidelines are issued by harmonization and standardization organizations in an attempt to address the lack of standards. However, many companies have adopted concepts from existing standards and best practices based on their own interpretations. Those interpretations may result in an unnecessary increase in cost associated to the application of

standards that are either too stringent or too lax for the manufacturing of these novel therapeutic products. A broad discussion is needed to harmonize best practices and to address unique challenges for CTP manufacturing equipment. This perspective article attempts to describe points to consider and is meant to engage broader discussions with respect to the design, specification, validation, corrective and preventative actions, and documentation requirements for CTP manufacturing equipment. Broader industry input is needed to develop harmonized global standards. We envision that the same standards would be applicable in the manufacturing of all stages of clinical products, although pre-clinical use of these practices may facilitate the translation to clinical phases.

Importantly, cell manufacturing equipment should lead to the production of safe and effective CTPs, so they should be designed with safety (including sterility) and performance in mind. Here, we consider cell manufacturing equipment to be a system consisting of various components that are collectively used in one or more unit operations in a cell manufacturing process. Specific equipment components may include parts that come into contact with the cells that are often built as single use: consumables, and parts that do not come into contact with the cells (hardware and software). Important considerations for the equipment systems also include connection of parts, including connection to upstream or downstream unit operation systems. The use of proper equipment will help to ensure the quality of CTPs.

GENERAL CONSIDERATIONS

Current CTP manufacturing does not lend itself to sterilization at the end of the production; therefore, CTPs must be produced under aseptic conditions to ensure safety and sterility. Manufacturing of CTPs usually occurs in areas that are selected and designed on the basis of appropriate manufacturing guidelines, for instance ISO (which would dictate the classification of cleanroom [7]). As an example, use of class 100,000 gowning and storage rooms and class 10,000 cell manufacturing suites is commonly used. As the industry advances, some CTPs are manufactured within closed systems under less stringent cleanroom conditions. Single-use systems such as tubing and collection bags have been developed as closed systems and these systems allow cell manufacturing to be performed in lower grade cleanroom spaces as determined by a risk-based approach. It is important to note that if the process includes an open step, then that step should be performed in a suitable operating environment (such as a biosafety cabinet within Clean Room Class B).

With increasing use of disposable processing units or single-use systems, efforts are underway to better integrate various equipment components. Ideally, single-use systems can be integrated to enable fully closed manufacturing that connects upstream and/or downstream processing equipment. In the absence of fully integrated systems, suitable sterile connectors should be used to minimize risks of introducing contaminants into the process. Alternatively, tubing can be sterile-welded and sterile-sealed to allow connection between upstream or downstream processes.

Cell material in the manufacturing process must be carefully documented and maintained to ensure traceability. This aspect is being integrated and optimized as the industry is moving toward scaling out. If multiple cell manufacturing operations occur in parallel in the same cleanroom, each production stream must remain contained and must maintain separation, and processes for documentation and traceability may require additional validation and assurance. This is an area that most likely will be addressed by software development and data collection.

SAFETY & STERILITY

Any material that comes into contact with cells during the manufacturing process may introduce contaminants that could be carried into the final CTP. As CTPs are not terminally sterilized, it may be very difficult to remove certain impurities. Therefore, equipment parts that come into contact with cells should be designed and selected based on the best available information to minimize safety and sterility concerns of the final CTP [8].

When equipment comprises of single-use components, it is important to ensure stability of such consumables. CTP manufacturers should check for expiration dates determined by validated testing protocols, and usage limits regarding temperature, pressure and chemical compatibility provided by the equipment manufacturer. Integrity should be maintained throughout reasonable use including shipping, set-up, process run and take-down when used as directed by the equipment manufacturer.

Biocompatibility

Materials that come into contact with cells, either directly or indirectly, should be biocompatible. Materials that come into direct contact with cells include sample collection containers, harvest bags, bioreactors, tubing for transfer of cells, and direct-contact sensors. Plastic components such as bags should be animal product free and ideally meet the USP VI requirements. USP Plastic Class VI is one of six designations for plastics from General Chapter of the United States Pharmacopeia and National Formulary (USP-NF) and is directly applicable for medical devices, particularly implantables. During the CTP manufacturing process, any plastic that has prolonged contact time with cells should ideally be a USP Class VI material.

