Cell Therapy and Closed Process Manufacturing

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INTRODUCTION

Cell therapy is still relatively young in terms of commercial manufacturing and its associated regulatory landscape. Current manufacturing operations are generally small-scale, have typically involved several open processing steps, and utilise single-use technology for benchtop process equipment. Figure 1 shows an example block flow diagram for an autologous cell therapy process. The traditional approach for this industry sector has been to carry out the open processing steps in a Grade A Biosafety Cabinet (BSC) within a Grade B manufacturing suite, which allows the operators direct access to the equipment components to perform the often delicate operations.

This approach is very onerous with respect to the gowning and sanitisation activities associated with the transfer of people and materials into the suite. These procedures are necessary to maintain the environmental conditions within these areas, which also involves high energy costs. Therefore, it is desirable from both operability and an operational cost perspective that methods of operation be developed (or employed), allowing the classification of the manufacturing suites to be downgraded. The key to downgrading the manufacturing areas is to implement robust methods for closing the process or moving from BSCs to isolator technology where this is not practical.

DOWNGRADING CLEANROOM CLASSIFICATION

Certain operations cannot be practically closed, but that does not mean that engineering controls cannot be implemented to allow the manufacturing area to be downgraded. The European Medicines Agency (EMA) guidance also highlights a desire for manufacturing companies to implement the best available technologies. 'The Manufacturing Authorisation (MA) holder must, in respect of the methods of manufacture and control provided for in the MA application, take account of scientific and technical progress'[1]. Use of isolator technology is seen as an improvement from a technology perspective over a BSC, but use of an isolator for the small-scale manual operations associated with a cell therapy process is not without its challenges.

One example of an operation that cannot be easily closed in cell therapy manufacturing is the make-up of the transduction pack (if applicable to the process) to be added to the culture bag. The formulated pack itself can be sealed within a single-use bag, but the make-up of the pack will involve the open addition of a viral vector (VV) from a glass vial. The make-up of the transduction pack can potentially be carried out within an isolator, therefore closing this open operation to the external environment. The transfer of the VV is a delicate operation; therefore, there can be a reluctance to move from a BSC, where the operator has direct contact with the equipment, to a glove-box isolator for operational reasons. Consequently, achieving an ergonomic design for the isolator is critical in achieving the transition to this equipment.

The main cell processing activities are carried out using equipment such as Miltenyi Biotech's CliniMACS® range (CliniMACS Plus and CliniMACS Prodigy)[2] and Cytiva's[3] Sepax C-Pro and Xuri Wave Bioreactor systems.

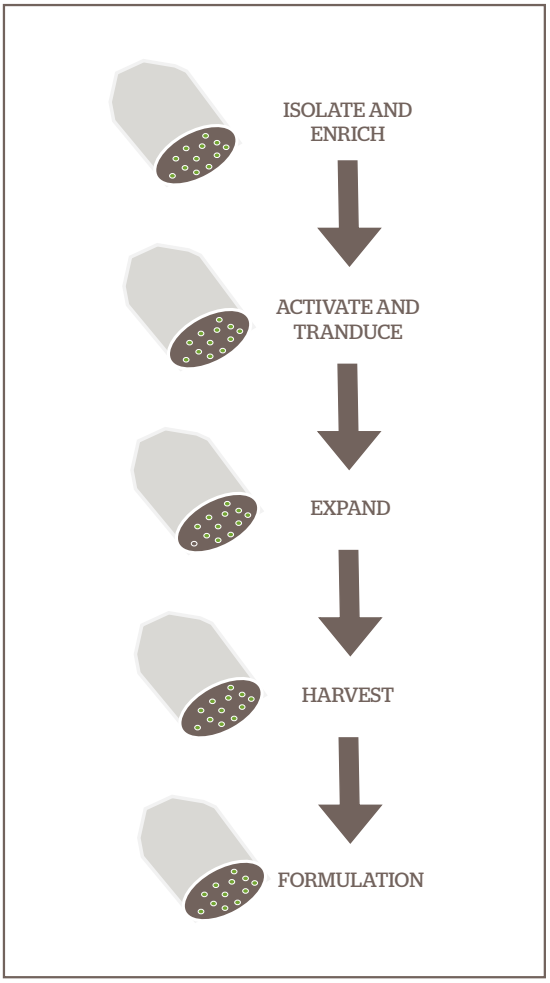

Figure 1: Autologous cell therapy

There is a drive within the Biotech industry to downgrade the cleanroom classification of the manufacturing areas through robust methods of process closure, which also applies to the field of cell therapy. Downgrading the cleanroom classification of the manufacturing areas reduces capital and operational costs and reduces construction and CQV activity schedules, therefore reducing time to market.

Small-scale, single-use manufacturing systems incorporate tubing sets that are too small for use with sterile connectors, but tube welding can still be employed. Therefore, closed processing can be facilitated if the single-use equipment kits and the bags that connect to them are provided with closed, weldable ends.

Vials or bags are used when filling the formulated drug product (DP). Due to the small batch size associated with a cell therapy manufacturing process, fully-automated filling systems are not available, and therefore this is commonly a fully manual and open operation. Vial filling operations, by their nature, are not closed, and therefore, the large-scale vial filling operations are carried out within isolator systems.

One advancement in filling technology for cell therapy processes is the M1 Filling System[4]. This semi-automated filling station fills one vial at a time and uses a needle to pierce the septum installed on the pre-sterilised vials provided for use with this system. The perforation in the septum is then sealed with a laser after the vial has been filled and the needle retracted. The M1 Filling System provides a more robust method of vial filling compared to fully manual operation. This operation lends itself more to use within an isolator, thus providing the ability to move away from a BSC and downgrade the manufacturing suite. Filling into bags can be carried out in a fully closed manner; however, the samples that need to be taken during filling of the DP cannot necessarily be filled into sample pillows. The samples taken for sterility (BacT), and mycoplasma testing need to be filled into containers that are compatible with the test equipment. This is typically an open operation. Therefore, the filling of DP into bags cannot be considered fully closed due to the sample filling requirements. However, this operation can be carried out in an isolator, which would allow the suite to be downgraded.

CONCLUSION

To date, there has been a reluctance for cell therapy manufacturing facilities to move away from Grade B manufacturing suites even with the implementation of closed processing or the use of isolator technology. This is likely due to concerns regarding the robustness of the process closure and to provide extra security for handling the product. There is the potential to effectively operate cell therapy facilities in lower grade cleanroom manufacturing environments, and this is starting to be seen with newer commercial facilities. The ability to do this will lead to shorter start-up times, lower operating costs, and more energy-efficient facilities.

REFERENCES

[1] Concept paper on Good Manufacturing Practice and Marketing Authorisation Holders; European Medicines Agency; 1st September 2016.
[2] https://www.miltenyibiotec.com/IE-en/products/cell-manufacturing-platform/clinimacs-prodigy.html#gref
[3] https://www.cytivalifesciences.com/en/us/solutions/cell-therapy
[4] https://www.asepticteсh.com/products/m1-filling-station