cell & gene

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Qualification Considerations For A "Factory-in-a-Box"

By Moria Feighery-Ross and Wai Wong, Pharmatech Associates

The cell therapy market is rapidly expanding into a multibillion-dollar industry, but its production is cost-prohibitive due to the limited manufacturing space and number of personnel required, while capacity is not easily scalable and is limited by processing time.

A “factory-in-a-box” encloses the manufacturing of a product or process in an easily transportable container that requires minimal utility and environmental support. These boxes are designed to replicate the manufacturing process that normally occupies large, controlled manufacturing spaces and requires a number of personnel to support each step of production. Where these modular factories are utilized, manufacturing capacity is limited only by the floor space to house them, which translates to reduced capital investment for scaling up and no lost time to construction. With a “factory-in-a-box,” a dramatic increase in throughput of products fabricated in these systems can be expected to have significant impact on manufacturing capacity.

In fact, the potential offered by the factory-in-a-box can be a game-changer for the current cell and gene therapy industry, where the available in-house and CDMO production is outstripped by demand, stretching out drug development timelines and limiting opportunities. In industry, Nokia and other companies are already providing solutions that use modular smart manufacturing to allow product development and scale-up without extensive and costly facility modifications. These modular factories could be ideal for meeting market demands for cell and gene therapies where rapid deployment requires an agile and easily scaled manufacturing solution.

Factory-in-a-Box For Cell Therapy Processes

When considering the qualification requirements for a factory-in-a-box, we must first understand the processes that occur within them. Among the many types of manufacturing processes that could be replicated in a factory-in-a-box, let’s look at a standard cell therapy process. Typical processes in cell therapy manufacturing include isolation, enrichment, expansion, harvesting, filtration, and formulation; each step has analysis points to verify the process is meeting specifications and ready to proceed. To perform this in a modular factory unit, cell materials and reagents are introduced to the box and are moved from station to station within the box as it processes and analyzes the materials to make the final product.

Facility Environment And Installation

The facility in which the box would be placed requires a basic controlled environment, including regulating temperature, humidity, and environmental air quality. Within the module environment, more stringent environmental control may be required than outside, depending on the design of the system and requirements of the product. Some systems have fully enclosed fluid paths that are never exposed to the environment. Inside the box, purified water or WFI, nitrogen and other gases, and vacuum may also be required to support the process, as well as utilities for the analytical equipment within.

When a factory-in-a-box uses a cartridge-type system, where the cartridge fully encloses the starting materials and is loaded into the unit and moved from one process step to the next, the beginning of the process where the critical materials are loaded into the cartridge requires a clean, controlled, aseptic environment to protect the material and cartridge from contamination prior to its introduction into the closed environment of the module. Isolators or biosafety cabinets and transfer systems, or an integrated loading area, might be utilized; any of these will require additional qualification considerations, such as environmental controls and interconnectivity.

New Challenges For Operational Qualification

In a typical manufacturing plant, each piece of equipment in the process is qualified separately to its individual operational requirements. The overall manufacturing process is then qualified in performance and process performance qualifications (PQ and PPQ). A factory-in-a-box brings about new challenges to operational qualification, because when a process is completed within this environment, the individual items of equipment are all housed within a single unit. While the process is not quite continuous, it is fully automated and presents challenges similar to those of a continuous process. Qualification activities for a factory-in-a-box must begin with a thorough risk assessment of both equipment and process. Due to the nature of this operational design, issues of the interruptions or faults inherent in every process are further enhanced because they must be qualified as a train. This box cannot be opened during

production to remediate an issue with a step in the middle without breaching the environment and sacrificing the product. In addition to containing the production equipment, testing is performed within the module. This means that all analytical equipment, both in-process and final product verification, must be qualified at the same time as the rest of the unit. It is crucial to understand the inputs and outputs of each step in the process and assess the potential failures at one step and the risk of affecting the subsequent steps.

Computer Software Assurance And Controls Systems

The control systems and software used here are complex: each factory-in-a-box will have proprietary software unique to its ecosystems, functions, and manufacturing processes. When determining the requirements and path to control system qualification and computer software assurance of a factory-in-a-box system, begin with a data flow diagram[1,2,3] to understand how data are gathered, passed between operations within the process, and recorded into the process history.