Indirect materials include culture media and buffer mixers, storage and delivery vessels, and tubing (non-cell contact). Materials with documented biocompatibility that are approved for direct medical use may provide more assurance as cell manufacturing equipment components. The biocompatibility of other materials should be assessed using existing standards, such as ISO 10993, or a risk-based approach. Materials containing potential allergens such as latex should be avoided.

Particulates

Cell processing equipment should not introduce a significant amount of particulate matter, defined as any amount that might compromise the safety or quality of the final product. Removal of foreign particles by terminal filtration is limited to particles that are significantly larger than cells; removal of sub-visible particles is difficult by filtration. New

separation technologies may help to address some of these challenges.

The appropriate upper limit of particles for a given CTP will likely vary from product to product and depend on the potential impact of particles on CTP's safety or efficacy. Other factors may include the nature and route of administration, the size and chemical composition of the particles. The cell therapy manufacturers are working to develop methods to evaluate particulate burden, including efforts to identify the particulates (size and nature), possible particle ingress routes into the equipment or cell process, and acceptable level for the intended use. Cell therapy equipment manufacturers are also actively developing and implementing controls in their manufacturing process to mitigate the risk of particle contamination or generation. These efforts would benefit from broad collaboration leading to standardized methods.

Extractable & Leachables

Extractable materials are chemical compounds that can be extracted from the system components that come in direct or indirect contact with the cellular material under extreme process conditions. Leachable materials are a subset of extractables that enter the manufacturing process stream under normal operating conditions and may potentially be detected in the final CTP. The potential for leaching of toxic compounds from system components that come in contact with the cellular material should be evaluated for parts comprised of plastic materials. Extractable and leachable materials may be a concern for single-use materials as the field moves toward their wider adoption.

Leachable materials include volatile, semi-volatile, and non-volatile organic compounds as well as inorganic elements. Examples of potential leachable compounds include plasticizers and cyclic esters derived from adhesive materials. In-process leachables (compounds released during the manufacturing process) may be of particular concern in cell therapy manufacturing as the leachables may directly impact cell viability and function, even if they are not present in the final cell therapy product.

Cell manufacturing equipment should be designed to reduce the use of toxic leachables. Leachability can be assessed using a wide range of methods, such as chromatography and spectroscopy. Studies on leachables should ideally be conducted under a wide-range of operating conditions including time, temperature, pH, representative media buffer, or combination of operating conditions with maximal operating extraction propensities.

Sterility & non-pyrogenicity

In addition to a lack of terminal sterile filtration and pyrogen removal step, a reduced window for microbial testing associated with CTPs makes it critical to maintain sterility and non-pyrogenicity of equipment. Strategies to ensure sterility of equipment include autoclaving of parts and *in situ* sterilization. Sterility and endotoxin certifications should be obtained for all materials for which the manufacturer has made a sterility claim. The equipment should be designed and utilized such that the number of in-process connections, such as tube welding, is minimized to reduce risk of contamination. In addition, equipment should be designed to

allow in-process sampling without opening the system. In cases where the sample must be done under an open environment, sampling frequency and technique should be assessed for the risk to compromising sterility and non-pyrogenicity (e.g., sanitization of sample port with alcohol prior to entry may help reduce bioburden load). Even for closed systems, pre-use integrity should be demonstrated by the manufacturer by pressure hold to minimize risk of containment breach. Sterilizing grade filters should be assessed for integrity post-use by an appropriate method such as bubble point, diffusive flow or pressure hold test. Testing the integrity of the sterilizing filter immediately after its use helps determine whether a breach in the fluid path had occurred during the sterilization process.

Toxicity of chemical sterilants

Single-use materials are increasingly employed to avoid potential risks associated with the use of chemical sterilants. For non-single-use materials, a chemical sterilant may be necessary to sterilize equipment or one or multiple equipment components. Chemical sterilants are generally selected based on toxicity, efficacy, kinetics of activity, material compatibility, ease and cost of use, and disposal process. In addition to selecting the most appropriate chemical sterilant, clean-in-place and steam-in-place processes should be validated for effective sterilization and removal of cleaning agent. The potential toxicity of chemical sterilants should be factored into considerations for utilizing components pre-sterilized by the assembly manufacturer versus conducting in-house cleaning and sterilization.

