CELL & GENE THERAPY INSIGHTS

RAW MATERIALS FOR CELL & GENE THERAPY: GETTING IT RIGHT FROM THE START

SPOTLIGHT

INNOVATOR INSIGHT

Addressing particulates, extractables and leachables and the quality of single-use systems for cell and gene therapy manufacturing

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Cell and gene therapies (CGT) continue to demonstrate great promise and the recent commercial successes over the past year have further strengthened excitement and support for the industry. While improvements and advancements continue, manufacturing of CGTs continues to offer challenges. Experiencing manufacturing challenges is expected with an emerging industry, but manufacturing CGTs also presents some unique complexities when compared to similar industries. Production of CGTs, and specifically patient-specific products, rely exclusively on single-use systems (SUS) as the raw materials. Since the product is the output of the process, the quality of the raw materials used in the manufacturing process is critical. CGT raw material quality includes a wide range of aspects, many of which require specific attention given the heavy interaction of the cells and the SUS. For the context of this paper, the main focus will center on the growing need to further understand how to address particulate matter and extractables and leachables for CGT products.

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Advances and investment in the cell and gene therapy industry have grown significantly and the recent commercial approvals have further strengthened the excitement and enthusiasm for these therapies. As the demands for these therapies continues to increase, measures to improve manufacturing efficiencies, scale and reproducibility will be challenged. Given the unique aspect of not only generating CGTs, but also demonstrating reproducible consistency from product to product, the quality of the raw materials

used for each process is extremely critical. The raw materials or components used to manufacture CGT products can vary greatly depending on a number of inherent factors directly impacting the product quality attributes [1,2].

Raw materials (RMs) for CGTs often includes ancillary materials or the two are used interchangeably which can be complicating. As previously described, the term ancillary material (AM) is not a globally recognized term by regulatory authorities and is then referred to as a raw material [1]. To further complicate matters, the components defined as RMs can be different depending on the industry perspective. In some instances, manufacturing RMs for CGTs have been defined as the starting materials, reagents and solvents used in the products, whereas AMs are commonly included as the RMs that are not intended to be present in the final product [2]. In biomanufacturing, RMs include the chemicals (e.g., media, buffers, excipients, process agents, cleaning solutions), the single-use disposable systems and the packaging [3]. Single-use systems (SUS) or disposables, for the purposes of this paper are considered as critical raw materials or critical ancillary materials (region dependent) in the development and manufacturing of CGTs.

SUS are widely accepted and generally essential to the production of CGTs, especially patient-specific therapies, based on the nature of the starting materials and the manufacturing processes. In many of the current CGT manufacturing processes, it is entirely safe to assume that every step includes a single-use container or component. SUS, which consist of but not limited to tubing sets cell expansion containers, and in-process or final containment, offer the process flexibility necessary for development, clinical and commercial production [4].

While highly important to enabling the manufacture of CGT products, SUS can also significantly impact the quality of the process and the product as many of the components are in direct contact with cell-based materials (as indicated in Table 1). Many of the current established patient-specific CGT manufacturing processes are continuous in nature as the starting cell-based material through numerous manipulations is also the final cell-based product. As such, any single-use product or material that contacts the cells during the process could introduce impurities or contaminants [4,5]. As most of the SUS used for CGT manufacturing have been designed or intended for the bioprocessing and blood management industries, ensuring the compatibility and quality of each component that comes in direct contact with the cells is highly critical.

Whether the CGT products experience direct or indirect contact with SUS materials, there is a list of common quality attributes of the materials including items like biocompatibility (e.g., USP Class VI), free of animal-derived components (or have a statement detailing and minimizing risk if animal-derived components do exist), sterility (including endotoxin and pyrogen control), extractable and leachable (E&L) materials and particulates [5]. While these attributes can all collectively impact the CGT product and ultimately the intended recipients, the focus of this discussion will target the latter when addressing SUS. Particulate matter along with E&L pose unique challenges

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TABLE 1

Commonly used single-use systems for CGT manufacturing.

