Testimony Submitted by Leading BioSciences

Introduction

Leading BioSciences (LBS, www.leadingbiosciences.com) is grateful for the opportunity to comment on the U.S. Government response to the Ebola outbreak. Headquartered in San Diego, CA, LBS is a clinical-stage, platform pharmaceutical company. We are focused on developing therapies and diagnostics to treat gastrointestinal (GI) breakdown and to halt multi-organ failure resulting from shock. Our pipeline includes therapies for treating GI breakdown resulting from three common forms of shock: cardiogenic shock following heart surgery, septic shock, and hemorrhagic shock.

LBS applauds the Senate Appropriations Committee for its approval of the Obama Administration's $88 million request for emergency Ebola funding in October 2014. LBS was pleased to see $30 million of that $88 million directed to the U.S. Centers for Disease Control (CDC) and Prevention's Biological Advanced Research and Development Authority to accelerate development and manufacturing of experimental Ebola drugs and vaccines. However, we were disappointed that therapies to reduce the lethality of Ebola infection are not eligible.

Vaccines will have limited benefit for those individuals who contract the virus in the next 4 to 6 months, and experimental antivirals may have unknown challenges in production and safety. Until these investigational products will be widely available, the standard treatment for Ebola recommended by the CDC remains supportive therapy with active treatment of disease symptoms: "balancing the patients' fluids and electrolytes, maintaining their oxygen status and blood pressure, and treating patients for any complicating infections." Indeed, current evidence suggests that treatment of symptoms can be effective in reducing the mortality associated with Ebola virus infections, most notably here in the United States.

Our testimony here today will outline why incorporation of symptomatic treatments in the Ebola response may promote survival for patients treated here in the United States and in West Africa. LBS' drug, LB1148, has the potential to treat one of the most dangerous symptoms of Ebola infection – multi-organ failure from hemorrhagic shock – with 1,700 manufactured doses available on November 14, 2014 and tens of thousands of additional doses potentially available within 60-90 days. We believe LB1148 can treat the most critical symptoms of Ebola, allowing patients enough time to fight off the virus itself spontaneously or with an experimental antiviral treatment. More information about LB1148 is available in this video.

LBS acknowledges that Congress must pass a spending bill during this work period, and the Committee is likely to weigh a supplemental request for additional emergency funding to respond to the Ebola crisis. LBS commends the Committee for its support for biomedical research and for supporting initiatives that will assist the industry in commercializing innovative solutions to treat Ebola. More importantly, however, LBS encourages the Committee to expand the focus of clinical response efforts beyond preventative vaccines and anti-viral therapies to also include therapies that can help decrease the lethality of the virus, promoting survival.

Ebola Virus Disease

As the Committee is already aware, Ebola is a severe, often fatal illness in humans. Ebola virus infections cause a severe form of viral hemorrhagic fever, for which no prophylaxis or curative treatments are available, leading to mortality rates as high as 90 percent. Research has shown that the infection itself is not typically a direct cause of death. Instead, most patients experience prolonged periods of hypovolemic, hemorrhagic and septic shock, leading to multi-organ failure and death.

Ebola infection occurs as the virus enters the body through an opening in the mucosal barrier or a break in the skin. Symptoms of infection may develop within as few as 2 days or as many as 21 days. These initial symptoms (eg, fever, fatigue) can be difficult to differentiate from other illnesses, such as malaria, typhoid fever, and meningitis.

During the infection, the Ebola virus replicates and spreads throughout the body. In particular, the Ebola virus damages the cells that form the linings of blood vessels, specifically the epithelial and endothelial cells, which leads to dysfunction of the vascular system. As a result, the vascular system is unable to maintain a barrier to keep blood and fluids in the vasculature, a condition called capillary leak syndrome. Consequently, fluids escape from the blood vessels, lowering blood pressure (hypotension) and contributing to shock. These micro-hemorrhages occur throughout the body, particularly in the GI tract, leading to bloody diarrhea and disrupting function of the gut barrier. Patients enter a state of hypovolemic or hemorrhagic shock, accompanied by profound necrosis, or cell death, in the adrenocortical regions of the brain, which may also prolong hypotension. This prolonged shock state is a major contributing factor to the cascade of multi-organ failure.

Late symptoms of Ebola are often shock-related and fatal. Shock-related symptoms include decreased blood pressure, a rapid, weak, or absent pulse, irregular heart rate, and mental confusion. Shock can progress to multi-organ failure, including liver dysfunction, kidney failure, cardiovascular shutdown, and respiratory failure. Both the National Institutes of Health (NIH) and the CDC assert that Ebola patients typically die from low blood pressure and the resulting shock, which can last five to eight days. For example, according to the NIH website, “Ebola patients usually die from low blood pressure and the resulting shock rather than from blood loss.” Similarly, according to the CDC, patients with the fatal disease die typically between days 6 and 16 of complications, including hemorrhagic shock and septic shock, which lead to multi-organ failure.

Treating these fatal symptoms of the disease could keep patients alive while broadening the opportunity for experimental Ebola therapies and/or the patient’s own immune systems to eliminate the virus. However, there are currently no treatments approved for shock and multi-organ failure other than standard supportive care.

