Biodefense in the Pandemic Era

Planning for the future

David M. Hone, Dale E. Taylor Jr., L. Revell Phillips and Erin D. Reichert,
Vaccine and Therapeutic Division , Chemical and Biological Defense Department,
Research and Development Directorate, Defense Threat Reduction Agency | **APRIL 24, 2020**

EXECUTIVE SUMMARY

The current scope and role of the Research and Development Chemical and Biological Defense Department (RD-CB) within the Defense Threat Reduction Agency (DTRA) is to develop materiel, medical products and capabilities that enable the Warfighter to remain lethal in areas contested with chemical and biological (CB) weapons of mass destruction (WMD). The focus of the RD-CB is on CB-WMDs delivered by aerosol, based on the documented intent of state-sponsored CB-WMD programs, as well as recent real-world experiences in the Middle East. The Sudden Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV2) pandemic and the resulting national human and economic toll demonstrate a clear and present vulnerability of the US to contagious infectious diseases. Indeed, another pandemic with a similar magnitude and impact might create an enduring economic burden that would severely hinder the ability of the US and its allies to meet global strategic goals. This sets the stage for an era in which there will be significant temptation for both state and non-state actors to intentionally execute a biological attack to extract a similar human and economic toll to that of the SARS-CoV2 pandemic. Without a doubt there is a critical need to revamp the scope and purpose of biological defense within DTRA RD-CB to adapt to this new reality and maintain biological weapons in the gray zone. This prospectus, therefore, recommends a change to congressional authorization and funding for DTRA RD-CB to develop a broader rapid-response capability that includes abilities to develop and deploy sensors, diagnostics and medical countermeasures (MCM) to address emerging and reemerging contagious pathogens with pandemic potential.

BACKGROUND

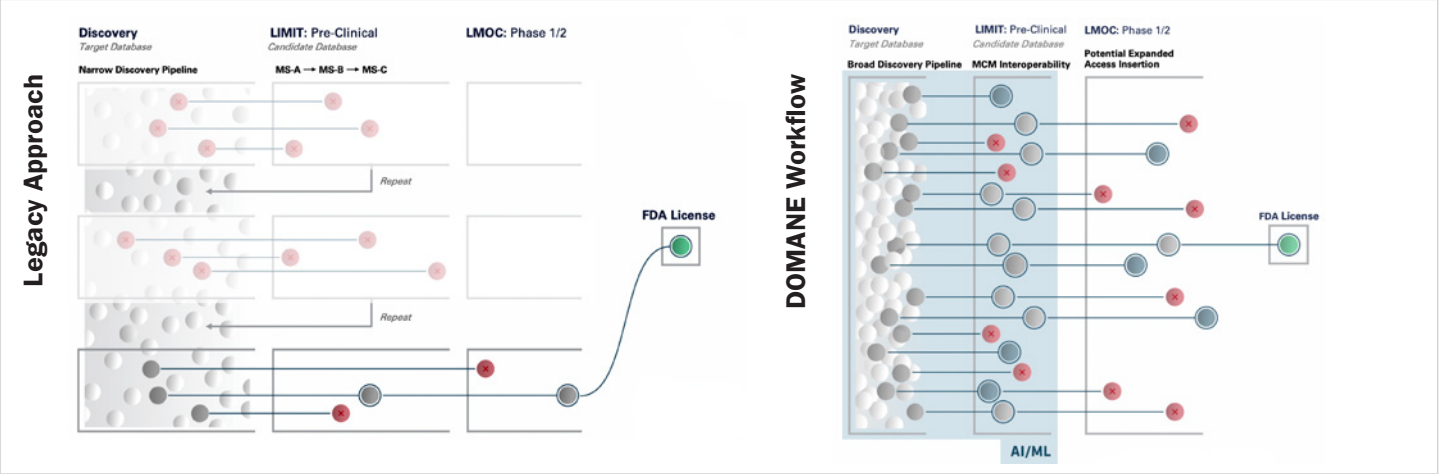
A core goal of the DTRA RD-CB is enable the Warfighter to operate effectively in battlefields exposed to CB-WMDs. The scope of DTRA RD-CB developmental programs includes the discovery of physical and non-physical solutions, including development of sensors, personal protective equipment, diagnostics and MCMs in order to address known threats and avoid technological surprise. However, rapid growth in technological capabilities and vastly expanded knowledge base in this area of responsibility are fueling the broadening and acceleration of CB-WMD threat agent spectrum. As a result, a unique core competency of DTRA RD-CB is the experience and know-how to rapidly and effectively develop products and MCMs to quash CB-WMDs. Until recently, the availability of advanced biological engineering technologies added an unquantified strategic element to the great power contest. In the era of pandemic infectious diseases, the strategic impact of biological WMDs is no longer in the realm of speculation. DTRA RD-CB has used its foresight to invest in a series of innovative developments that enable rapid diagnostic and MCM discovery and maturation through to initial clinical use. The Ebola Virus Disease (EVD) outbreak in 2014-2015 created a circumstance for DTRA RD-CB to demonstrate its rapid-response expertise and capabilities to address a biological concern with a weaponization history. The result of this action was the design, development and deployment of a Transportation Isolation System (TIS), the first Ebola diagnostic and Ebola MCMs.

