COMMENTARY: Moving beyond regulatory analytical requirements for better biotherapeutics

BY KEN HOFFMAN OF CYGNUS TECHNOLOGIES

THE BIOPHARMACEUTICAL industry must look for ways to reduce costs and improve the analytical information derived from in-process control and lot release testing. The recombinant therapeutic protein sector is maturing, as evidenced by the emergence of programs such as biosimilar drugs. This results in competitive factors driving companies to reduce costs.

Similarly, makers of cell and gene therapy, as patient-specific treatments, need to find ways to lower the costs to make this exciting new mode of therapy available to a wider patient base. In addition, vaccines are now being applied to treat conditions other than infectious disease, such as cancer, and as a result, vaccine developers are being encouraged to adopt analytics that are better than those used historically.

Ken Hoffman, president of Cygnus Technologies

There are several analytical methods that must be developed for biotherapeutics. These include testing for impurities, contaminants, immunogenicity and product attributes of the drug itself. Impurity analysis measures the presence of known, expected components from the bioprocessing steps that must be cleared from the final drug substance by multiple purification steps to levels deemed inconsequential.

The most important of these are host cell proteins (HCPs) from the cell line used to recombinantly express the product. Contaminant testing involves the detection of adventitious agents such as endotoxin, bacteria, mold, fungus and virus that should not be present in the final drug substance. Immunogenicity testing includes a variety of assays to determine if the patient has developed any potentially adverse immune reactions to the treatment. Product attribute testing focuses on the biological activity of the drug to characterize its pharmacokinetics and pharmacodynamics and assure consistency from lot to lot. From a regulatory perspective, it should be recognized that the predicate analytical methods submitted by the pioneer drug companies and accepted by regulators in early submissions tend to become the minimal industry standard to which subsequent submissions are compared.

Traditionally, analytics are viewed as costs of development. What often goes under-appreciated is that well-designed analytics offer opportunities to reduce drug and process development time and costs, improve the efficiency and lower costs of production, and lower routine quality control costs, while also providing more comprehensive data to better assure lot-to-lot process control and ultimately product safety and efficacy. Technology always moves faster than regulatory guidelines, and today we have in our analytical repertoire new and improved methods that can lower costs while better assuring positive outcomes in the clinic.

Despite the value of these new improved methods, many companies are reluctant to adopt them for several reasons. To the extent some companies view interactions with regulators as potentially adversarial, they will tend to avoid change at almost any cost and use previously accepted methods rather than attempt to justify new and superior technologies. Unless the company can see advantages to cost and product performance, there will be a tendency to "check the box" by employing conventionally accepted methods. While companies are reluctant to embrace even positive change out of concerns about increased regulatory scrutiny, in fact regulatory agencies are not averse to change and, to the contrary, recommend that companies seek continuous improvements in their processes.

A case in point is analytics for measurement of HCP impurities. HCP analysis was mandated by regulatory agencies in the early submissions for recombinant therapeutic proteins. HCP analysis was required based on theoretical concerns for patient safety, such as the potential for adverse immunological reactions or other off-target biological effects. Increasingly, we are seeing documented cases where HCPs have caused various types of adverse reactions in some patients. HCPs can act as adjuvants that generate an antibody response to the drug substance itself. These anti-drug antibodies can result in the drug effects being neutralized either by inactivation of the drug, decreased bioavailability or increased clearance from the body. Other HCPs can have off-target biological activity in the patient. This can occur when the HCP is conserved in nature, meaning it has a very similar biological structure and function to a naturally occurring protein in the patient. That similar HCP can either have undesired biological activity in the patient or result in the patient making antibodies that cross-react to similar proteins, effectively blocking its regulatory function, thus creating a clinical problem outside of the biotherapeutic target.

The conventional process to monitor HCPs was established by the then-existing technology offered to regulators by the pioneers in recombinant protein therapeutics. While the regulatory guidelines have been revised recently, the minimal requirements have changed little in 20 years, as it is difficult for regulators to hold new submissions to a higher standard than the early drugs, provided those drugs have largely proved to be safe and efficacious.