Validation of the post-sterilant washing process will help ensure that sterilants have been sufficiently removed prior to introduction of any cell-contacting materials. For liquid sterilants, those which are easily removed by rinsing may be more desirable.

EQUIPMENT PERFORMANCE

In addition to the aforementioned safety and sterility considerations, appropriate equipment for one or more cell manufacturing unit operations should be selected based on performance characteristics, including product yield, processing efficiency, instrument response times, sensitivity, mechanical properties, temperature control and airflow, among others. Performance characteristics should be optimized for the intended use.

Equipment performance with respect to cell quality attributes

Assessment of properly functioning equipment is ultimately determined by the quality of the final CTP. Typical endpoints of properly functioning equipment are therefore measured by quality attributes of the CTP prior to lot release. In general, key cell quality attributes include cell recovery, viability, and function as determined by the immunochemical, biochemical, or other assays.

Cell recovery generally refers to the “total cell yield” after processing through an equipment. For equipment not used for cell expansion, concentration, or otherwise altering the cell quantity, cell recovery may be defined as

the ratio of cell quantity before and after processing. In these processes, the operation of equipment should not lead to significant cell loss. Equipment material selection, particularly with respect to cell-material interaction, as well as physical design may be important to minimize cell losses. Cell viability is another important quality attribute used to evaluate the effect of equipment on cells. In general, equipment should be designed to maintain cell viability. Cell viability can be determined immediately post-processing to understand the performance of equipment on CTP manufacturing. Other quality attributes associated with cell function can also be important for the intended CTP following equipment processing. Unlike cell viability and cell recovery, cell function is generally assessed after a period of expansion and/or differentiation. Measurements of morphology, biomarker expression, degree of cell clumping, relevant cell surface markers such as phenotypic markers, markers of cell activation, and tests for acute damage (such as apoptosis) or delayed cell damage (such as attachment efficiency and proliferative ability) can be used. The authors note that many methods are available to determine cell viability and function, and the selected method should have sufficient measurement assurance for the intended purpose [10,11].

Characterization of the equipment parameters and their effects on CTP may include operation of the process equipment at the minimum and maximum of equipment set-points and times. In-process controls at critical steps should be established as appropriate.

Equipment components should be selected to support the desired CQAs of a given CTP. Important considerations include proper cell-material interaction. For example, materials for making a component intended for cell transfer should lead to minimum cell loss; materials for making components intended to culture and expand cells should have appropriate cell-material interaction. The field is still working to better understand how best to design materials with controlled cell-material interactions. Given the broad range of CTP and unit operations, equipment components should be selected and optimized based on the CTP.

Selection of process parameters to maintain CQA & minimize cell damage

Processing parameters for equipment may include, temperature, time, and a range of physical forces. The operation of the cell processing equipment must not cause physical damage to the cells or inadvertently affect cell CQAs. Equipment should be designed to have controls in place to prevent excessive temperatures or physical forces from occurring. A robust manufacturing process should have performance data demonstrating that repeated operation of an equipment or component at the minimum and maximum operating conditions does not cause functional alteration or damage to the relevant cellular elements due to excessive heat production, pressures, centrifugal forces, or fluid shear stresses throughout the entire flow path.

Controls should also be in place to ensure that the flow path components, during equipment operation, are free of abrupt transitions, sharp edges, inadvertent clamping, or kinks

that may damage cellular elements. These controls should be validated through evaluation of processed cell products covering a range of cell types that the equipment is intended to process.

Performance with respect to physical & structural integrity

Cell processing equipment should maintain physical and structural integrity. Physical integrity testing and evaluations of physical interactions between the equipment and the cell samples ensure that the equipment meets its performance characteristics and product quality is not compromised. In a manufacturing setting, equipment should be qualified and validated before use, as well as routinely for the requalification/revalidation as determined by risk analysis. In addition, with upper and lower levels of performance defined for critical parameters, the performance trending should be monitored, allowing the user to act preventively before the occurrence of a failure. Quality Assurance should provide oversight of all equipment-related manufacturing and facility operations.