It is well-documented that these capabilities, developed through DTRA RD-CB oversight, played significant roles in the 2014-2015 EVD West Africa outbreak. The TIS was ready for transport of infected individuals by United States Transportation Command (USTRANSCOM) during the EVD outbreak. Orthogonally, the DTRA RD-CB's EZ-1 diagnostic was the first available diagnostic for EVD and used extensively to identify infected individuals. One of the Ebola MCMs, a recombinant Ebola vaccine, now known as Ervebo, transitioned from DTRA RD-CB to Merck Vaccines Inc in late 2014 for use in a ring vaccination clinical trial while the outbreak was still ongoing. Indeed, the rapid insertion of Ervebo into clinical trials played a key role in quelling EVD outbreaks in West Africa and more recently in the Democratic Republic of Congo. Moreover, the rapid deployment of Ervebo during the outbreak generated key safety and efficacy data that cut years off the development pathway, reduced the developmental cost for this vaccine. Importantly, this year, only 5-years after entering the clinic, Ervebo was approved by the US FDA for use in humans. Taken as a whole, the coincidence of an infectious outbreak involving a pathogen with a weaponization history demonstrated the effectiveness of DTRA RD-CB to react in real-time to counter an emerging infectious disease. But we can do better. The narrow scoping of programmatic requirements has significantly constrained DTRA RD-CB during subsequent outbreaks, including the Zika virus outbreak in South America in 2015-2016 and the ongoing SARS-CoV2 pandemic. Regarding the latter, DTRA RD-CB Vaccines and Therapeutics Division has proposed to utilize the DOMANE (Development of MCM Against Novel Entities) and LIMIT (Layered Integrated MCM Intervention Technologies) concepts in the form of an adaptive clinical trial that would sequentially assess the therapeutic efficacy of vaccine and therapeutic interventions given alone and in combination. These concepts accept the risk that individual MCMs against novel biological threats are likely to be suboptimal. The strategy, therefore, would employ an innovation think-tank, computational biology and adaptive clinical trial methodologies to systematically identify effective combinations of suboptimal MCMs. This strategy is ready to be tested and proven out in a clinical trial setting. The SARS-CoV2 outbreak allows for the opportunity to activate DOMANE and conduct the necessary human clinical trials to test and optimize this strategy. Once this strategy is validated, it can be further refined to identify new MCMs for traditional biological threats as well as novel and emerging threats. As a real world assessment of the DOMANE and LIMIT concepts are within the programmatic scope of DTRA RD-CB, a small effort to initiate an adaptive clinical trial brought together a high-caliber scientific and medical team to generate testable hypotheses and monitor clinical trials with repurposed drugs to identify a combination of medical interventions that is greater than the parts alone.

