The FDA requests increased product consistency of C&GT manufacturers - better analytics required

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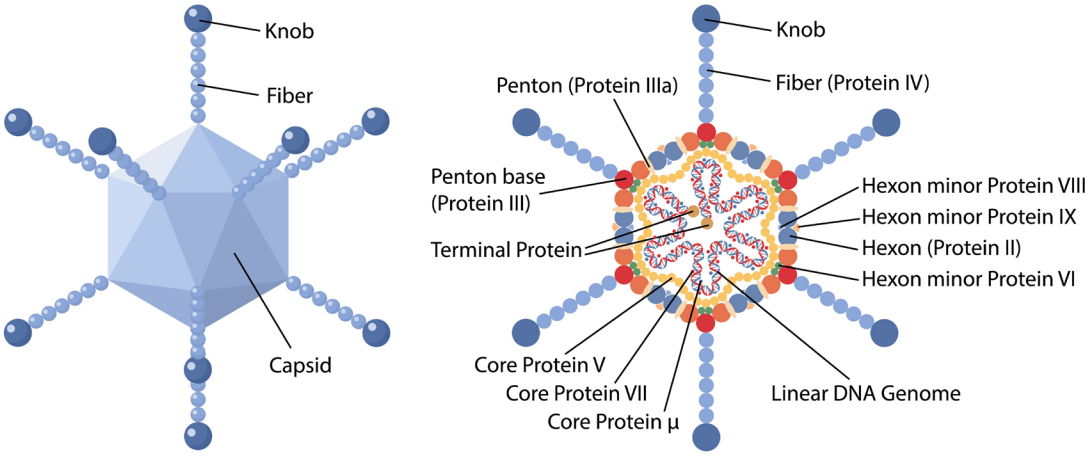
By the fourth quarter of 2021, the FDA had approved 22 Cell & Gene Therapy (C&GT) products [5]. With the market expected to triple within the next seven years, we are likely to see a significant increase in approvals across the sector. However, acceptance is not assured; lately, the FDA has asked C&GT developers to step up their game and do more to measure the consistency of their products.

In an interview at the World Medical Innovation Forum's virtual 2021 meeting [1], Peter Marks, head of the FDA's biologic drugs division, stated that C&GT developers must do a better job of consistently measuring their products.

"People tend to under-appreciate the need for some metric a potency assay or critical quality attribute that allows one to follow the product over time," he said. "Many times, developers get very excited about the fact that their product produces an important effect. So they don't worry as much about reproducibly making that product."

Peter Marks also expressed that the FDA likes consistency in products and reproducibility in manufacturing. Even though it is not always clear which characteristics or attributes of C&GT to monitor, developers must still try.

Adenovirus Structure



“Pick something. Pick some quality of the cell. Pick something that you think might correlate and measure that”

Peter Marks, head of the FDA’s biologic drugs division

“Pick something. Pick some quality of the cell. Pick something that you think might correlate and measure that,” Marks said. “We’ll take any offers that are reasonable.”

Recent FDA delays in approvals suggest a need for further documentation

Recently, several C&GT developers had to revise their development timelines as the FDA requested additional information about the production processes [3, 4].

Part of the reason is that analytical methods for assessing manufacturing quality parameters such as purity, potency, and consistency, have improved. Therefore, the FDA now expects C&GT developers to provide this information.

Though the delays may suggest closer scrutiny by the agency, it may also be a symptom of the significant increase in applications. The prediction is that the FDA will approve 10-20 CGT products yearly by 2025 [2]. With the increasing number of applications and maturation of technologies, the barrier is being raised. Thus, biopharma companies must have all relevant CMC data available and ensure that there are no gaps in their regulatory submissions.

In response to the many new products in development, the FDA and EMA recently published a set of guidelines for developers of C&GTs. This, together with the rapid acceleration of product discovery and manufacturing, is significantly increasing the amount of work for analytical testing laboratories in the sector [6].

Consistency is more challenging with C&GTs

The rapid growth in the number of products creates a supply challenge for competent manufacturing CMOs and analytical CROs with sufficient experience. While science is

accelerating rapidly, C&GTs remain challenging to make where manufacturing technologies and analytical procedures struggle to keep up.

C&GT products are unique and unlike anything that the industry has produced before. Not surprisingly, these products' knowledge, data, and expertise are still evolving.

When producing C&GT products, it is impossible to take processes relevant to protein products and use them directly to manufacture C&GT products. For example, the ability to scale up C&GT products has proven very challenging. For ezample, one production batch only provides material for treating a few patients. Thus, there is little to spare to develop analytical test methods and validation procedures.

The complexity of C&GTs requires multiple analytical assays

One of the new attributes that C&GT developers must monitor, according to the guidelines, is process-related impurities [4].

The manufacturing processes of C&GTs are usually quite complex. The procedures often use new virus packaging cell lines. Furthermore, various proteins from multiple sources are added during cell growth and harvest, e.g., bovine serum or human albumin in the growth medium, antibodies on affinity columns, benzonase treatment after harvest, etc.

The different process-related impurities require analytical methods for detection, process clearance, and purity in the drug product before clinical administration.

The most common way to monitor the process-related impurities for traditional biologics based on recombinant protein and molecular antibodies is using an ELISA (Enzyme-Linked-ImmunoSorbent-Assay). Biologic developers thus use the results to monitor the consistency of batches and for release tests of clinical GMP batches.

However, a standard commercial ELISA cannot measure all the different impurities in a C&GT, and developers need several assays – if they can even find a suitable ELISA. Therefore, many new cell lines require the development of a product-specific ELISA, which is very expensive, time-consuming, and challenging.

Rapid growth in C&GTs calls for new analysis techniques

The rapid scientific development within the C&GT sector calls for new high-tech analysis techniques for analyzing C&GT products and in-process samples [6]. Likewise, the industry

needs to simplify the process and reduce costs to help C&GT developers create consistent and safe products.

Liquid chromatography-mass spectrometry (LC-MS) is an example of a high-tech analysis technique [4] that has the required sensitivity to detect the low level of impurities and the specificity to differentiate the different types of impurities. This technique has progressed rapidly over the past ten years and can thus match the challenges of analyzing complex C&GT products.

LC-MS measures multiple proteins from various species and origins - simply by using one assay. The technique requires only a tiny amount of product sample, and also the running cost is a fraction of that of a custom-made assay. With such an array of benefits, it is no wonder that the C&GT industry is increasingly turning to LC-MS to keep up with increasing demands for documentation of quality attributes from the regulatory agencies.

References:

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[6] "Overcoming unique challenges to support rapid development of diverse products." BioPhorum 2021

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