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Rely on Data, Not Lore to Meet Rising Demand

The COVID-19 pandemic has forced countless difficult decisions to be made in the face of unprecedented uncertainty. Patients, consumers, and industry professionals alike are looking for guidance, support, and answers. With increased demand on pharmaceutical manufacturers to develop a COVID-19 therapeutic alongside all the existing treatments that are still needed by millions, there follows the growing need for strict quality control processes, and the ability to test and release large volumes of newly manufactured vaccines.

Naturally, a lot of questions have arisen. How are pharmaceutical manufacturers going to keep up with production demands? How will we ensure these vaccines are safe and effective? Do we have enough raw materials, consumables, and reagents to properly test these vaccines?

Now more than ever, the pharmaceutical industry is under the microscope to release products faster while still maintaining the highest level of quality and safety. To overcome some of these challenges, many firms have considered implementing new or different technologies and methods.

However, sound science and data-driven decisions have always be the foundation of pharmaceutical manufacturing. While hundreds of thousands of scientists are working around the clock to develop vaccines, therapeutics, and diagnostics in response to this pandemic, patient safety should always be top of mind, and can only be achieved through accurate, consistent, and validated quality control processes.

During scale-up production, there are many critical and rapid changes occurring, which can be complicated. Critical quality control tests, such as Bacterial Endotoxin Testing (BET), are required by regulators to ensure products are free of harmful Gram-negative bacteria and contamination that could be fatal to the patient. These tests are required to confirm the products are safe.

The Limulus amebocyte lysate (LAL) test is responsible for more than 80 million quality control tests per year, to detect the presence of bacterial endotoxins in parenteral products and medical devices. Recently, commercial preparations of a synthetic reagent, such as recombinant Factor C (rFC), have been made available, although, this complex assay lacks science and real-world data to support utilizing these reagents for raw materials and final product release testing.

So, why would a manufacturer implement a test that has so much uncertainty, especially during this critical time?

The commercially available rFC assays are not a new and novel technology. Developed in the 1990s, its adoption has been slow due to the lack of compendial acceptance and the inability to show equivalency to the LAL test. Manufacturers should be able to undoubtedly prove, with data, that any alternative method to LAL is able to detect all naturally occurring, real-world endotoxins at a level that is equivalent to or better than LAL. Charles River Laboratories' preliminary study data, shared in November 2019 during the Pharmalab Congress, yields that all recombinant reagents underpredict environmental endotoxins present in water samples compared to LAL. (1)

> *Reid, Nicola. "Recombinant reagents underpredicted the amount of endotoxins recovered using LAL reagents, by a concerningly high percentage, which means large volumes of dangerous, naturally occurring endotoxin is being missed by recombinant reagents. These short comings on a recombinant products ability to recover endotoxin, that is knowingly present, cannot be overlooked." June, 2020.*

This study showed that all recombinant reagents lacked specificity. Specificity is the ability of the test method to detect all endotoxins present in a sample. To accurately determine specificity, the test must be performed with naturally contaminated samples, providing endotoxin that you would

naturally encounter in the manufacturing environment. These natural endotoxins and their pyrogenicity is what should be our biggest concern when it comes to patient safety risks. Pyrogenicity must be proven, just as it was when LAL was studied for years in comparison against the rabbit pyrogen test, where naturally contaminated raw material and finished product samples were used to properly address specificity. (1)

> *Hoffmeister, Alan. "Purified endotoxin standards and laboratory derived native endotoxins do not exist in nature. They are created under defined laboratory conditions and thus have no clinical relevance. Using these standards in calibration of reagents is acceptable, but using them in studies to try and prove equivalency is not enough." June, 2020.*
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> *Reid, Nicola. "For comparability testing for any alternative reagents to the LAL test, including recombinant reagents, naturally contaminated products that contain environmental endotoxin should be utilized to ensure relevance to pharmaceutical operations, manufacturing processes, and product formulations presenting real-world risks that could occur in any pharmaceutical manufacturing facility." June, 2020.*

Furthermore, pharmaceutical companies are required to manage their own quality control programs and provide evidence of processes and a state of control during Food and Drug Administration (FDA) inspections and audits. During an audit, every change to a process requires justification, and it is the manufacturer's responsibility to audit the supplier when utilizing a non-licensed, nonregulated product. This is not required when using FDA-licensed LAL reagents, as the LAL manufacturers have biannual FDA inspections and unannounced audits, to ensure all current good manufacturing practices (cGMP) and requirements have been met.

The FDA has not licensed any recombinant products, nor has the United States Pharmacopeia (USP) incorporated recombinant products as a compendial method within the regulatory guidance, as of June 2020. There is no justification or data of equivalency to the LAL test. Furthermore, as stated by the European Directorate for the Quality of Medicines (EDQM), when manufacturers use unlicensed, unqualified products for final release testing, it is 100% the drug manufacturer's responsibility if a patient has an adverse reaction, becomes ill, or dies, not the test supplier's (Hoffmeister, 2020). The USP' s recent decision to cancel the proposed inclusion of recombinant technology in compendial chapter <85>, is to ensure patient safety is at the forefront during this global COVID-19 pandemic. Risking patient safety and product quality is not an option in the race to market for the most coveted therapies in the world. This decision was made based on an overwhelming response of public comments received, that the pharmacopeia needs more real-world data to confirm that the alternative method is indeed as rugged, robust and specific to the gold standard, LAL test.