Physical integrity

Physical integrity for processing equipment used in CTP manufacturing processes refers primarily to requirements around containment of potentially infectious material. Depending on the intended unit operation, different materials may be needed to ensure physical integrity. For example, packaging should be suitable for the equipment and all components to maintain the physical integrity of the equipment during storage, shipping, and handling. If the storage involves extreme temperature, then the component must maintain

sufficient physical integrity at and below these temperatures. Likewise, equipment components that may exert strong physical force must be able to maintain physical integrity at or above these forces.

As a typical equipment may have many connection points, these connection points should be inspected to monitor the presence of leaks. Inspection may include containers, associated piping, valves, and appurtenances, and other potential sources of leaks.

Physical properties

Physical properties should be selected based on the equipment's intended use. A number of ISO (The International Organization for Standardization) and ASTM (American Society of Testing and Materials) standards are available for determining the physical properties of plastics, as most components that come into contact with cells are made of plastics (Table 1). Additional methods and/or standards may be used for non-plastic components as appropriate. The equipment vendor may provide data associated with these physical properties to help select the most appropriate parts.

CONNECTING UPSTREAM AND/OR DOWNSTREAM PROCESS INTO CELL MANUFACTURING WORKFLOW

A cell processing workflow generally requires a series of operations performed using different processing methods, equipment types, machines and instruments. The integrated process must maintain the integrity of the material, equipment and/or cell therapy product and prevent partial or whole cross-contamination. Successful

incorporation of equipment into the cell manufacturing workflow includes the maintenance of sterility and integrity, which is achieved by using suitable connectors and/or closed systems to maintain uniformity and exclude potential external contaminants.

A critical aspect is compatibility and suitability of connectors. Standardized connection systems may provide greater access to a broader range of equipment. In the absence of standardized connectors, equipment users may require extra connections between processing steps or unit operations, thereby introducing risk for additional sterility concerns. In these cases, extra precaution must be taken to ensure connector compatibility. If there are no compatible connectors available, qualified and sterile transfer bags with appropriate attachments and tubing must be used to transfer materials between unit operations. In addition to final release testing, in-process testing should be in place to ensure the cell product meets the specifications and that each instrument or machine operates as intended. This also minimizes failures or non-conformances associated with the final product not meeting specifications due to manufacturing process deficiencies.

VALIDATION OF EQUIPMENT & OPERATION PROCESS PARAMETERS

Validation of manufacturing equipment includes the hardware and software to produce the CTP product. Validation must provide a high degree of assurance,

TABLE 1
Existing ISO and ASTM standards for determining physical and mechanical properties of materials

Physical Data	Tests	
Tensile strength	ISO 527-3:1995(2010)	ASTM D882
Elongation	ISO 527-3:1995(2010)	ASTM D882
Yield strength	ISO 527-3:1995(2010)	ASTM D882
Modulus	ISO 527-3:1995(2010)	ASTM D882
Toughness	ISO 527-3:1995(2010)	ASTM D882
Seam strength	ISO 527-3:1995(2010)	ASTM D882
O ₂ transmission rate	ISO 15105-1:2007(2015) ISO 15105-2:2003(2013)	ASTM F1307
CO ₂ transmission rate	ISO 15105-1:2007(2015) ISO 15105-2:2003(2013)	ASTM F2476
MVTR	ISO 15106-2:2003(2013)	ASTM F1249
Haze	ISO 14782:1999(2015)	ASTM D1003
Glass transition temperature	ISO 6721-4:2008(2016)	ASTM D5026
Film thickness	ISO 4593:1993(2014)	ASTM D374
Operating temperature range	Performance testing	

via appropriate documentation, that all parts of the equipment will consistently and repeatedly work as intended. Validation includes three core elements: 1) installation qualification (IQ), 2) operational qualification (OQ), and 3) performance qualification (PQ). IQ includes checking purchase orders, proper hardware installation, and software verification according to the manufacturer's specifications. OQ confirms the equipment operation by testing the design requirements. OQ may include testing of software and hardware functions under normal load, and under realistic stress conditions to assess whether equipment and systems are working correctly. PQ confirms that the equipment is capable of performing or controlling the intended unit operation(s) while operating in a specific environment. In general, these include testing equipment against the original specifications.

