CELL & GENE THERAPY INSIGHTS

BEST PRACTICES FOR ENSURING CELL & GENE THERAPY SUPPLY CHAIN SCALABILITY

CHANNEL CONTENT

PODCAST INTERVIEW

Precisely for CGT: automating aseptic filling for lowest volumes

"...do not be afraid of digital transformation. Follow the opportunities that pharma 4.0 offer for your process and facility."

Roisin McGuigan, Editor, Bioinsights, **speaks to**
Barbara Fischer, Process Consultant, Single Use Support

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Q The number of approved cell and gene therapies is increasing. However, prices remain incredibly high – from several hundred thousand to millions of US dollars. What are the most important factors to consider when looking to make significant cost savings?

BF: There are two major factors that could substantially contribute to lowering the costs of producing regenerative medicines and gene therapies: automation and

standardization. On one hand, standardization is essential. In cell therapies, for example, scalable and reproduceable culture conditions are required to maintain cellular function during *ex vivo* culture. Furthermore, large capacity automated bioreactor systems have the potential to reduce costs effectively, particularly for allogeneic therapies.

Autologous cell therapies are by their nature currently mainly produced manually, in very small-scale and in dedicated suites. Reimagining this process with clear regulatory framework in the background could be an option to continue culturing the cells for other patients to reuse them if they are suitable. In any case, CGTs require skilled and expansive personnel. Unfortunately, manual intervention is amongst the leading causes for deviations, resulting in significant delays of production, product release, or even batch losses. These points should be addressed by the automation of processes, and I would also stress the importance of pharma 4.0 and digital transformation. Standardized, replicable, and automated processes with high output lower costs.

Q What are the biggest hurdles that need to be overcome to address the issues of standardization and scale-up, and speed up this process?

BF: Currently, most processes are carried out literally as manufacturing, meaning many steps are done manually. Standardization of process control and monitoring is a key factor, and it starts with the effective monitoring of cells. Microscopic examination for assessing morphological and functional properties of cell cultures is the routine method used for the evaluation of cell cultures. I see a need for automation with the prerequisite of developing machine learning algorithms and artificial intelligence. In general, the higher the degree of automation and digitalization, the higher the potential to own a standardized and controllable process for all steps from cell bank to filling.

One hurdle may be the investment. As a manufacturer, you need to ensure the systems you are using are scalable and flexible enough to meet rising demands and changing process requirements when switching from one product or process to another. You must not only consider the process flow and variable volumes involved, but also different monitoring points and critical process parameters. It is a choice between investing time to find a suitable solution or embracing the possibility of making additional significant investments.

For cell therapy products, it is essential to have robust cell lines that can undergo as many divisions as is needed for large scale manufacturing. This must be addressed and tested during development to avoid a rude awakening during scale-up or commercialization.

Another hurdle is time; finding the time to make a detailed plan as part of the development process. This plan should include the potential of the product with respect to volumes and batches per year, and the highest possible degree of automation. This does not only include the process and equipment used but also primary packaging, considering all potential options from vials to single-use bags. The question is: which of these primary packages are suitable for all process steps and unit operations, and flexible enough to be used from early development to scale-up? I see it as a bit like planning a kitchen or the configuration of a new car. You should consider all the nice-to-haves from the beginning and then rate them with respect to criticality

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in the form of a risk-assessment. If necessary, deselect options that are rated as non-critical or with low criticality.

> "The question is: which primary packages are suitable for all process steps and unit operations, and flexible enough to be used from early development to scale-up?"

Q What specific trends are you seeing currently in the selection of primary packaging?

BF: Common container types used in this sector include cryovials with screw caps, plastic or glass vials, and single-use bags. Primary packaging needs to provide the robustness and physical properties to ensure product quality and safety during multiple handlings across visual inspection, labelling, packaging, cooling, freezing, and thawing. Containers for drug product solutions in particular have to withstand a lot.

Each solution comes with its own advantages and disadvantages. For example, cryovials have a long history, especially in master working cell banks, and are well known and convenient when it comes to handling. Additionally, they are cost-effective, which may be linked to their broad and year-long usage, that facilitates optimized production processes and a decrease in prices. On the other hand, there are clear disadvantages. In most cases, operating with vials means operating with open systems and increased potential for product contamination. Consequently, they need to be filled in an isolator or a filling line situated in a conventional clean room. Both are very costly with additional risks of deviations. Also, the vials have quite limited volumes per dose.

