Large Scale Manufacturing Development of Adherent Stem Cells

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To transform the promises of cell-based therapies into reality, a robust and scalable process is required that is compliant with cGMP regulations. From clinical to commercial manufacturing, processes need to produce progressively larger batches with consistent product quality. Process optimization can help streamline the scale-up and allow the cost of goods (COGs) to remain as low as possible. By accomplishing these processes, it can make affordable and sustainable therapies reach the market more quickly.

Here we present a case study and results from the large scale development expansion of a process using human stem cells obtained from adult bone marrow for the production of Athersys adherent stem cell product, MultiStem®. The expansion was made possible by using the Quantum® Cell Expansion System from Terumo BCT.

Figure 1 · 10 Quantum systems in 32 m² technology transfer laboratory at MaSTherCell

Objectives

Develop a large scale expansion process using the Quantum system. One bioreactor was used as a platform for the production of MultiStem, an adherent stem cell product. Batches of approximately 1 x 10^9 cells were achieved and shown to maintain essential cell quality attributes. The goal of this study was to demonstrate the ease of extending these first results to large batch sizes using multiple Quantum systems. Moreover, through efficient tech transfer and process optimization, a second objective is to achieve equivalent yields with a constant quality of the cells while significantly reducing the number of operators needed was achieved.

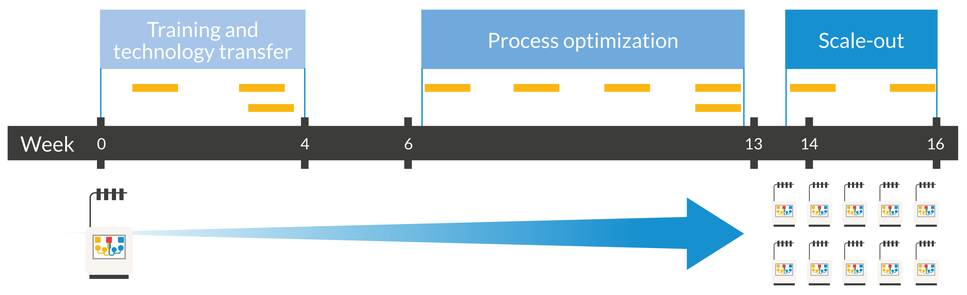
Challenges

Sixteen weeks to multiply by 10 the production in 32m² room only with 100% of the cells released while maintaining the cell expansion process to 6 days. In addition, the number of full time equivalent (FTE) is limited to two operators.

Material & Methods

- Quantum cell expansion system
- MultiStem cells - human stem cells obtained from adult bone marrow or other nonembryonic tissue sources
- Cell culture media
- QC testings
  - Sterility – BacT ALERT
  - Endotoxins – LAL (Limulous Amoebocyte Lysate) - kinetic chromogenic
  - Mycoplasma - qPCR

After completing the training and technology transfer in 4 weeks, the Quantum systems were installed and operated by 2 laboratory technicians in a small, non-classified production room (32m²) including a single biosafety cabinet and two 3m-long benches. Each batch maintained the quality standards that were previously demonstrated for the 1 x 10^9 cell batches, while meeting all safety requirements.



Each six-day cell expansion in the Quantum system is represented by ▬. Extensive quality control testing (not indicated) required approximately two weeks following each expansion run.

Figure 2 · Production process from technical transfer through clinical manufacturing*

Results

Two sequential batches of 9 to 1 x 10^9 cells were produced using ten Quantum systems. The cell expansion process was run for a total of six days. Due to the process optimization that was performed as part of the technology transfer, the quantity of seed stock required was reduced by 20% and media consumption was reduced by 10%. As shown in figure 3, variability in yield between each run was limited to 12%, and viability was maintained above 95%. The figure 4 & 5, demonstrate that each batch successfully passed the QC testings and maintained quality standards previously demonstrated for the single Quantum system. Safety requirements like sterility, endotoxin and mycoplasma testing met the lot release specifications in the produced batches. The cells quality profile was consistent between the single and the 10 Quantum system runs (Figure 4).

In addition, the 900 % increase in process capacity (i.e. from one Quantum system to 10 Quantum systems) was maintained by two technicians. Figure 6 reflects the actual labor necessary for each of the technician throughout the process, including all preparation and operation pertaining to cell seeding, expansion and harvest. Combined with process automation and optimization, this ultimately led to a 40% reduction of the cost of goods.