Shock, the GI Barrier, and Organ Dysfunction

Based on years of research, evidence suggests that organ dysfunction during shock is linked to the failure to protect the body from the powerful components of the digestive system. A normal

intestine has a sealed mucosal epithelial barrier that maintains luminal contents, including the potent enzymes that digest food in the GI tract. Breakdown of this mucosal barrier is considered an early, driving factor in shock-related multi-organ failure. During shock, blood flow is sent preferentially to the brain and heart by diverting blood from other tissues, particularly the small intestine. This blood diversion causes a prolonged period of insufficient blood flow (hypoperfusion), and eventually a restriction of the blood supply (ischemia) in the small intestine. Over time, as the mucosal lining of the small intestine receives inadequate oxygen and nutrients, this protective gut barrier breaks down and loses its ability to contain potent pancreatic digestive enzymes. The enzymes can leak into the intestinal wall submatrix, leading to the pathological breakdown of the intestinal wall and the creation of toxic byproducts that further activate a cascade of the disease process. The digestive enzymes and biologically active factors eventually gain access to the lymphatic and circulatory systems, initiate systemic inflammatory cascades, and result in the downward spiral of multi-organ failure. These events are consistent with the observed disease course in patients with Ebola.

Preclinical work in models of hemorrhagic and septic shock suggests that modulation of gastrointestinal breakdown by inhibiting digestive enzymes can prevent or relieve organ damage and multi-organ failure. Multiple studies have shown that using molecules that inhibit digestive enzymes in the intestinal lumen reduces inflammation and mitigates multi-organ failure.

LB1148 as Part of the Ebola Solution

LBS's lead product, LB1148, is the result of 15 years of research and testing. LB1148 has three main functions: 1) inhibition of key digestive enzymes that drive the GI breakdown, 2) facilitation of transport of the inhibitor along the entire length of the digestive track, and 3) provision of a balanced electrolytes and energy source to promote healing of the GI barrier.

LB1148 contains four compounds – all of which separately have well-characterized and established safety profiles. The broad acting serine protease inhibitor inhibits numerous digestive enzymes in the lumen of the small intestine and helps preserve gut integrity during acute periods of shock and hypoperfusion. The three enhancing components of LB1148 support the activity of the protease inhibitor by facilitating sufficient coverage of the full-length gut epithelium while preserving healthy tissue. The second osmotic agent serves to increase the osmotic load in the large intestine to facilitate the protease inhibitor distribution along the gut epithelium. The third component is a carbohydrate acting as an energy source for the intestinal villi and epithelium, especially under ischemic conditions. The fourth component – electrolytes - balance the solution by creating an isotonic solution that minimizes stress on the cells in the GI tract. The components of LB1148 are reconstituted in 700 mL of water prior to administration. LB1148 is designed to be administered orally or via a nasogastric tube directly to the stomach, making it suitable for use in a wide range of clinical settings.

Under informed consent, this treatment strategy has already been used in more than 200 patients in Taiwan, including a Phase 1 safety study with no related safety issues reported. In other trials with the active ingredient, thromboembolic events and allergic reactions have been reported. Strong preclinical data shows that LB1148 improves morbidity and mortality following shock. In

a preclinical study of hemorrhagic shock, the drug improved survival from 20 percent to more than 90 percent.

LB1148 could be used immediately to reduce organ dysfunction in Ebola patients, both here in the U.S., as well as in West Africa. Manufacturing of LB1148 has been completed and Quality Control release is expected this week. LBS will have 1,700 doses of LB1148 available to treat patients by November 14, 2014. Our drug supply and manufacturing process is scalable such that an additional 20,000 to 60,000 doses could be available within 60-90 days. Additionally, the components of LB1148 may be stored safely at room temperature requiring no refrigeration or special handling. Essentially, LBS has an investigational therapy that could be quickly deployed to patients here in the U.S. or to patients anywhere in the world the virus may reach.

LBS has responded to the Ebola crisis by accelerating an Investigational New Drug (IND) submission for expanded-access, compassionate use of LB1148 for multi-organ failure linked to hypovolemic, hemorrhagic, or septic shock caused by Ebola virus infection. LBS is eager to provide patients infected with Ebola access to a therapy that uniquely addresses the fatal symptoms of the disease. Once there is a definitive decision on the IND filing, LBS will work with key policymakers in Congress and the Administration and also work health authorities to determine next steps.

Requests of the Senate Appropriations Committee

Our observation is that policymakers and industry have been primarily focused on the critical need for vaccine testing and development and for exploring treatments that fight the Ebola virus directly. These strategies may not benefit the patients who are infected and critically ill today. Our opportunity and the opportunity of the Ebola response is to address the immediate and unmet need of providing an effective therapy for shock and organ failure to those who have and those who may become infected with Ebola in the future.

Therefore, in any FY15 omnibus appropriations bill, continuing resolution, or other emergency spending measure, LBS encourages appropriators to direct significant funding to the CDC and the NIH for efforts to validate the effectiveness of near-term innovations for treating shock and multi-organ failure in Ebola patients. We believe that by making such funding available to U.S. biopharmaceutical companies, like LBS, the federal government will incentivize R&D and commercialization of therapies that reduce the lethality of the Ebola virus. In addition, because our research finds that shock triggers organ failure when digestive enzymes enter the bloodstream, we believe the CDC and NIH should receive emergency appropriations to promote therapies, such as LB1148, that can mitigate gastrointestinal breakdown.

In conclusion, LBS encourages the Committee to work with the FDA to ensure the agency is appropriately resourced to review and process IND applications that will help get therapies that address the fatal symptoms of Ebola to infected patients as quickly as possible. It is important to act quickly as a treatment like LB1148 could have significant survival impacts on those already infected. A vaccine is obviously a critical need, but vaccines offer a long term solution, not a solution today. We appreciate the Committee's consideration. Please do not hesitate to contact us if LBS can serve as a resource on these important issues.