Single-use	Intended purpose	Material (common)
Collection bags	Starting materials	PVC (polyvinyl chloride)
Transfer/processing bags	Wash; manipulation	PVC
Transfer (tubing) sets	Fluid transfer; sample removal; reagent addition	PVC, ABS (acrylonitrile butadiene styrene), C-Flex®, Silicone
Cell expansion container	Cell culture or expansion	Polyolefin, EVA (ethylene vinyl acetate), FEP (fluorinated ethylene propylene), PE (polyethylene)
Media containers	Culture media; cryomedia; buffer storage	PVC, polyolefin, EVA, FEP, PE, PETG (polyethylene terephthalate glycol), LDPE (low density polyethylene)
Cryopreservation container	Final fill; in-process frozen storage	Polyolefin, EVA, FEP, PP (polypropylene), COC (cyclic olefin co-polymer)

for CGTs and this includes the single-use suppliers, CGT manufacturers, testing facilities, regulatory agencies and the intended patient population. Particulates and E&L for SUS have been investigated and addressed extensively in the literature to support their utility for manufacturing biologics [6–9]. Furthermore, the Bio-Process Systems Alliance (BPSA) has played a significant role in developing guidance documents and recommendations to address both topics with respect to SUS for bioprocessing and manufacturing of biologics [10,11]. The information described in these documents and the literature, while helpful, does not address the unique manufacturing challenges presented with CGTs. Some literature certainly exists highlighting the challenges and concerns for particulate matter and E&L for CGT [12–14], but additional effort and attention is needed to offer guidance to the industry.

One of the main concerns for the industry with respect to particulates and E&L is due to the general unknown. With the industry still evolving, no clinical studies exist to date detailing any potential negative impact of these impurities. The risks of particulate matter in injectable products have been discussed extensively by Bukofzer *et al.* [15]. Additionally, a number of guidance documents have been developed to aid in managing particulate matter and E&L risks for SUS to support the bioprocessing and biopharma industries. These studies and documents, while informative, are not specific to CGTs. Since the CGT industry does not currently have industry specific guidance, suppliers and manufacturers have been reliant on the practices taken by other industries. Due to the lack of available guidance and general awareness regarding particulates and E&L for CGTs, the approach to this point has been to try and follow what other industries are doing or evaluate on a product-by-product basis. To date, the main driving forces behind the overall concerns for particulates and E&L are the lack of data specific to CGT products combined with the often-complex manufacturing processes involving SUS. As the industry matures, studies and data will likely become available to help address the relevance of particulates and E&L for CGTs.

Particulate contamination of CGT products can present significant potential risks to the products and the intended patients as many of these products will be administered through intravenous injection, but the overall severity of the risks is often unclear as it depends on the intended administration route, dosage volume, particulate properties (size, shape, composition, number) and the target location or fate of the particulate [13]. Given the data detailing the risks associated with injectable products [15] and the similarities to CGT products, managing particulates in CGT manufacturing continues to be a challenge to the industry. The central factor in addressing particulates stems from the cell being the final product which to date has eliminated the use of a final filtration step as can be accomplished in the biologics industry [5,12,13]. Removal of particulates from the final products, which are greater in size comparison to the cells is a possibility, but performing this type of a step presents several risks to the products and will likely require extensive testing and validation. Removal of smaller, sub-visible particulates represents a different challenge. Visual inspection of final product containers for particulate matter is common practice in in the pharma industry [15], and this form of inspection is also applied by those developing CGT products. Visual inspection of CGT products is inherently challenging since the final products tend to be opaque and therefore 'clouding' the ability of the visual inspector to observe particulates. Even if a visible particulate is detected, many of the products are singular and patient-specific eliminating the option to simply discard the batch. From an industry perspective, production of CGTs is still relatively new and until recently, few commercial products and manufacturing processes existed which limited data and corresponding knowledge on how we address and manage particulates. The knowledge gained from these commercialized products and manufacturing processes will prove to be valuable to the entire industry on how we handle particulates. Benefits will enable the development of industry appropriate guidance along with better methods to reduce or monitor particulates to ensure patient safety.

