

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 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.¹ 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.¹ Since at least the mid-1900s, botulinum neurotoxin has been used (with varying degrees of success) as a biological weapon.²

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.³ 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.⁴ The neurotoxin can also be aerosolized, creating a fifth type of illness, inhalational botulism, with symptoms almost identical to its other forms.

DynPort Vaccine Company LLC

A CSC Company

64 Thomas Johnson Drive

Frederick, Maryland 21702

+1.301.607.5000

www.csc.com/dvc

Answers for Success



¹ CDC, Bioterrorism Agents/Diseases

² Arnon, SS, et al. p.1059-1061.

³ CDC, Surveillance for Outbreaks of Botulism

⁴ 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 cases⁵. 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

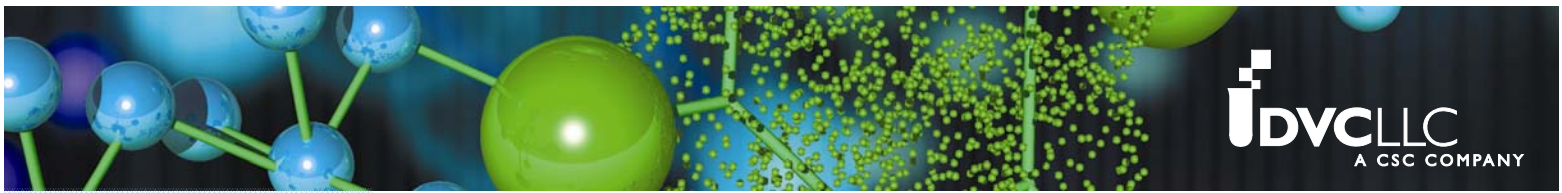
To measure the potential impact of a risk on quality, program schedule, and cost, DVC employs a Risk Severity Index, which quantifies the overall severity of a risk event. To derive the Risk Severity Index, the probability value of the risk event occurring is multiplied by the highest potential impact 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.

DynPort Vaccine Company LLC
A CSC Company
64 Thomas Johnson Drive
Frederick, Maryland 21702
+1.301.607.5000
www.csc.com/dvc

Answers for Success



⁵ 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.⁶ 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 13 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

⁶ 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, Civil and Health Services Group. For more information, visit 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.

This program is funded by Department of Defense Contract DAMD17-98-C-8024.

ACKNOWLEDGEMENTS

Special thanks to Ian Henderson, Ph.D. and Amy Kaczmarek, M.S., M.B.A.

REFERENCES

Ashford, DA, Kaiser, RM, Bales, ME, Shutt, K, Patrawalla, A, McShan, A, et al. Planning against Biological Terrorism: Lessons from Outbreak Investigations. *Emerging Infectious Diseases* [serial on the Internet] 2003 May [cited 2007 Jul 10]; 9 (5): 515-9. Available from: <http://www.cdc.gov/ncidod/EID/vol9no5/02-0388.htm>

Anon, SS, Schechter, R, Inglesby, TV, Henderson, DA, Bartlett, JG, Ascher, MS, et al for the Working Group on Civilian Biodefense. Botulinum Toxin as a Biological Weapon: Medical and Public Health Management. *JAMA* [serial on the Internet]. 2001 Feb 28 [cited 2007 Jul 3]; 285 (8): 1059-1070. Available from: <http://jama.ama-assn.org/cgi/content/full/285/8/1059>

CDC Bioterrorism Preparedness and Response Program. The History of Bioterrorism: Botulism [podcast on the Internet]. Atlanta (GA): Centers for Disease Control and Prevention; 2006 Jul 31 [cited 2007 Jul 10]. Available from: <http://www.bt.cdc.gov/training/historyofbt/05botulism.asp>

Centers for Disease Control and Prevention [homepage on the Internet]. Atlanta: CDC [cited 2007 Jul 3]. Bioterrorism Agents/Diseases. Available from: <http://www.bt.cdc.gov/agent/agentlist-category.asp>

Centers for Disease Control and Prevention [homepage on the Internet]. Atlanta: CDC [cited 2007 Jul 3]. Botulism. Available from: <http://www.bt.cdc.gov/agent/botulism/>

Centers for Disease Control and Prevention. Surveillance for Outbreaks of Botulism (Appendix A): Summary of 2003 Data [monograph on the Internet]. Atlanta: CDC [cited 2007 Aug 20]. Available from: http://www.cdc.gov/ncidod/dbmd/diseaseinfo/files/Botulism_CSTE_2003.pdf

Food and Drug Administration [homepage on the Internet]. Washington: FDA [cited 2007 Jul 19]. Vaccines Licensed for Immunizations and Distribution in the U.S. Available from: <http://www.fda.gov/cber/vaccine/licvacc.htm>

Investigational New Drug Application, 21 C.F.R. Sect. 312.36 (2003).



Nantel, AJ. Clostridium botulinum: International Programme on Chemical Safety Poisons Information Monograph 858 Bacteria [monograph on the Internet]. Geneva: World Health Organization; 1999 [cited 2007 Jul 10]. Available from:

<http://www.who.int/csr/delibe/epidemics/clostridiumbotulism.pdf>

New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible. 21 C.F.R. Sect. 314 and 601 (2002).

World Health Organization. Botulism Fact Sheet No 270 [monograph on the Internet]. Geneva: World Health Organization; 2002 [cited 2007 Jul 10]. Available from:

<http://www.who.int/mediacentre/factsheets/fs270/en/>