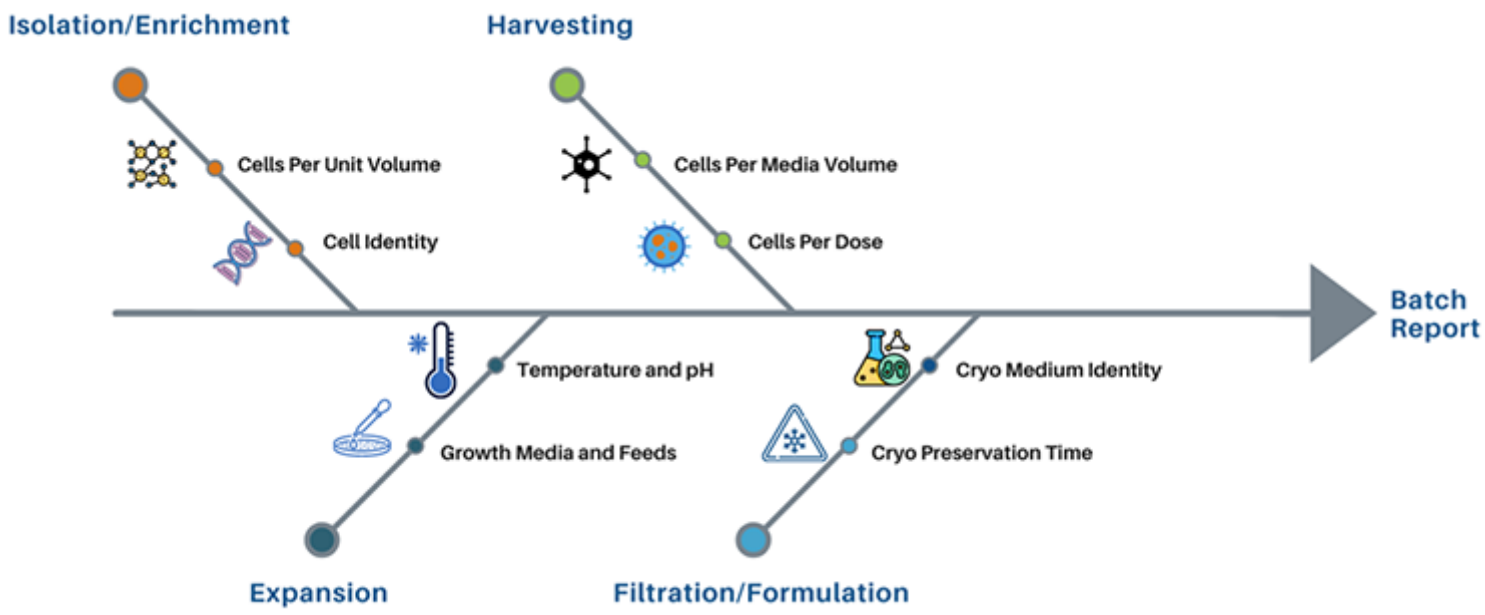

Figure 1: Example of cell therapy manufacturing data flow, created by Pharmatech Associates with information, based on the ISPE guidance.

Data generated at any given step may represent a critical process parameter informing the current and next steps in the process or a critical quality attribute measured and reported as part of the batch record, or both. The process depicted in Figure 1 — a fishbone diagram with the batch record as the backbone and each process step as one of the ribs — shows a clear flow of data joining the record without passing through a human operator. Subsequent to testing performed during equipment and software qualifications, we are assured of both the quality and integrity of the data.

Data Integrity And Human Interference

While these systems add a huge amount of complexity to controls qualification due to interconnectivity, we do not need to worry as much about data integrity over the course of production as we do in a step-wise process where measurement and process data are obtained and moved to the next process step or process batch record. Unlike a traditional manufacturing facility, there are no human factors that affect process data generation, collection, transfer, and use while everything is still within the box. So even though each item of equipment comprising the factory-in-a-box may have its own controlling software, the individual control modules are not accessible to an operator, only the main controlling interface. Audit trails, access logs, event logs, and transfer of data to a historian or to archival are all simpler to validate when they are only done once. Compliance with 21 CFR Part 11 and related international standards is simplified – we test for that compliance once for the entire system rather than at each process step. In an integrated system such as a factory-in-a-box, the risks to data are greatly reduced. The ISPE GAMP Good Practice Guide: Data Integrity – Manufacturing Records[3] states:

Where a process is well-defined (‘we know exactly how to do this’) and consistent (‘if we do it like this, we always end up with the correct result’), has no manual intervention (‘it all happens automatically’) and an objective output (‘we all agree on the result’), data integrity controls can be achieved by validating the system and maintaining it in a validated state.

The factory-in-a-box is a pure example of this concept: each of those statements is fulfilled. Even when one of these systems is in use as a development tool – in which case you could say the process isn’t yet well defined – the controls architecture is defined for each iteration; each production run in the box will proceed in the same manner once programmed.

Conclusion

The development cycle for cell and gene therapies can be shortened using these closed systems because a larger number of distinct processes can be piloted in the same research space with minimal concerns for cross-contamination. Then, when a drug candidate is ready to move forward through clinical trials into commercialization, manufacturing capacity can be increased dramatically by simply multiplying the number of boxes deployed, from one or two at pilot scale to 50 or more for full production. It’s easy to project the potential scope of impact of these therapies to improve health and quality of life by treating and preventing many forms of disease, but the limits of capacity must be addressed before this can be realized.

As these boxes are introduced to the industry and as more companies adopt them, the validation of the units and their processes will be highly scrutinized by the FDA and other regulatory bodies around the world. The validation considerations outlined here will be key to successful deployment and implementation.

References

1. ISPE GAMP® RDI Good Practice Guide: Data Integrity by Design, Section 4.3
2. ISPE GAMP® RDI Good Practice Guide: Data Integrity by Design, Section 5.4
3. ISPE GAMP® RDI Good Practice Guide: Data Integrity – Manufacturing Records

About The Authors:

Moria Feighery-Ross, CQA, is a senior validation engineer for Pharmatech Associates, working in the regulated life sciences industry for more than 10 years. With technical expertise in validation and quality management systems, she provides end-to-end support for pharma, biopharma, and medical device companies of all sizes, with emphasis on development, remediation, new facility startup, and validation. Feighery-Ross holds a B.S. in biology from the University of California, San Diego.

Wai Wong leads the commissioning, qualification, and validation practice for Pharmatech Associates, with more than 20 years of equipment, facility, and process validation experience in the pharmaceutical, medical device, and biologic industries. He has expertise in navigating compliance with the validation requirements of the FDA, EU, and PIC/s. A Six Sigma Green Belt, he holds a B.A. in molecular and cell biology with emphasis on biochemistry from the University of California at Berkeley.