Many sources contribute to the accumulation of particulates and with manufacturing, a major source has been attributed to the cleanroom personnel which includes the staff and activity [16]. As described in the 2016 paper by Clarke *et al.*, particulates have potential ingress routes at every step due to the complexity of CGT processes – this includes the abundance and types of materials used along with the extensive number of handling steps. The reduction of particulates therefore is a collective effort, which includes both suppliers and CGT manufacturers [12,13]. SUS are invaluable for the development and production of CGT products. They are ideal for smaller batch sizes and enable significant process flexibility – both of which are key in the development and clinical manufacturing success of CGTs. SUS also represent a likely source of particulate contribution and therefore signify a natural focal point for monitoring and reduction [5–7]. SUS in the form of containers, tubing sets, filters, fittings and sensors for example are present from the starting material to the final product.

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The final product container tends to be the focal point for assessing particulates, and rightfully so, but as noted particulates are a cumulative process with respect to CGTs [13]. Efforts to reduce particulates in SUS are an ongoing effort as a means of continuous improvement and suppliers of SUS, like Charter Medical. Some of the ways suppliers can look to achieve possible reductions include more carefully controlled cleanroom manufacturing environments, minimizing welding and cutting operations whenever possible, optimized process flow to reduce excessive movement in the manufacturing space, reduced handling of materials, obtaining and using higher grade materials (e.g., medical grade), introducing qualified cleaning processes, and performing 100% visual inspection.

Standards for particulates such as USP <788> and USP <790> are commonly applied for SUS in the bioprocessing industry, however no specifications have been standardized to date [6,7,10]. While generally performed by suppliers to support many of the single-use containers, the incorporation of these compendial standards are less likely applied to the more common used SUS used for manufacturing CGTs. This is due in part to the evolving nature of the industry, the borrowing of SUS intended for other industries and a lack of defined requirements [13]. Blood collection bags and blood transfer packs (processing bags) are good examples of SUS used extensively in CGT manufacturing due to patient-specific starting material that have been designed with alternative industry standards. Furthermore, single-use containers are often assumed to be the primary source for particulates, but single-use fluid tubing or processing sets (transfer sets) should be considered. Tubing sets, applied extensively during CGT manufacturing, can regularly be overlooked as significant particulate contributors given their simplicity and transient use. Particulates are difficult to visualize and assess in tubing sets due to their design and lack of clarity and should be evaluated within the process. It's therefore important to use SUS (e.g., containers and tubing sets) designed for the CGT industry as more of these products are and will become available [17].

Continued advances will be required to assess particulate load in all facets. Particulate measurement typically has two main aspects that includes human visual inspection by the manufacturer during assembly and the end-user prior to application and rinsing or flushing of the components used in the CGT manufacturing process [6,13]. Visual inspection steps designed to monitor the pre-used, empty SUS (containers, tubing sets) for particulate can be inherently challenging based on the clarity of the materials used and the complexity of the potential designs. Well-developed visual inspection systems and personnel training can be helpful, but additional measures will be necessary. Furthermore, visual inspection does not address the sub-visible particulates they may be part of SUS. The incorporation of a flush step by the CGT manufacturers prior to use can help to reduce or eliminate particulates and also aid in providing valuable data and feedback to suppliers. This information will help in determining the likely source and aid in developing reduction and improvement strategies. Ultimately, component suppliers and CGT

manufacturers will work together in an effort to develop more efficient practices to manage or reduce particulates. This may come from suppliers developing and offering SUS designed to support the CGT industry or the collective reduction of processing and handling steps by both suppliers and manufacturers. Other options may include the use of new devices for filtration or unique methods to separate the cells and particulates similar to other industry practices.

Advances will continue, but the overall goal of zero particulates is an unachievable specification for SUS [6,10,13] and for the CGT industry based on the nature of the collective processes and components (raw or ancillary materials). SUS suppliers will continue to make dedicated improvements to control and reduce particulates to support the industry while CGT manufacturers will need to continue optimizing process steps and monitoring particulate load per their respective manufacturing processes. A common goal for suppliers and manufacturers alike is to work together to minimize and optimize processing steps as this will aid in reducing particulate matter. The continued goal for the industry should be to minimize and control particulates without setting unnecessary or unreasonable expectations which could significantly impact SUS suppliers, CGT manufacturers and more importantly patient access to these potentially life-saving products.

