

Developing biodefense IVDs is still a priority

John Conroy

In a scary world, nonclinical diagnostic testing spies a few challenges and many opportunities.

As anthrax scares go, this one had as benign a beginning and ending as possible in today's terror-obsessed world. A New York City musician who returned from Africa in February with unprocessed animal skins tested positive for anthrax. The 44-year-old man bought the skins, which contained anthrax spores, to make traditional African drums, authorities said. Complaining of flu-like symptoms, the musician collapsed while on tour with his dance troupe in Pennsylvania, where he was hospitalized.

Notable for their slightly more prosaic origins, similar stories of viral, toxic, or bacterial misadventures have made news of late. In France, government authorities reported finding cases of a possibly deadly strain of H5N1 bird flu on a turkey farm. In the United States, 60% of Americans are worried about the spread of the virus, according to a new poll. A cat in Germany died after reportedly eating an infected bird. And in early February, at least a dozen U.S. senators and 200 staff members were quarantined in a parking garage of a Senate office building after a nerve gas alarm sounded. They were permitted to leave three hours later when tests proved negative.

A routine cleaning substance may have triggered the attic sensor that set off the alarm at the Russell Senate Office Building. However, the false alarm points to just one of several challenges facing nonclinical diagnostic testing: getting the right reading in a rough, uncontrolled environment. By the same token, a senator's spokesman mentioned in a newspaper account of the evacuation

that false alerts have become a fact of life for lawmakers and their staffs. "We get a few of these a day," the spokesman told the *Houston Chronicle*.

As these stories attest, challenges and opportunities abound for IVD firms in a world where infectious diseases and bioterrorism agents are just a plane flight, mail drop, cargo dock, or car ride away. Market applications include tests for biodefense, avian flu, West Nile virus, food, animals and pets, water quality, and genetically modified food. Testing formats include ELISA, rapid lateral-flow technology, and real-time polymerase chain reaction (PCR).

Market Analysis

In a report on the IVD market, Kalorama Information (New York City) provided an in-depth look at three of these nonclinical market segments. Among the highlights are the following:

- **Environmental and biowarfare.** The report noted that new technologies have emerged since the 9/11 attacks to improve the detection, prevention, and surveillance of bioterrorist attacks. These technologies include rapid tests for smallpox, anthrax, and salmonella, as well as improved vaccines and information-awareness networks to expedite tracking the symptoms of chemical and biological events.

- **Food microbiology.** In 2003, the global market for food microbiology tests was an estimated \$864 million with an annual 9% growth rate. A worldwide emphasis on production of safer foods has sparked a sharp increase in the number of tests performed, according to Kalorama. In 1999, users ran 440 million tests. The 2003 report estimated that by 2005, the numbers of tests run would reach 625 million, a 7%



Researchers at the California Animal Health and Food Safety Laboratory and Lawrence Livermore National Laboratory demonstrated that the Newcastle disease virus could be detected using an environmental air sampling system, which is much less labor-intensive and time-consuming than conventional swab sampling.

PHOTO COURTESY LAWRENCE LIVERMORE NATIONAL LABORATORY

annual increase. *Listeria monocytogenes*, *Escherichia coli*, and *Vibrio parahaemolyticus* are among the microorganisms that can cause food-related illnesses.

• **Veterinary medicine.** Global concern about the spread of bovine spongiform encephalopathy (BSE), or mad cow disease, has increased the market for BSE test kits, the research firm says. In 2003, the market in Europe and Japan for postmortem kits stood at approximately \$140 million. Kalorama forecasts the market will double between 2007 and 2009. More than 1500 cases were detected in Europe in 2002. Canada, which exports more than 70% of its beef to the United States, performed BSE tests on approximately 900 of 11 million cows in 2003. The United States tested 19,900 of 96 million cows in the same year. In March 2004, the U.S. Department of Agriculture (USDA) said it plans to expand its BSE surveillance program with rapid-

test kits from Bio-Rad Laboratories (Hercules, CA), Idexx Laboratories (Westbrook, ME), and other IVD manufacturers.

Given the state of the world these days, the environmental and biowarfare sphere presents a world of business opportunities. In its report, Kalorama cited the U.S. Project BioShield program, a \$5.6 billion program featuring expedited approvals and government procurement. The goal of the 10-year program is to create "a medical arsenal to combat bioterrorism." The United States spent \$890 million in 2004 and authorized an outlay of \$2.5 billion in 2005 for products such as vaccines, therapeutics, and testing devices.

Since the 9/11 attacks, demand has increased for tests that can detect anthrax, botulism, malaria, ebola virus, ricin, and other bioterrorist agents, Kalorama noted. However, few tests are available for these pathogens. The critical need for new tests has spurred "research

for highly sensitive, field-type techniques for pathogens that are likely to spill over into clinical testing in microbiology and virology."

In addition, no rapid assays to test individuals for infection by biowarfare agents or other similar pathogens are on the market, Kalorama said in the 2004 report. Many IVD companies have been working with various U.S. federal agencies to develop rapid-response diagnostics and environmental sensors in order to detect biological or chemical agents at very low concentrations. However, the research firm said that such tests or devices have not reached the market, and no such products are expected to be commercially available before 2009.

IVD companies working with U.S. government agencies to develop rapid tests for biowarfare agents include Invitrogen (Carlsbad, CA) and MicroFluidic Systems (Pleasanton, CA). The former company launched Biological Defense Systems (BDS) in July 2004 to further explore biosecurity applications based on the company's pathogen research, according to Kalorama. MicroFluidic Systems received a \$4.5 million contract from the Advanced Research Projects Agency at the U.S. Department of Homeland Security (DHS) to develop an automated system for identifying airborne bacteria, viruses, and toxins.