The approach to validation may be very different for the wide range of equipment in CTP manufacturing. For processing equipment, validation of the process and qualification or certification of the equipment is a part of Process Validation.

For computer-controlled equipment, Good Automated Manufacturing Practice (GAMP) has guidelines for computer system validation useful to both equipment providers and users. The GAMP framework addresses how systems are validated and documented. GAMP examines the systems development lifecycle (SDLC), a conceptual model that lays out the deliverable documents required by GAMP, of an automated system to identify issues of validation, compliance and documentation. Additional details on the risk-based approach that is recommended to validate software that operates equipment is described in “Good Automated Manufacturing Practice” edition 5 [12]. On the other hand, some of the equipment being used in the industry was never designed for cell manufacturing and hence cannot be readily integrated with a company’s manufacturing execution software (MES). In addition, if a component of a cell manufacturing equipment is a registered medical device, it might not be possible to change its software under the existing framework. These aspects will benefit from standards unique to the CTP manufacturing equipment.

CORRECTIVE & PREVENTATIVE ACTIONS

Corrective and preventative actions (CAPA) represent another

set of important considerations for CT manufacturing equipment. Equipment systems, particularly hardware, can be repaired. Some equipment components, such as software, maybe upgraded during its lifetime. CAPA is designed to collect and analyze information to identify actual and potential problems. Appropriate and effective corrective or preventive actions should be communicated, implemented, and documented once a problem is identified. CAPA also includes verification and validation of the effectiveness of corrective and preventive actions. Data source for CAPA may be internal or external, such as post-market care.

In addition to CAPA to ensure safety and performance of equipment, the design of equipment should include a mechanism for recovery of the cells in the event of equipment failure. Based on the mechanism, users should design and implement a procedure to assure maximal recovery of cells and minimize the risk of contamination. As a precautionary measure, secondary containment is generally implemented on the single-use processing equipment to manage potential spills. Equipment supplier should implement safety measures, such as alarms, to prevent conditions that may cause damage to cells by excessive temperature, physical forces, etc. If such conditions occur during cell manufacturing, users need to assess potential damage to cells and document assessment results and actions in consequence. Equipment must be monitored on a regular basis, and adequate power backups should be available for all critical equipment. Backup equipment should be identified when only one device is in use by the laboratory or manufacturing

► **TABLE 2****Information to be documented to enable equipment selection and to ensure proper functions**

Validation documentation	Purpose
Equipment (including technical features) and its intended use	Selection of proper equipment for the intended process
Performance characteristics	Selection of proper equipment for the CTP
Documentation associated with IQ, OQ, and PQ	Provide assurance that equipment will consistently work as intended
User and Technical Manuals	Ensure appropriate operation of the equipment
Documents related to chain of custody management system	Maintaining chain of custody during movement, storage, and processing

site. For equipment that relies on consumables for its operation (such as CO₂ incubators and liquid nitrogen freezers), adequate backup liquid nitrogen or CO₂ storage capacity should also be considered and implemented. Change controls from equipment manufacturers to potential users will assure consistency and reliability in the performance of selected equipment.

DOCUMENTATION

The documents should be developed to enable appropriate equipment selection, ensure proper function during manufacturing process. In addition, a Drug Master File (DMF) or a similar document developed by equipment manufacturer can be useful to support CTP manufacturer's regulatory filing. **Table 2** lists information to be documented.

Documents stating the design specifications and range of operation (e.g., flow rates, pressures, centrifuge speeds, and temperatures) will help the selection of appropriate equipment for the intended use. If the equipment may be programmed by the user, a list of the programmable ranges should be provided. User and technical manuals should describe

calibration, qualification, cleaning and maintenance methods. Chain of custody documents are used to track and document the movement, handling and temperature of the material at every step in the manufacturing workflow and logistics chain. Tracking and chain of custody management systems exist and should be implemented to ensure appropriate material management. New guidelines and criteria for electronic records and signatures by US regulatory agencies as well as laboratory information management systems facilitate the automation and implementation of chain of custody management [13].