Particulates are an obvious choice of concern for the CGT industry due to the potential health risk, but concerns about extractable and leachable materials have elevated. Extractables are chemical compounds from both direct and indirect contact materials that migrate when exposed to an appropriate solvent under exaggerated conditions whereas leachables are typically a subset of the extractable compounds that migrate into the final product formulation as a result of material contact under normal manufacturing conditions [5,8,9]. E&L are very often associated with SUS due to their common inclusion of additives, which can in the material formulation and stability. Common additives may consist of antioxidants, stabilizers and processing aids such as lubricants or antislip agents [9]. Many of the common SUS materials used in a CGT process as described in Table 1 contain varying degrees of additives. Materials like PVC tend to have more additives compared to FEP materials where additives are limited. Given the extensive use of SUS for CGT manufacturing, the cell-based product and the variety of possible contact surfaces and contact time, it is reasonable to believe that CGT products could be impacted by leachable compounds. For biopharmaceutical companies, regulatory guidelines require that the product contact items are not reactive, additive or absorptive to ensure drug product quality and safety [8]. Organizations including the BPSA, BioPhorum Operations Group (BPOG) and DECHEMA were formed to support, encourage adoption and provide guidance of SUS for biopharmaceutical production and highly recommend that E&L testing programs be implemented early in the development process to reduce the risk for possible late-stage manufacturing changes [11,14,18]. Although specific guidance does not currently exist for the CGT industry, risk-based approaches should to be considered.

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Extractables testing for SUS is typically completed by the supplier of the materials in an effort to support the manufacturer and the intended application. The extractables study design is determined through a combination of industry guidance, the intended application or use of the SUS and the E&L testing facility. Extractables testing studies conducted by suppliers of SUS typically comprise filling or soaking SUS components in model solvents, and testing the resultant extracts for compounds released to the solvent by the treatment [9,11]. Length of exposure and temperature ranges are extended to exaggerate the chemical conditions of actual use. The data from the extractable study is intended to support the manufacturer or end-user of the material to estimate the types and amounts of leachable material that may be generated by the SUS during its intended CGT use. This enables the CGT manufacturer and regulatory agency to assess potential risks of the materials to patient safety and to demonstrate compatibility with the CGT product. Additional leachable studies may need to be conducted by the CGT manufacturer based on product specific identified risks.

A thorough understanding of the CGT process is necessary for an effective E&L program. Unintended E&L contaminants (similar to particulates) can enter throughout the entire CGT manufacturing process and accumulate. An impurity or contaminant (leachable) entering a CGT production stream could affect cell growth or expansion in-process or ultimately impact a specific critical quality attribute of the final cell-based product. Studies have been reported in the literature describing the potential associated risks of leachable contaminants and the importance of evaluating and understanding E&L [19,20]. We should keep in mind that that while manufacturing of CGT products is highly reliant on SUS, the conditions experienced during manufacturing (e.g., length of contact material exposure time, solvent/solutions) are typically less invasive in comparison to those in the biopharma industry. Common contact materials for CGTs may include collection bags, processing containers, cell expansion bags, tubing sets, filters, connectors, syringes and final container vials or bags. Regardless, a risk analysis of each product contact material used in the process should be evaluated. Some of the variables to consider include:

- Proximity to the final product
- Extraction capability of the solution
- Contact time
- Contact temperature
- Product contact surface area
- Pre-treatment of the material
- Material compatibility/resistance
- Supporting extractable testing provided by supplier

Overall risk is typically affected through multiple factors and are commonly divided into process-related and dose-related groups. Process-related factors include items such as contact area and contact time whereas dose-related factors will include dosage volume, dosage frequency [9,14].