Kalorama said the market for biowarfare-based molecular tests, which reached approximately \$31 million in 2003, will grow 2% annually and reach \$34 million in 2008. The tests are being used by the U.S. government at post offices and federal buildings to detect anthrax.

Preparing for Bioterrorism

Although no rapid assays exist for biowarfare agents, other such tests to detect anthrax, ricin, and other bacteria have been developed by a number of IVD companies. Cepheid (Sunnyvale, CA) is the main supplier of tests for the U.S. post offices. Genelex (Seattle), Ocean Optics (Dunedin, FL), and Response Biomedical (Vancouver, BC, Canada) also offer rapid tests.



A lab technician using the GeneXpert system by Cepheid (Sunnyvale, CA).

Increased demand for its point-of-care Ramp system, test cartridges for West Nile virus, and on-site detection of anthrax, smallpox, ricin, and botulism toxin has bumped Response Biomedical's revenues to \$1.4 million in 2003, according to Kalorama's 2004 market report. Response sold more than 125 Ramp systems in 2003. More than 70 of the biological field detection kits have been sold to the U.S. Marine Corps, South Korea, the University of California at Los Angeles, the New Jersey state government, and the city of Philadelphia, as well as other public health and first-responder agencies throughout the United States.

Response Biomedical says the handheld system is 100% reliable at detecting anthrax at the 4000-spore level with no false positives. Results are available in 15 minutes instead of the two days it takes to receive results from culture-based tests, according to the company.

Joanne Stephenson, vice president of

business development at Response, says it is difficult to track the growth of non-clinical diagnostic tests because "it's such a segmented industry," and point-of-care and rapid field tests tend to get

lumped in with their laboratory- and hospital-based counterparts.

Although market numbers may be hard to differentiate, the market for non-clinical testing products is definitely



The Ramp bioterrorism field testing system by Response Biomedical Corp. (Vancouver, BC, Canada).

PHOTO COURTESY RESPONSE BIOMEDICAL CORP.

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The Veratox test kit by Neogen Corp. (Lansing, MI), which is used for determining aflatoxin levels in grain.

growing because of recent governmental regulations, Stephenson says. "I know from a biosensing point of view, there are now specific mandates in different areas that different organizations and facilities need to be prepared to respond...to a biological attack and to diagnose it and have some sort of plan in place for decontamination. That's where we're seeing a lot of the growth."

These mandated plans apply to entities such as universities and hospitals in the United States, she says, adding that the new rules have come into effect only within the last two years.

Response's customers are looking at its testing kits "from a productivity point of view," Stephenson points out. Large organizations with big mailrooms, for example, "have a lot of potential for white-powder incidents." If they rely on the local hazardous materials team, they can lose at least half a day of productivity following an incident. By setting up an in-house response team, a business can maintain productivity following a negative reading, she asserts.

One of the key differences between clinical and nonclinical diagnostics is the uncontrolled nature of the environment for nonclinical tests, Stephenson says. In fact, both the environment and training are uncontrolled. There is no consistent competency training and gen-

erally no regulatory requirements, or very low regulatory requirements, she notes.

Regarding the Canadian supplier's success with public first responders, Stephenson notes that once a rapid on-site testing system becomes accepted in the world of hazmat teams and fire departments, it becomes an entrenched part of the equipment base.

"You're looking at a 20-year life span for anything they institute when they start taking on new pieces of equipment or new actions," she says. "They're responsible for preparing for the long term. They're continuing to train. In that world, there's no fly-by-night. Nothing comes and goes in two or three years. Once it's been accepted, it's in their psyche from a business standpoint."

Meeting User Skill Sets

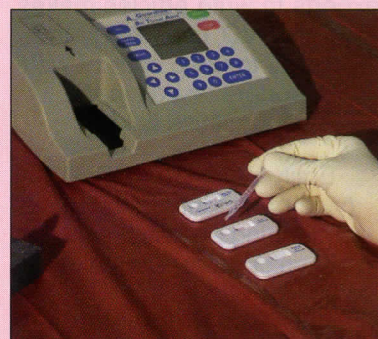
David Persing, MD, PhD, executive vice president and chief medical and technology officer at Cepheid, knows firsthand the benefits of business acceptance on a grand scale. Cepheid is the main supplier of molecular surveillance test cartridges to the U.S. Postal Service. Its GeneXpert system uses real-time PCR to analyze crude samples in minutes. The tool integrates sample preparation, DNA amplification, and detection, and can draw results from a raw

sample in 30 minutes or less in the field, according to the company.

The GeneXpert uses 13-chamber cartridges for sample preparation, combined with amplification and detection in an automated instrument with a rapid nucleic acid analysis capability, the company says. Skilled technicians using current manual techniques over the same set of analytical procedures require from six hours to three days to accomplish the same task.

The system forms the detection engine of the biohazard detection system which was developed in collaboration with Northrup Grumman and Applied Biosystems. This system is used in post offices across the United States for anthrax testing in mail-sorting facilities. "According to U.S. Postal Service reports, the system has used over 2.1 million GeneXpert cartridges in screening more than 25 billion pieces of mail being sorted at about 275 different centers," Persing says.

He believes the GeneXpert system is a good example of a test module design for nonclinical diagnostics. "It's a model for how to implement the various sophisticated technologies in an environment that's challenging," Persing says. "In the industrial setting, you don't have access to highly trained and skilled personnel on a 24/7 basis. You have to use the skill set that's already there. The challenge is designing the test to meet the skill set of the people you're trying to market to. The most remarkable statistic is that despite these challenges, we've never had a false positive. Given the rep-



Dosing test strips for evaluation in the Guardian reader system by Alexeter Technologies LLC (Wheeling, IL).