For more than 45 years, LAL testing has resulted in the detection of all endotoxin contaminants found in raw materials, in-process samples, and finished products. Given the current race to market for a highly coveted vaccine, manufacturers should continue to make confident, scientifically driven decisions to facilitate their quality control processes and should not be swayed by misleading media coverage, making false claims to raise fear surrounding supply and raw material shortages. Such stories have been published based on inadequate and incorrect information that is not scientifically supported.

LAL is an aqueous extract of blood cells from the Atlantic horseshoe crab (HSC), and the biomedical industry's role in ongoing conservation efforts continues to be a positive attributing factor to its sustainability, having driven the development of laws to protect the HSC against commercial bait fishing along certain East Coast regions. The Atlantic States Marine Fisheries Commission (ASMFC) published data in 2019 on horseshoe crab stocks after their thorough benchmark assessment. The assessment found no evidence that LAL production had adverse effects on HSC stocks. The assessment did find, however, that bait fishery is the major threat to the HSC population. ASMFC found that biomedical manufacturers and their conservation efforts have contributed greatly to maintaining a stable and even flourishing HSC population. (3) The net effect of the biomedical industry for horseshoe crab sustainability is positive because of over 20 years of consistent and unique conservation efforts. Horseshoe crabs thrive where LAL is produced and baiting is banned. (2) Our global reliance on the HSC is too important to neglect protection and conservation of this amazing species, especially since it's the only compendial, specific, and dependable resource for accurate bacterial endotoxin testing.

As part of standard contingency and risk mitigation planning, manufacturers are always a step ahead, forecasting, preparing, and planning for the next pervasive, widespread disease. They have strategies and processes in place for large production scale-ups and are ready when a pandemic, such as the one we're currently in the middle of, might occur. There will always be an increased need in production year-over-year, and being equipped and prepared removes the worry of meeting the expected supply and demand. Vaccine manufacturers have agility in the supply chain to respond safely by maintaining established and well supported suppliers that are responsive and able to sustain the supply of raw material and reagents required for testing. Large manufacturers rely on global data and effective efficacy testing from other sites, enabling a prepared and quick response to maintain and protect drug production pipelines in the long term.

The anticipated increase for vaccine manufacturing may elude to an increased demand for LAL and in turn, an increased need for its raw materials. With the predicted therapy supply needed, the supply of LAL will not need to increase to accommodate and successfully fulfill these needs. This and any future global pandemics will not influence or strain the horseshoe crab collection among LAL suppliers. In fact, stopping biomedical use of the HSC would have the opposite effect and cause their numbers to decrease significantly. Conservation activists should be focusing on the real issues, such as overfishing, use as bait, and the gradual loss of the horseshoe crabs natural habitat. Activists should develop a better understanding that without biomedical use, the legal protection of the horseshoe crab is not guaranteed, and the populations where they are thriving would again become vulnerable.

Technical advancements have minimized the use and volume of LAL per test, while still maintaining the horseshoe crab's protected status.

> *Dubczak, John. "Charles River attained FDA approval in 2006 for a LAL-cartridge based system that reduces the amount of LAL needed by 96% compared to the traditional assay." June, 2020.*
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> *Hoffmeister, Alan. "We could produce 700 million tests, with the raw material we currently have, without bleeding a single extra crab, if all tests were carried out using LAL-cartridge technology." June, 2020.*

We believe the adoption of a recombinant technology as an alternative to LAL must be based on substantial, scientific data where equivalency to the LAL test can be proven, without dispute. Evaluating a different technology without relevant, harmonized criteria and a risk-based or data-driven strategy could be detrimental for final decision-making on releasing safe product to market. Any new or alternative technology should be released only when we are certain that it is equal to or better than LAL. Datasets published, as of today, that are available in the public domain demonstrate that the current recombinant technologies available do not meet these requirements.

As our industry works to discover, formulate, produce, and distribute safe and effective therapies to combat the coronavirus outbreak, we are confident that manufacturers have plans, as well as supply chains in place, to meet increased production and testing demands. Additionally, maintaining sound scientific processes is compulsory to ensure patient safety. We know a treatment will soon be ready for us, our families, and future generations to come, and we all must feel confident in our roles and efforts put forth in our fight against this pandemic and protecting our futures.

References

1. Reid, Nicola. Nov. 2019. A Global Perspective For Quantifying All Endotoxins Within Pharmaceutical Water Systems. In a 2019 Pharmalab Presentation.
2. Cooper JF. 2019. "Horseshoe Crabs Stock Status: Sustainable, Flourishing In Southeast". https://eureka.criver.com/horseshoe-crabs-stock-status-sustainable-flourishing-in-southeast/
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About the Author

Rachael Kerr, a Senior Technical Writer for Charles River Laboratories, has more than 18 years of industry experience ranging from hands-on expertise in Microbiology, Formulation Science, Pharmaceuticals and Biotechnology. Rachael has a Bachelor's degree in Biogenetics from Cornell University and went on to attend graduate school at the University of Pennsylvania, studying Microbiology and Anatomy & Physiology. After 8 years in Scientific Marketing with Charles River Laboratories, Rachael is now combining her scientific laboratory knowledge and background with her marketing skills to create scientific content offering industry insight within articles published in many scientific journals as well as scientific content for Charles River's partners and customers.