

### **Category A Biothreat Agents**

*Bacillus anthracis* - Anthrax  
Botulinum neurotoxin from  
*Clostridium* species - Botulism  
*Yersinia pestis* - Plague  
*Variola major* - Smallpox  
*Francisella tularensis* - Tularemia  
Filovirus and Arena Viruses – Viral hemorrhagic fevers

### **Category B Biothreat Agents**

*Brucella* species - Brucellosis  
Epsilon toxin from *Clostridium perfringens* – Fatal Enterotoxemia  
*Salmonella* species, *Escherichia coli* O157: *Shigella* species - Food safety threats  
*Burkholderia pseudomallei* - Glanders  
*Burkholderia pseudomallei* - Melioidosis  
*Chlamydia psittaci* - Psittacosis  
*Coxiella burnetii* - Q fever  
Ricin Toxin – Severe pulmonary incapacitation/tissue necrosis  
Staphylococcal enterotoxin B – Toxic shock syndrome  
*Rickettsia prowazekii* - Typhus fever  
*Alphavirus* - Viral encephalitis  
*Vibrio cholera* – Cholera/water safety  
*Cryptosporidium parvum* – Cryptosporidiosis/water safety

Source:

<http://www.bt.cdc.gov/agent/agentlist-category.asp>

## U.S. DEPARTMENT OF DEFENSE CBMS-JVAP PROGRAM

### BIOLOGICAL DEFENSE: BOTULINUM NEUROTOXIN VACCINE DEVELOPMENT

*Clostridium botulinum* neurotoxins are the most potent naturally occurring toxins known. One gram of botulinum neurotoxin—the weight of a standard paper clip—would be enough to kill one million people in inhalational form.<sup>1</sup> Working with the U.S. Department of Defense Chemical Biological Medical Systems-Joint Vaccine Acquisition Program (CBMS-JVAP), DVC is developing a vaccine to protect against this formidable threat.

### A POTENTIAL BIOTERROR THREAT AGENT

Labeled a Category A biological threat agent by the Centers for Disease Control and Prevention (CDC), botulinum neurotoxin is considered a serious potential threat.<sup>1</sup> Since at least the mid-1900s, botulinum neurotoxin has been used (with varying degrees of success) as a biological weapon.<sup>2</sup>

Botulinum neurotoxin causes illness in four naturally occurring forms: infant, wound, adult colonization and foodborne botulism. Of these, infant botulism is the most common, although foodborne botulism is the most widely publicized and most preventable.<sup>3</sup> Symptoms include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth and muscle weakness that moves down the body. Ultimately, paralysis of breathing muscles can cause a person to stop breathing unless mechanical assistance is provided.<sup>4</sup> The neurotoxin can also be aerosolized, creating a fifth type of illness, inhalational botulism, with symptoms almost identical to its other forms.

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Answers for Success



<sup>1</sup> CDC, Bioterrorism Agents/Diseases

<sup>2</sup> Arnon, SS, et al. p.1059-1061.

<sup>3</sup> CDC, Surveillance for Outbreaks of Botulism

<sup>4</sup> CDC, Botulism



## PREVENTING THE THREAT

There are seven serotypes (A-G) of *Clostridium botulinum*, four of which (A, B, E and F) cause naturally occurring human botulism cases<sup>5</sup>. Serotypes A and B are the most frequently isolated botulinum neurotoxins. Due to subtle differences between the seven serotypes, one vaccine is not effective for protection. However, by including different botulinum antigens, or components, a vaccine can be designed to protect against more than one serotype.

DynPort Vaccine Company LLC (DVC), a CSC company, is working with CBMS-JVAP to develop a recombinant vaccine to protect against serotypes A and B (rBV A/B). Like many products in DVC's advanced development pipeline, the rBV A/B vaccine candidate was conceived and initially developed at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). The responsibility for the advanced development of this vaccine was transferred to DVC in 2000, including nonclinical testing and production under current good manufacturing practices.

## PROACTIVE PROGRAM MANAGEMENT

To reduce development risk and increase the likelihood of the program's success, DVC employs proactive regulatory and risk mitigation strategies, in addition to a variety of other program management tools.

Highest Potential Impact Value  
x Probability Value =  
**Risk Severity Index**

To measure the potential impact of a risk on quality, program schedule, and cost, DVC employs a Risk Severity Index, which quantifies the overall severity of a risk event. To derive the Risk Severity Index, the probability value of the risk event occurring is multiplied by the highest potential impact value, which prioritizes risks. Potential risks for this type of program vary widely, including changes in regulatory requirements or guidance, scientific risks such as unexpected test results and a variety of manufacturing considerations. The greatest risks are assumed directly into the program, which helps prevent future schedule and cost impacts.