While leachable contaminants from SUS can affect a CGT product throughout the entire process, the final product and final product storage container are often deemed the most critical due to proximity to the intended patient. Adding to the potential risk for CGT final products

– the majority of these products are cryopreserved, which includes the inclusion of DMSO (dimethyl sulfoxide) as a critical cryoprotective agent. DMSO is also a very strong solvent material and likely one of the stronger solvents associated with current CGT products and manufacturing processes. The inclusion of DMSO is not typically used for biopharmaceutical final products and is not addressed or recommended in traditional industry-related E&L testing guidance and is often not provided with SUS supporting extractable testing reports offered by suppliers – see BPSA Recommendations for Testing and Evaluation of Extractables from Single-Use Process Equipment for information specific to SUS for bioprocessing. While not common for bioprocessing SUS, E&L testing on SUS intended for CGT applications should consider the inclusion of DMSO. Some suppliers, like Charter Medical, offer SUS intended for CGT having extractable testing and data packages that include DMSO. It may be assumed that the risk for leachables is minimal due to the extreme frozen (typically below -150C), but what happens during exposure when filling (chilled or ambient conditions) or thawing? The CGT industry can look to the blood industry and the historical use of DMSO and cryopreservation in SUS for storage and transplant of hematopoietic stem cells for confidence, but while some aspects are similar (cell-based) the products and processes are ultimately different. This represents just one example of the unique differences in the use of SUS for CGT manufacturing and the need to develop industry specific guidance.

So, how should the CGT industry handle E&L now and for the future? First and foremost, manufacturers need to understand their process to establish an effective science and risk-based assessment plan. Higher risk SUS materials within the process can then be evaluated to determine possible requirements. Many of the SUS materials used for CGT manufacturing and available to the industry have been borrowed from other industries and likely don't have the appropriate extractable testing and data or any extractable data period. If quality extractable testing and data is available from the SUS supplier, manufacturers may be able to use the data to determine the potential for those extractables to be present as leachables in their product [9]. The results of an appropriate extractables study can provide a comprehensive list of compounds that have the potential to become leachables and reduce or eliminate the need for additional testing. Additional measures to reduce potential E&L risk include, working with SUS designed to reduce the use of potentially toxic leachables and to reduce or optimize processing steps minimizing the variety of contact materials exposed to the products. The current analytical techniques and methods used to assess E&L have been described extensively and offer guidance to the CGT industry [9,11,18,21]. While the analytical techniques used are sufficient, the described protocols supporting the bioprocessing industry need to be modified to support the specific intended use and applications for CGTs. As mentioned above, CGT specific process steps exist that are not currently supported with many of the routine extractable studies. Some areas of consideration include the number and types of solvents,

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the temperatures and the time. The inclusion of DMSO as a solvent should be considered for example. Elevated (warmer) temperatures are typical, but since many CGT final products are cryopreserved, perhaps E&L studies need to consider cryogenic temperatures. Active collaboration between manufacturers, suppliers and the regulatory agencies is critical and seeking out groups like the BPSA, who have recently dedicated their efforts to supporting and developing guidance for SUS and the CGT industry will prove beneficial.

SUS are a mainstay for current and future manufacturing of CGTs. The use of SUS is necessary based on the nature of CGT products and the process flexibility required – especially for patient-specific products. For all the positives that SUS offer to the industry, they also present specific quality-related raw material challenges including particulates and E&L. Evaluating and minimizing potential quality risks associated will come from the combined efforts of SUS suppliers and CGT manufacturers. Suppliers should continue to evolve and implement strategies to control and reduce contaminants. Manufacturers must continue to assess the true risk of these potential contaminants based on the nature of their processes to determine any possible impact to their products and intended target. Process knowledge and optimization between both entities will help to improve and guide the industry forward in developing better, safer products. CGT manufacturers and suppliers must continue to work closely together to ensure guidance requirements are developed to aid CGTs. Relying on guidance from other industries are helpful as CGTs evolve, but developing our own specific guidance will ensure product and patient safety while at the same time enable the success and continued growth of the CGT industry.

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The author has no relevant financial involvement with an organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock options or ownership, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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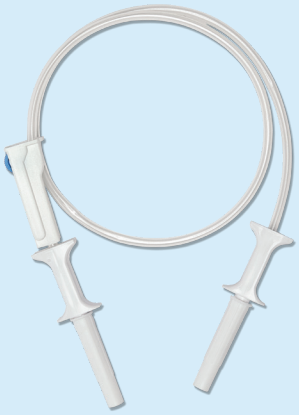

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