Cell Number & Viability

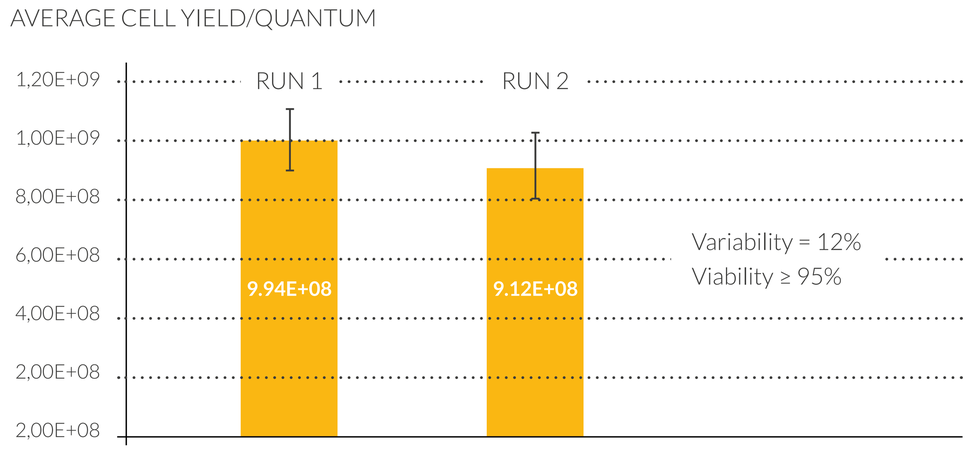


Figure 3 · Cell number & viability

Cell Quality Testings

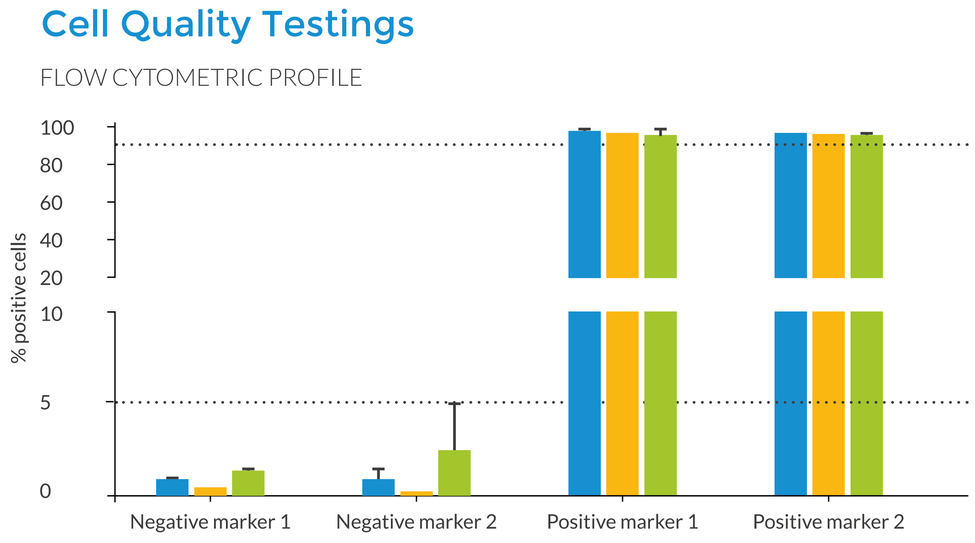


Figure 4 · Cell Quality ▮ Tech Transfer Runs ▮ Single Quantum System Runs ▮ 10 Quantum System Runs

Safety Tests

		RUN 1	RUN 2	RUN 3
QC Tests	Expected results	Result	Result	Result
Sterility (ep 2.6.27)	No growth	No growth	No growth	No growth
Endotoxins (chromogenic kinetic method)	PASS	PASS	PASS	PASS
Mycoplasma (qPCR)	Negative	Negative	Negative	Negative

Figure 5 · Safety tests; Sterility, Endotoxins, Mycoplasma

Labor-Saving Process

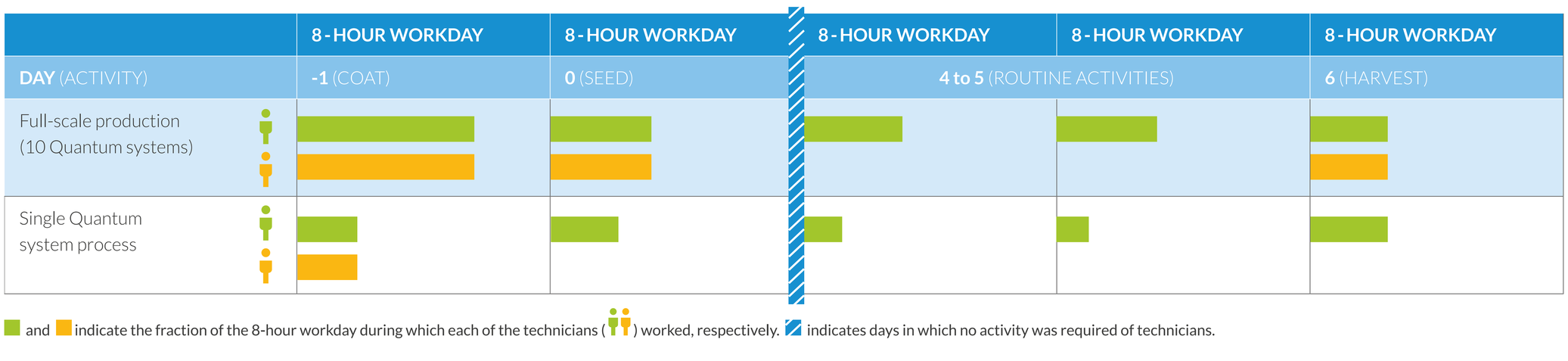


Figure 6 · Full-scale production versus single Quantum system process workflows*

Conclusion

The transition from a single Quantum system to a scaled, 10-Quantum process was successfully demonstrated in sixteen weeks with product showing comparability between both processes. Using this scaled approach, multiple 10-Quantum system processes could be operated concurrently to produce larger batches when demands arise.

MaSTherCell is a dynamic and global Contract Development and Manufacturing Organization (CDMO) on a mission to deliver optimized process industrialization capacities to cell therapy organizations. The heart of MaSTherCell is a team of highly dedicated experts in addition to a validated and flexible facility located in the strategic center of Europe.

* Case Study: How Quantum cell expansion systems increased cell production quantitites from one billion cells to commercially relevant batch sizes, Terumo BCT