A Q&A

Process-Related Impurities in Biologics: Best Practices, New Technologies, and Outsourcing

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New methods help identify individual host cell proteins in final drug product.

Impurities can negatively affect the stability, safety, and efficacy of protein therapeutics. Host cell proteins are a major part of process-related impurities during biologics production, and therefore must be carefully monitored and controlled. With Host Cell Protein ELISA being a critical component of ensuring process consistency and product purity, regulatory agencies have measures in place to ensure the Host Cell Protein ELISA used by a sponsor is fit for this purpose. *BioPharm International* recently spoke with Ken Hoffman, president of Cygnus Technologies, about best practices and new technologies for host cell protein detection and identification as well as the value of outsourcing process-related impurity analytics.

BioPharm International: As a well-recognized technology and thought leader for bioprocess impurity analysis, what is Cygnus's value proposition to the industry?

Hoffman: By outsourcing to experts in impurity analysis, small biotechs and large biopharma companies can tap into proprietary and enabling technologies. This ensures the successful development of value-added analytics. Cygnus also offers off-the-shelf generic impurity test kits that can be used very early in drug development to better optimize their purification process. This ensures better product safety and improved clinical trial outcome.

BioPharm International: What are the challenges of convincing companies to outsource impurity analytics?

Hoffman: There are two common objections to a company's willingness to outsource. First is they deem their process so unique that analytical methods can only be developed in-house. The second objection is that they cannot rely on outsourcing of analytical methods considered critical to QC release testing of their approved drug. Companies now recognize that they lack the in-house expertise to develop good host cell protein and other impurity assays. They have discovered that by outsourcing to a company focused in the development of GMP analytical kits, those companies are in a better position to guarantee a long-term and uninterrupted supply of test kits.

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BioPharm International: What proprietary-enabling technologies are responsible for Cygnus's success?

Hoffman: The linchpin method for host cell protein analysis is an immunoassay commonly referred to as ELISA. Many scientists can read papers and develop a credible immunoassay for a single molecule or a single-protein species. However, host cell protein detection is more complex. It requires simultaneous detection, in the same test well, of hundreds to thousands of different individual host cell proteins. A good immunoassay is only possible if you know how to generate a good antibody, and you can only generate a good antibody if you choose the correct antigen. Many of our assays are used as reference methods for the industry and they have achieved that reference status through our proprietary methods. These methods are antigen selection and characterization, immunogen preparation, immunization protocols, antigen affinity purification of the antibody, and our ability to develop those antibodies into robust immunoassay kits.

BioPharm International: What are some hot topics and best practices for host cell protein analysis?

Hoffman: Regulators are always looking for improved methods of impurity analysis. While immunoassays like ELISA are the mainstay of impurity detection, ELISA only gives the number of total host cell proteins not individual host cell proteins that comprise that total.

Fortunately, two newer methods can identify host cell proteins in final drug substances. The first method, developed by Cygnus, is antibody affinity extraction (AAE). AAE is more sensitive and specific than the two-dimensional Western Blot. For the first time, AAE can give us a look at individual host cell proteins that co-purify with the final drug substance. Cygnus routinely recommends and uses AAE as the state-of-the-art orthogonal method to better qualify ELISA and to provide improved information on individual impurity content.

The second method is the result of advances in mass spectrometry. Several modalities of mass spectrometry detect low levels of individual host cell proteins, but these methods require extensive upfront sample processing via liquid chromatography methods, often in two dimensions. Host cell protein detection by mass spectrometry (2D-LC-MS/MS) implies a complex and expensive process whereby one must fractionate individual host cell proteins by liquid chromatography, often in two dimensions, while at the same time removing most of the drug substance that would interfere with detecting low levels of individual host cell proteins. This complexity and cost of sample processing can be solved by AAE fractionation, which removes all the drug substance and simultaneously concentrates the host cell proteins. This is achieved in a single step and with a single sample, thereby reducing the cost of mass spectrometry while improving sensitivity.

BioPharm International: Are there changes in regulatory requirements for host cell protein and other impurities?

Hoffman: Guidelines have been revised by the FDA and EMA. In addition, the USP has drafted new and harmonized guidelines for impurity analysis. Unfortunately, these guidelines are not explicit on many points, such as the absolute allowable limits of host cell protein, nor do they specify preferred methods. Further, they reference older analytical techniques as acceptable, even though better technologies such as AAE and mass spectrometry exist. This is because it is problematic for regulators to hold new drug licensing submissions to a higher standard than previously approved drugs already proven to be safe and efficacious. For that reason, regulators must allow the use of traditional methods. The challenge for Cygnus is to convince the industry to embrace new and improved methods even though they may not be explicitly required by regulators. In this sense, Cygnus encourages companies to use new and improved methods of impurity analysis. Our message to the industry is to convince drug companies to characterize their drug products beyond current regulatory standards.

BioPharm International: What new products or services are in the pipeline for Cygnus?

Hoffman: Most of our previous work has been in the field of recombinant therapeutic proteins. Those products involve therapeutic monoclonal antibodies that represent about 80% of the biopharmaceuticals on the market. Today, there is tremendous R&D investment in cell and gene therapy technologies, and Cygnus is proactively developing a menu of impurity assays for this market. We hope that our analytical tools will better ensure the safety and efficacy of these exciting new therapies. In addition to cell and gene therapy fields, Cygnus recently completed a full menu of host cell protein assays for all common cell lines used in vaccine production.

Cygnus Technologies LLC is focused on supplying highly specialized analytical products to the pharmaceutical and biotechnology industry for use in process development and quality control. The company offers a range of well-validated, robust generic kits and immunoassay reagents. Cygnus Technologies is part of Maravai LifeSciences.