On the other hand, we also see a constant increase in the usage of single-use bags in this area. They also have clear advantages, such as their ability to operate in closed systems, customized options, and the ease of adaptability to changing requirements of system setups. Usually, the systems are designed to minimize manual interventions, thus preventing human errors which can result in quarantined or even rejected batches. Unlike vials, there is no need to operate in a clean room or isolator, minimizing tasks with respect to room requalification, specific monitoring, and extensive cleaning and decontamination procedures. This in total leads to higher throughput. Single-use systems are also more versatile, allowing scale-up and scale-out without total redesign of the equipment – or even the facility.

On the other hand filling and draining of single-use containers requires specific equipment, a one-time CapEx investment that should be considered. There is a clear trend towards the usage of single-use bags in the biopharmaceutical industry. Manufacturers find this technology to be both agile and cost effective. Many newly-established facilities are designed to be used with single-use technologies, and more and more are being reconfigured. This technology has proven to be reliable, especially in the relatively new field of commercial production of regenerative medicine and gene therapies, with high personalization and individualization. We are only at the beginning of a new era of therapeutic possibilities, and there is an opportunity to implement these innovative processes using state of the art technologies from the beginning.

Q What are the key challenges and limitations when using single-use bags in small volume manufacturing?

BF: Single-use bags that are filled with small volumes of 100 ml, 50 ml, or even below 10 ml are available and easy to use. They are already in use, but mostly in 100% manual handling. A challenge for manufacturers could be finding the right filling unit which also provides the required accuracy.

So, what are the general requirements that a filling unit ideally needs to satisfy for filling single-use bags? The system should be fully automated to provide a 'plug and play experience' for the operator. This includes not only the filling of multiple bags but also the sampling and the sealing. Sealing especially can be tricky and time consuming when working with small volumes. If the whole process is done by the system, then the operator only needs to push the start button and come back when the filling is done to collect the bags. Automation comes with standardization, repeatability, and traceability, substantially reducing variabilities.

Another requirement is to have a completely closed system. This is the best prevention against contamination, and it also addresses costs. When a filling operation does not require a conventional Grade A clean room but can be done in a Grade C or D clean room, it saves a lot of resources for continual environmental monitoring and requalification. This also forces the line to be idle from time to time, so throughput is increased with a closed single-use assembly system that fills single-use bags while decreasing manufacturing overheads.

Last but not least, there is the issue of accuracy. CGTs are highly potent and filling volumes are extremely low, and manufacturers need to be aware of the nominal filling values and accepted ranges. When talking to a supplier, this should be addressed and stated in the user requirement specification from the beginning, with state-of-the-art scales that communicate with a control unit. Each single-use bag should be individually weighed in a controlled manner during the filling.

Q What are your top recommendations for manufacturers who are transferring a process from manual to automized production?

BF: Start to make a realistic plan for scale-up, scale-out and varying demands as early as possible. Engage the quality control teams, the operators, and the validation teams early in the planning as they may be able to provide valuable input from their first-hand experience. Consider full automation from the beginning, including sampling, in-line monitoring of process parameters or, for example, reaction to pre-alarms. Stay flexible by choosing modular yet scalable solutions that support your processes with high accuracy at all stages.

My recommendation: do not be afraid of digital transformation. Follow the opportunities that pharma 4.0 offer for your process and facility. Try to make your processes and facilities fit for the present, and fit for the future.

> ""We are only at the beginning of a new era of therapeutic possibilities..."

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BIOGRAPHY

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Dr Barbara M Fischer holds a PhD in Biology and is currently Process Consultant at Single Use Support. In this role, she is working together with established pharmaceutical manufacturers and start-up companies to find the most suitable solution to sustain the product quality through its journey ensuring optimized utilization of resources. Barbara has in-depth experience in low bioburden and aseptic GMP manufacturing of liquid and powder formulations from downstream processing to fill finish.

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SINGLE USE SUPPORT.

PIONEERING BIOPHARMA

Precisely for CGT

Automating aseptic filling for lowest volumes

Manual handling for dispensing volumes less than 100mL into single-use bags has never been the gold standard. There is now a reasonable way to turn your back from manual operations and to enter a new filling experience for small volumes:

Automized Plug & Play
Full automation whilst providing options to fill multiple bags, but also sampling and sealing in one.

Closed system
Best prevention against contaminations paired with high cost-efficiency and increased throughput

Accuracy
Controlling filling accuracy is even more important at low volumes, such as cell and gene therapies

Automation
Comes along with standardization, repeatability and traceability

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