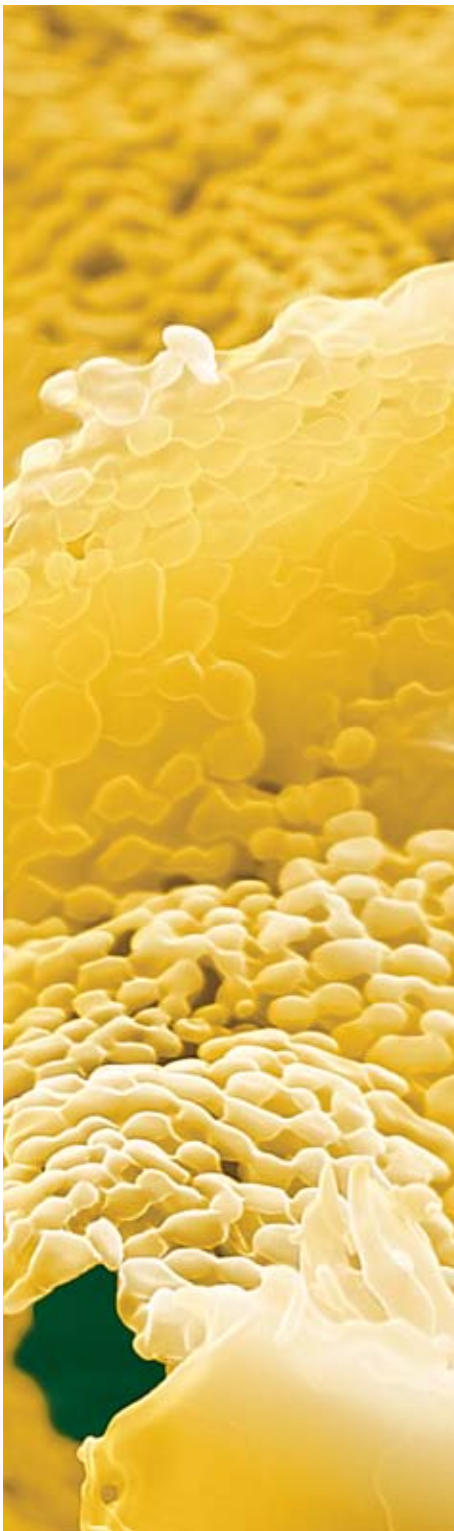


# Business *Awareness*

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## Rapid Testing – or how Lonza protects lives

When children are very young, they are brought to the pediatrician to be immunized against a number of childhood illnesses and debilitating diseases. People who are allergic to bee stings or peanuts carry around a special “pen” that allows them to inject themselves with the drug they need to counter the allergic reaction. Other people have to inject themselves daily with insulin to help treat their Diabetes. And again others may have had a hip joint replaced or a pacemaker implanted.

With the aid of a primitive creature called horseshoe crab, Lonza – namely the Rapid Testing business unit of Lonza Bioscience – helps make vaccines, injectable pharmaceuticals and implantable medical devices like these safe for patients, therefore improving the quality of life of many people.

Leveraging Lonza Bioscience’s competence as a leader in several high-value segments of the life-science industry, the Rapid Testing business unit offers test sys-

tems for pharmaceutical and other customers in quality control laboratories – and also supplies Lonza’s Quality Control laboratories throughout the world with test kits for safety testing of their drugs. The biggest product line of Rapid Testing is endotoxin detection. The endotoxin detection products made at the Lonza facility in Walkersville, MD [USA] play an important role in assuring that only products which are safe from endotoxin contamination are released for consumer or patient use.

### When the horseshoe crabs’ blue blood clots

But how did assuring the safety of drugs and medical devices become linked with the horseshoe crab? The timely research into how this animal fights bacterial infections lead to the discovery of a system that has allowed us to make products like the flu vaccine, insulin, pacemakers, and replacement hips safer.

Life Science Ingredients	Custom Manufacturing: Exclusive Synthesis & Biopharmaceuticals		Bioscience
Nutrition Ingredients	Small Molecules	Mammalian Operations	Cell Therapy
Microbial Control	Peptides	Biopharma R&D Services	Rapid Testing
Performance Intermediates	Biochemicals	Microbial Operations	Media
	Pharma Sales and Marketing		Cell Discovery
			Molecular Biology



The ancestors of the Atlantic horseshoe crab, *Limulus polyphemus*, and its relatives date back hundreds of millions of years. Today, *Limulus polyphemus* and its Asian cousins *Tachypleus tridentatus*, *Tachypleus gigas*, and *Carcinoscorpius rotundicauda* are the surviving species of the horseshoe crab. The horseshoe crabs spend most of their life in the ocean. In the United States, mature crabs come ashore late each spring to lay and fertilize eggs. Biologists who observed this yearly ritual became interested in the horseshoe crab's immune system. The warmer spring ocean water along the shore at breeding time may expose the crabs to bacteria. When threatened with bacterial infection, the blue blood of the horseshoe crab clots. The clot surrounds the bacteria, protecting the rest of the animal from infection. Toxins from bacteria, such as endotoxin, will also cause the blood to clot.

