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Gene Technology

Short Communication

Pricing Pressure of Advanced Therapy Medicinal Products can be Diminished by Contemporary Manufacturing Process Development

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ABSTRACT

The manufacturing of Advanced Therapy Medicinal Products (ATMPs) is still very expensive. Thus, the price tag of the therapy is high. When all the manufacturing steps are optimized, we have possibility to bring costs down. Scalable and cost effective manufacturing process should be defined as early as possible in the product life cycle. Today technology solutions are providing all the tools for process development and optimal process but more work needs to be done before we reach the goal.

Keywords: Gene; Gene therapy; Plasmids; Cell therapy

INTRODUCTION

The development of Advanced Therapy Medicinal Products (ATMPs) to clinics and beyond is accelerating. Patients are waiting for better treatments, scientists are eager to provide their innovations, and investors are waiting to see success after their major input. At every level, we are all working against the time. The speed means also more and more pressure towards the manufacturing of the ATPMs. It is impossible to spend several years of product life cycle for manufacturing development so solutions need to be applicable and easily accessible.

Still today, most of the early gene therapy innovations are coming from academia. Academic centers may not have access to modern manufacturing systems and early studies are done using viruses produced with an old fashion manufacturing process in cell culture flasks using adherent cells. That is totally understandable and acceptable. The first challenge comes when the most promising product would be taken further towards the translational stage and phase I, and there is no time to make a thorough manufacturing process development. A rational manufacturing solution should be closed, disposable, scalable, controlled and, of course, GMP compatible. A major process change later would become a regulatory challenge and might delay the access to the market. Thus, the manufacturing process should be defined as early as possible and all the changes minimized.

If viral vectors have been produced earlier in flasks, process change to adherent cell bioreactor may not affect to major components used in the small scale process: still, same Master Cell Bank (MCB), plasmids and transfection reagent or Master Virus Seed Stock (MVSS), medium and Fetal Bovine Serum (FBS) can be used. The first fully disposable fixed-bed bioreactor for virus production up to 500 m2 was launched about decade ago (Pall Biotech). Today there is other disposable adherent bioreactors available and these have been used for different viral vector productions, such as AAV, lentivirus, adenovirus, or several viral vaccines (reviewed in our latest article) [1]. The scalability of the process has been straightforward [2-4]. Microcarries have been another option for scaling up adherent cells but technology has been seen as more challenging and less comparable to flask approach [5]. Laborious handling of the carriers and difficulty in separating microcarriers from the vector during downstream are factors affecting in utilizing the application [6].

Only few ATMPs have received marketing approval. The high cost of ATMPs is raising a lot of universal discussion among the healthcare people, ordinary population as well as decision makers. The highest dose rate is known to be for SMA treatment by Novartis with a 2.1 million USD price tag. If we are getting more and more products approved and every treatment costs a fortune, who will be paying this all? Are we able to provide the future treatments equally to everyone or are we building something that will be only available for rich people? Though, the price discussion is not always straightforward and we should not focus on one dose price but rather compare what is the cost of lifelong (long term) one shot gene therapy treatment compared to the traditional treatments (if available) needed daily, weekly or monthly basis. Especially people, like me, working in manufacturing process development should really be focusing on future manufacturing solutions that will bring us cheaper choices and improve the possibility to bring gene and cell therapy for everyone in the future.

Traditional manufacturing processes for Lentivirus and AAV

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contains a plasmid transfection step. The manufacturing of high quality/GMP-grade plasmids in large scale is extremely expensive. The plasmid transfection also requires the use of a transfection reagent [7,8]. Golden standard calcium phosphate transfection is cheap but not reliable and reproducible in large scale. Thus, the GMP manufacturing is mostly using commercially available, consistent transfection reagents, but these can substantially increase the price of the batch. The production of viruses, such as adenovirus, which is based on infecting producer cells with master or working viral seed stock, can be slightly cheaper [9]. Most of the adherent systems are still using serum containing medium [6,10]. Serum increases the titers and adaptation of the cells into the serum-free system may not always be straightforward. Finally plasmids, transfection reagents and serum are seen as impurity residual in the later stage of the process and must be cleared from the final product causing more demand/expenses for the purification [11,12]. Altogether, manufacturing of viruses in large scale in adherent cells is very expensive, and unfortunately still contains often many handling steps and expensive components.

We should focus more onto the cost saving and those will become available through bioprocessing solutions. The manufacturing starts form the proper construct design. Serum free mediums are naturally desired to facilitate a cost-effective way to produce viral vectors. Many cell lines can be adapted to grow in suspension in stirred tank or wave type bioreactors where a bag is a cost beneficial option compared to the disposable fixed-bed bioreactor. A more economical option for plasmid transfection is the use of stable cell lines. The development of stable cell lines has been time-consuming but finally, it will decrease the cost of goods and increase reproducibility, quality and safety. Suppliers should also consider the most optimal logistics. The process optimization and control will increase the productivity having a direct cost-related impact. Next big challenges on the field are the deep process understanding though PAT (Process Analytical Technology) and controlling of the system through the big data collected [13]. How do we collect and analyse all the big data? Can we use artificial intelligence and machine learning to acquire useful information for process prediction, optimization, control and risk mitigation, leading to the improved manufacturing and the quality of the product. In addition, the trend is the implementation of the continuous and automated processes to replace the batch based processes. Many previously mentioned technological goals have been already achieved and should be now combined into the one complex bioprocessing solution.

As a conclusion, the technology development has brought us many kinds of solutions but it will still take time until we have all the current technologies and the improvements are implemented into our daily GMP manufacturing and we can see the effect on the price of the gene and cell therapy treatments. I am hopeful that this all will be possible and in the future ATMPs will be available for patients world-wide.

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