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<sup>5</sup> Nantel, AJ, p.7.





DVC's rBV A/B vaccine candidate is one of the first vaccines that will seek approval under the U.S. Food and Drug Administration (FDA) Animal Efficacy Rule, which is used to judge the effectiveness of products when efficacy cannot ethically be tested in humans, as in the case of biodefense vaccines.<sup>6</sup> As a pioneer in this field, DVC works closely with the FDA and industry organizations such as the Alliance for Biosecurity, seeking input at various stages of development. DVC also employs various regulatory strategies, such as pursuing Fast Track status, to ensure that products are eligible to use all available mechanisms to accelerate the review of marketing applications for licensure.

DVC's functional area experts, such as those in Manufacturing, Testing and Technical Services (MTTS) and clinical and nonclinical research, also play an important role in each program. For example, MTTS stations a "Person in the Plant" to monitor critical manufacturing and testing activities. This group is also responsible for process validation—a complex and comprehensive effort to establish, with a high degree of confidence, that a specific process will consistently produce a product meeting predetermined technical and quality specifications. The products manufactured and tested under the direction of MTTS are used in nonclinical and clinical studies designed and managed by experts in each field.

Managing intricate projects like process validation, nonclinical studies and clinical trials are examples of the expertise DVC provides as a biologics program integrator, by applying program management best practices to its advanced development product pipeline. DVC has a track record of proven success, including FDA licensure of a biopharmaceutical product. The company has advanced eight products into clinical studies in the last 10 years, including Phase 3 and overseas trials. In conjunction with partners around the world, DVC is performing research and development on a variety of vaccines and therapeutics for biodefense and infectious diseases.

## THE PATH FORWARD

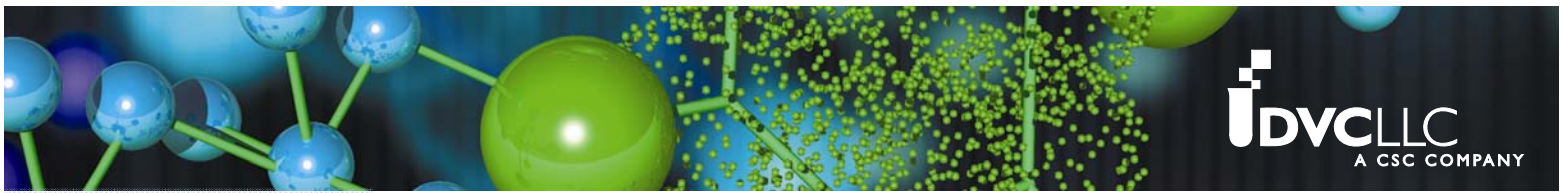
DVC's Investigational New Drug application for the rBV A/B vaccine candidate was submitted to the FDA in 2004, allowing entry into clinical testing. The program has been granted Fast Track designation by the FDA that may result in priority review of the Biologics License Application. The product is currently in Phase 2 clinical studies, furthering the rBV A/B vaccine candidate along the path to licensure.

CSC's expertise in providing health services to government agencies has evolved over the last five decades. Today, the company offers commercial

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<sup>6</sup> 21 C.F.R. Sect. 314 and 601.





best practices integrated to meet federal healthcare requirements, from the development of information technology systems to the delivery of biodefense products. DVC is part of CSC's North American Public Sector, Government Health Services division. For more information, visit [www.csc.com/dvc](http://www.csc.com/dvc).

*The safety and efficacy of this product in humans has not been established. This product is currently under clinical investigation and has not been licensed by the FDA.*

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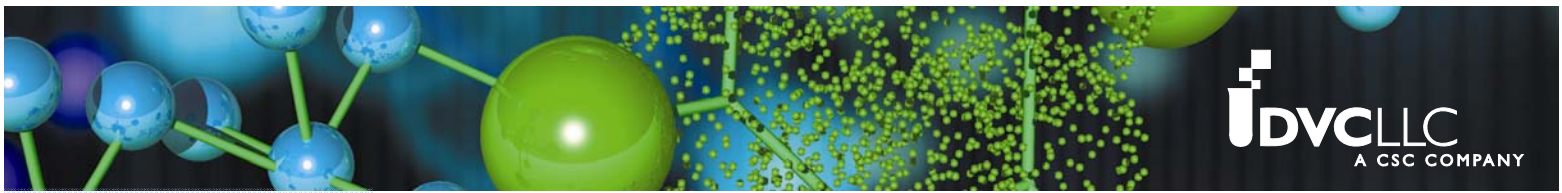
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