LOOKING FORWARD

CTP manufacturing equipment is rapidly evolving. Tremendous progress has been made toward fully closed automated systems [14, 15]. These efforts are anticipated to enable more efficient and robust CTP manufacturing for both scale up and scale out purposes. With increased automation, a critical piece is software development. The industry should establish common or integrable platform, to ensure subsequent technology advances can be readily adopted. Standards

discussions are underway within ISO/TC 276: Biotechnology to enable better integration so that CTP manufacturers may more readily select appropriate equipment for specific CTPs.

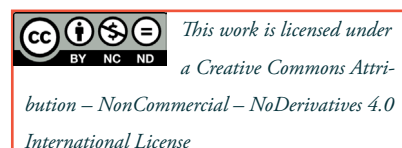
Other efforts are underway, such as coupling new analytical tools with manufacturing equipment to enable in-process monitoring. Equipment systems are being designed to obtain in-process real time information so that it can adjust processing parameters to achieve the desired CTP quality attributes. Finally, manufacturing processes are continuously optimized. For example, to shorten CTP manufacturing, component(s) of equipment, such as cell expansion bags, may be delivered to CTP manufacturer already containing basal culture media to remove that step from the manufacturing process. These and similar advances will undoubtedly streamline and provide better control of CTP manufacturing, but designs and other efforts must be taken from the onset of these innovations to ensure safety, performance, integration of manufacturing.

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REFERENCES

1. Levine BL, Miskin J, Wonnacott K, Keir C. Global Manufactuirng of CART Cell Therapy. *Mol. Ther. Methods Clin. Dev.* 2016; 4, 92-101.
2. Haddock R, Lin-Gibson S, Lumelsky N *et al.* Manufacturing Cell Therapies: The Paradigm Shift in Health Care of This Century. Perspectives, Expert Voices in Health & Health Care, National Academy of Medicine. <https://nam.edu/wp-content/uploads/2017/06/Manufacturing-Cell-Therapies.pdf>
3. Achieving large-scale, cost-effective, reproducible manufacturing of high quality cells- A Technology Roadmap to 2025. Report of the US National Cell manufacturing Consortium, 2016. http://cellmanufacturingusa.org/sites/default/files/NCMC_Roadmap_021816_high_res-2.pdf
4. Adair JE, Waters T, Haworth KG *et al.* Semi-automated closed system manufacturing of lentivirus gene-modified haematopoietic stem cells for gene therapy. *Nat. Commun.* 2016; 7, 13173.
5. ISO/TC 194 - Biological and clinical evaluation of medical devices.
6. Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products.
7. ISO 14644-1:2015 Cleanrooms and associated controlled environments -- Part 1: Classification of air cleanliness by particle concentration
8. Tappe A, Cutting J, Hammond M, Nunn H, Kline S. The case for a

- standardized assay to test suitability of single-use systems in cell culture applications. *BioProcess Intl* 14 (2016): 10-13.
9. Clarke D, Stanton J, Powers D *et al.* Managing particulates in cell therapy: Guidance for best practice. *Cytotherapy* 2016; 18(9), 1063-1076.
 10. Lin-Gibson S, Sarkar S, Ito Y. Defining quality attributes to enable measurement assurance for cell therapy products. *Cytotherapy* 2016; 18(10), 1241-4.
 11. Lin-Gibson S, Sarkar S, Elliott J, Plant A. Understanding and managing sources of variability in cell measurements. *Cell Gene Therapy Insights* 2016; 2(6), 663-673.
 12. GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems, ISPE, Feb 2008.
 13. CFR 21 part 11 Electronic Records; Electronic Signatures — Scope and Application.
 14. Smith D, Peterson A, Zonderman J, Kevlahan S, Hampson B. LB18-The future of T-cell therapy - fully closed and automated manufacturing using novel capture particles.” *Cytotherapy* 2017; 19(5), e11.
 15. Hara K, Kurakazu T, Gooljar S *et al.* Automated cell therapy manufacturing: proof of concept for non-invasive online quality monitoring during hiPSC expansion. *Cytotherapy* 2017; 19(5), e19-20.

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