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Current guidelines still reference and allow for use of less-sensitive methods like 2D PAGE and HPLC early in clinical trials, with the recommendation that companies develop a sensitive ELISA prior to Phase 3 trials. This current convention also requires that sponsors further qualify that ELISA for antibody coverage to HCPs present upstream in the purification process using two-dimensional western blot analytics. Unfortunately, 2D PAGE, HPLC and two-dimensional western blotting lack the sensitivity to detect the most important and clinically relevant HCPs, which are those that co-purify with the final drug substance.

Today, thanks to improvements in analytical methods such as the integration of ELISA data with orthogonal methods of mass spectrometry and antibody affinity extraction, we now have at our disposal analytical information that is "value added" to the entire drug development and manufacturing process. Furthermore, these methods exceed minimal regulatory expectations. ELISA is the reference method for determining the concentration of total HCP owing to its sensitivity, specificity and ease of use.

However, ELISA alone cannot provide information on the identity and relative concentration of individual HCPs. As such, a more comprehensive approach to HCP analysis should involve the integration of methods that can identify individual HCPs that co-purify with the final drug substance. Once identified and their biological functions known, companies can optimize their purification process early in drug development to reduce these impurities with the benefit of not only better assuring patient safety, but removal of HCPs that have adverse effects on drug stability and efficacy in early clinical trials.

One example of the latter benefit was seen in an FDA-approved drug in which the shelf life was limited due to instability of the drug. The lack of shelf life had significant cost implications in addition to reduced therapeutic efficacy over time. By using mass spectrometry analysis, it was determined that this instability was caused by a single HCP which, once it was identified, was further reduced to inconsequential levels with a minor change at one of the purification steps.

Such value-added features are often overlooked by companies when they do not fully appreciate the benefits. Reluctance to employ new methods can come from various departments within the company. Purification process developers can push back on improvements, fearing they will be disruptive to their legacy and platform methods. Resistance can also come when the regulatory affairs department takes a very conservative view that to avoid additional regulatory scrutiny, it should be better to simply meet the same criteria as with previous submissions.

Much of this reluctance is based on specious assumptions that should be challenged by full cost accounting and risk-benefit assessment. Once the costs, risks and benefits are determined, it is possible to rationally justify employing new, superior methods that exceed current regulatory expectations. The cost of these new, improved methods is typically a minor factor when weighed against costs of failed clinical trials or delays in clinical trials due to an unforeseen need to optimize the purification process, adverse patient reactions, poor drug shelf life and reduced drug efficacy. To take advantage of opportunity to reduce the time and drug development costs, most companies are increasingly outsourcing these more complex analytics to expert service companies rather than attempting to develop them in-house. ■

Ken Hoffman, president of Cygnus Technologies, founded the company in 1998 to provide analytical solutions to the rapidly growing biopharmaceutical industry. Prior to starting Cygnus, Ken worked in the clinical diagnostics field for three different companies, developing automated systems and extensive menus of assays for infectious disease, metabolic disease, drugs and hormones.

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Thus, trying to explain to my mom what happened and its implications can be excruciatingly difficult. (Then try tweeting it.)

But that's our job—as science writers, as science communicators, as scientists.

In an era of fake news, an era where the veracity of science is questioned at every turn, we simply cannot afford to look like we're holding information back or that we're overstating our findings.

The deniers can lie or conflate or mislead all they want; we cannot. It's not a fair fight, but it never has been.

Like Heathers and his 52.3K followers of *@justsaysinmice* (as of April 22), we must stay vigilant as we wander the internet or read the newspaper in search of science stories. And just as importantly—and perhaps more within our individual control—we must remain vigilant in the words we use to describe science, to avoid, wherever possible, the slightest hint of hyperbole.

As I said earlier, if you see me slipping, please call me on it. And my promise to you, as with any of my colleagues, is to give you as much salient information as I can in the space allowed.

If you cannot trust what I relate to you, what is the point? ■

You can read James Heathers' article "IN MICE, explained" online at: https://medium.com/@jamesheathers/in-mice-explained-77b61b598218

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