Viral Vaccine Manufacturing

Moderated by Amy Ritter

A Q&A with Tony Hitchcock, head of manufacturing technologies at Cobra Biologics.

Production of viral vectors for vaccines poses a distinct set of challenges. Tony Hitchcock, head of manufacturing at Cobra Biologics, spoke with *BioPharm International* about trends and challenges of manufacturing viral products in cell culture.

BioPharm: With the approval of Novartis' mammalian cell-produced influenza vaccine in 2012, production methods for viral vaccines seem to be undergoing a shift from egg-based manufacturing to cell-based. What advances in recent years have enabled this transition and what challenges still remain?

Hitchcock: The production of viral vaccines has been performed in egg-based systems for many years, and it is clear that while significant developments in the production of viral vectors from cell culture-based systems have advanced, many existing vaccine products will continue to be produced in this manner. For example, GlaxoSmithKline has just introduced a quadravalent flu vaccine from eggs, and Medimmune has invested significantly in the automation of egg-based processes at their UK facilities. These developments would indicate that for products, such as seasonal flu vaccine, existing production routes will be retained for the foreseeable future.

For manufacturers of products such as flu vaccines, while significant investment from national governments among others has been put in place to develop cell-based production process to enable response to pandemic flu, it is clear that egg-based processes are still sufficiently productive and cost effective to meet needs for seasonal demand. Combined with long-term safety profiles and in-place manufacturing capabilities, the drivers for adopting cell-based processes are not sufficient to justify their adoption. It is also clear that becasuse of the specialist nature of egg-based production facilities, the majority of manufacturing will remain as an in-house activity with limited opportunities for contract manufacturers in this field.

In January 2013, however, FDA approved Protein Science Corporation's Flublok vaccine, another non-egg-based influenza vaccine, which is potentially the sign of things to come. It will be interesting to see what the up the uptake of this product will be compared with the existing egg-based products, and how the large Pharma companies respond to this.

The real opportunities for the production of viral vectors from cell culture-based processes arguably lie with novel vaccine products, where there are no historical safety profiles in place. Other opportunities lie with products where egg-based systems are unsuitable, or where technical or product safety issues mean alternative approaches need to be sought to meet demands in terms of quantities of material or to achieve required levels of process robustness.

BioPharm: What are the risks associated with using cell-based manufacturing for vaccines, and how are these risks typically addressed?

Hitchcock: The potential risks with cell-based processes can be split into intrinsic and process related. In terms of intrinsic risks, these will lie with the origin, purity, and design of the viral vector and producer cell line. Process-related risks will lie with the potential to introduce adventious agents/viruses into the process stream. Unlike the production of protein products from mammalian sources, it is clearly not possible to introduce validated viral inactivation or removal steps to mitigate these risks. Addressing these requires application of GMP principles and approaches to development programs at a very early stage, focusing on the history, purity, and stability of the viral vector. It is now commonplace for viral vectors to be rescued from synthesised plasmids, allowing for absolute traceability of the viral vector

Tony Hitchcock is head of manufacturing technologies at Cobra Biologics.

and full sequencing to be performed of the plasmids and resulting viral product. Stability studies can also be performed to demonstrate genetic stability of vectors at an early stage of development.

With regards to producer cell lines, it is essential that the origins are known and that they are free from adventious agents and that generation of cell banks for both process development as well as GMP production works. Additionally, there is clearly a need for maintenance of segregation throughout development programmes to prevent contamination of viral stocks and cell banks.

BioPharm: How do you address the demands of producing such a diverse product? Are there aspects of the production process that are platformable?

Hitchcock: From the perspective of a contract development and manufacturing organization, the production of viral vectors poses a number of technical challenges from a cell culture, recovery, and analytical perspective. However, with recombinant viral vector systems, where the virus is essentially used as a delivery vehicle and the manufacturing approach that applies is independent of the gene payload it carries, a platform process can be developed. Therefore, the application of platform-based approaches can be applied for the production and analysis of key virus product areas, such as adenovirus, AAV, and lentiviral production.

BioPharm: Have you been able to implement quality-by-design (QbD) in your vaccine manufacturing process? Are there aspects of the production process that are more amenable than others to this approach?

Hitchcock: The complexity of these product types and the limitation of assays to be able to fully characterize them means that understanding and control of the manufacturing process is crucial to be able to develop, scale, and manufacture high-quality therapeutic products. Therefore, the determination of the "operational space" for key process steps is essential. Where possible, there is clear merit in adopting a QbD approach. However, especially in early phase development, there are often severe restrictions created by assay throughput and for some virus types such as lentivirus produced by transient expression systems, there is often very limited material available for high-throughput development platforms for use in purification and formulation studies. In other product types, such as those like adenovirus produced in suspension culture, there are fewer constraints with regards to material availability, and it is much easier to apply these approaches through all stages of development. ◆