PLANNING FOR THE FUTURE

A primary purpose of DTRA RD-CB is to defend the nation and Warfighter against CB-WMDs and in this role DTRA's team has transitioned numerous diagnostic and MCM solutions against biological threats to advanced developers in the US government and industry. When challenged to deliver solutions to counter infectious outbreaks, DTRA RD-CB has also risen to the occasion, as exemplified during the EVD outbreak. However, constraints in funding authorizations and the resulting programmatic requirements delayed and hindered DTRA RD-CB from activating its full panoply of expertise and capabilities to mount a rapid response to the SARS-CoV2 pandemic. That is not to say that programmatic focus is unimportant, as funds are limited, and computational and gene-engineering tools are significantly evolving the biological WMD threat palette. Moreover, current funding is fully encumbered by efforts to address the known biological threat landscape.

Figure 1 **Broad Drug Candidate Pipeline**



Therefore, the only realistic alternative for DTRA RD-CB to be in a position to exert its expertise and develop its capabilities in future rapid response to limit the strategic impact of infectious disease pandemics to the fullest extent possible is to expand both mission scope.

To address this, broader scope additional funding to RD-CB will be needed. The $1.5 billion budget for the CBDP needs to cover physical protection (boots, suits gloves, masks and shelters), sensors, diagnostics and MCMs against each chemical and biological WMD threat agent. The access of adversaries to ever-expanding tools and know-how to develop an endless stream of biological threat agents creates the circumstances for innovation at DTRA RD-CB. Hence, the program can no longer afford to pursue one-off bespoke technologies that target a single agent. Fiscal constraints, on the other hand, have fostered innovation to produce an affordable and sustainable biological defense strategy to address the ever-evolving biological threat environment.

Accordingly, DTRA RD-CB has developed the DOMANE and LIMIT concepts, which are strategies that are designed to limit biological WMDs to the Gray Zone[1], which is aligned with the National Defense Strategy. This fully integrated effort is designed to create a broad response readiness posture for rapid insertion to counter known and unknown biological WMD. In the FY23-27 Program Objective Memorandum, DTRA RD-CB plans to apply this strategy to develop a broad array of biological defense capabilities, platform technologies and products to counter hemorrhagic fever viruses and marine biotoxins.

Therefore, in order to prepare for surprise in the form of novel, enhanced, or advanced biological threats, DTRA RDCB will utilize and integrate platform technologies to create an efficient drug-candidate discovery workflow for rapid insertion to counter a biological WMD. In doing so, DTRA RD-CB will counter a broad variety of threat agents utilizing platform discovery, drug repurposing, drug design, drug manufacturing, and candidate-testing processes to harness the efficiencies offered by platform technologies and reduce developmental risks. This process also will identify common portals of biological threats, thereby providing knowledge baseline for broad-spectrum MCMs against novel threats that target such portals. In

1. Operating in the Gray Zone. Countering Iran's Asymmetric Way of War, The Washington Institute for Near East Policy.

addition, harnessing platform processes to target MCM development against novel biological threats enables DTRA RD-CB to tailor drugs rapidly without completely redeveloping key processes, thereby minimizing schedule and cost requirements. Examples of currently used platform processes include cell-based test systems, cryoelectron microscopy, learning data sets for machine learning drug docking, manufacturing and testing.

In all, the elements that comprise DOMANE and LIMIT are applicable to a broader RD-CB mission scope and apply knowledge and information generated by the international scientific community toward a rapid response capability against emerging and reemerging infectious diseases with pandemic potential.

RECOMMENDATIONS

A growing array of CB-WMD battlefield threats fully encumbers current RD-CB funding. This white paper, therefore, recommends that DTRA receive congressional authorization for additional annual funding phased in over five years beginning in FY22 to develop rapid-response capabilities, including sensors, diagnostics and MCMs against emerging and reemerging contagious pathogens with pandemic potential. The RD-CB Department within DTRA has an unparalleled history of transitioning devices and MCMs from the laboratory to advanced developers in the USG and industry. This DTRA department is an existing USG capability that operates within unclassified and classified venues to develop products and capabilities that counter biological WMDs and therefore is ready to address strategic vulnerabilities to pandemic infectious disease.

APPENDIX 1

Anatomy of a Rapid Response to a Pandemic Threat