### Research played an important role

One of the human symptoms of a bacterial infection is often a fever. This is a “pyrogenic” response to the bacteria. Too much endotoxin from a bacteria can also cause a fever. Serious bacterial or endotoxin exposure in human's blood stream may lead to blood clots, organ failure and even death. Patients with high levels of bacteria or toxins from the bacteria, such as endotoxin, in their blood have “septicemia”. One of the ways people can be exposed to a serious amount of endotoxin and developing septicemia would be if the blood stream was exposed to something that was contaminated with endotoxin, such as an injected vaccine or drug or an implanted medical device.

Manufacturers of such healthcare products spend years developing products to treat an illness, protect us from disease, or help us live healthier lives, such as providing assistance when our heart rhythms need correcting. Regulatory agencies, such as the U.S. Food and Drug Administration (FDA), provide guidance and oversight to help manufacturers in their efforts to keep bacteria and endotoxin out of their products. This includes making it obligatory for products to pass Quality Control testing for the absence of bacteria (sterility) and endotoxin.

Treating and preventing illness has long been the goal of physicians and researchers. Injecting patients with what was thought to be a cure, sometimes caused the patient to get sicker or even to die. So, in addition to finding new ways to treat diseases, researchers had to find ways to make their products safe from bacterial or endotoxin contamination.

With processes in place to make contamination-free products, manufacturers then needed methods to show that the products were safe. In the 1920s, a test for the presence of pyrogens in a solution was developed by Florence Seibert using rabbits. During World War II, there was a high demand for safe intravenous solutions and Florence Seibert's rabbit pyrogen test was used to check the products for contamination. The United States Pharmacopeia published the first pyrogen test in 1942. This test involved injecting the pharmaceutical into a rabbit and monitoring the animal for an increase in temperature, or a fever. If the rabbit spiked a fever, it indicated that the sample contained an unacceptable level of a pyrogen, such as endotoxin, and the batch of product could not be sold.

In the late 1960s, researchers studying the blood clotting system of the horseshoe crab found that it was extremely sensitive to endotoxin. Frederick Bang and Jack Levin developed an endotoxin test that involved mixing the blood-clotting factors that are in the amebocyte with a drug sample in a test tube. If sufficient endotoxin was present, they found that the liquid in the tube would clot in such way that when the tube was inverted top to bottom, the clot stayed in the bottom of the tube. This was the first "LAL" test for endotoxin. LAL stands for Limulus Amebocyte Lysate, which means the factors that are inside the amebocytes (blood cells) of the horseshoe crab, *Limulus polyphemus*. In 1977, the FDA approved the use of the LAL test as a replacement for the Rabbit Pyrogen Test to detect endotoxin in human and animal injectable pharmaceuticals and biologicals, and implantable medical devices.

## Lonza commercialized a first alternative

The first commercialized LAL method, the gel clot LAL method, is not very different from the original test made by Bang and Levin. This test provides a simple yes or no answer as to whether or not the product being tested is contaminated with endotoxin. The gel clot LAL products from Lonza fall within our PYROGENT® product line.

In the 1980s and 1990s, other methods were developed that would allow a manufacturer to determine the amount of endotoxin that may be in their product. Lonza's Walkersville facility was the first LAL manufacturer to bring the quantitative chromogenic LAL methods to market. In these tests, the mixture of LAL and test sample turns yellow in the presence of endotoxin, making it possible to calculate how much endotoxin is in the test sample.

In 2003, Lonza scientists commercialized the first alternative endotoxin detection test, called PyroGene®. This test does not require the use of horseshoe crab blood. The development of LAL diminished the amount of animal testing by virtually replacing the rabbit pyrogen test. The PyroGene® test will allow for further reductions in the usage of animals in biomedical tests.

The speed and ease with which the current endotoxin detection tests can be run in comparison with the rabbit pyrogen test has given the vaccine, pharmaceutical and medical device industries the ability to quickly, efficiently and confidently test their products for endotoxin contamination.



Lonza is dedicated to bringing further innovative rapid testing systems to the health-care industry to help manufacturers deliver their new products to the consumer and patient more quickly, while helping to make sure the products are safe.



**Lonza**