REPORT OF THE BLUE RIBBON PANEL TO REVIEW THE 2014 SMALLPOX (VARIOLA) VIRUS INCIDENT ON THE NIH CAMPUS

May 2017

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EXECUTIVE SUMMARY

In August of 2016, the National Institutes of Health (NIH) appointed a Blue Ribbon Panel to review the July 2014 discovery of six vials containing variola virus, the causative agent of smallpox, as well as over 300 other previously undiscovered biological samples on the NIH Bethesda, Maryland campus. The samples were found in an unsecured cold-storage room in a building occupied and managed by Food and Drug Administration (FDA) staff under NIH biosafety and biosecurity oversight.

The Panel includes a diverse group of seven external subject matter experts, and was constituted as a Working Group of the National Science Advisory Board for Biosecurity (NSABB), a federal advisory committee to the United States Government. The Panel began its work in August of 2016 and completed this final report in May of 2017. The Blue Ribbon Panel was charged with a number of tasks, including, 1) to determine how the smallpox virus vials came to be improperly stored and overlooked for years; 2) to identify any systemic issues that contributed to the lapse; and 3) to evaluate whether NIH had taken adequate corrective actions in response to this incident. It should be noted that this incident was one of several biosafety lapses involving federally regulated pathogens that occurred in the United States in 2014. These incidents caused considerable concern and led to substantial remedial activity throughout the United States Government.

Smallpox was a devastating, contagious disease that infected over 300 million people in the 20th century, killing up to 30% of those infected. It was declared eradicated by the World Health Organization in 1980, and by international agreement, the remaining acknowledged samples were to be placed under tight control and oversight in only two repositories: in the US, at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia and in Russia, now at The State Research Center of Virology and Biotechnology (VECTOR), Novosibirsk.

While there are now smallpox vaccines available in the U.S. should they be needed, routine vaccination of Americans ceased in the mid-1970's. As a result, nearly half of the population is unvaccinated, and, because vaccine effectiveness wanes over time, nearly the entire US population is potentially vulnerable to infection. The finding of viable smallpox virus samples outside of the established repositories was totally unanticipated and required an appropriate response and a rethinking of laboratory biosafety and biosecurity policy at NIH.

The Blue Ribbon Panel evaluation benefited from several prior comprehensive investigations of the smallpox virus incident, including by the Federal Bureau of Investigation jointly with the CDC, by the Government Accountability Office, and by Congress. The FDA also conducted an internal review. The Blue Ribbon Panel examined relevant federal and biosafety policy, regulation and guidance documents, as well as the many administrative actions taken by NIH in response to the 2014 smallpox virus discovery. The Panel visited pertinent sites on the NIH

campus, and interviewed those who had knowledge of or responsibility for the response. The Panel assessed that the incident has been now adequately evaluated and documented. Some questions remain, however, including the identity of the original owner of the samples and how they may have come to be in the cold-storage room. Unless further new information surfaces to solve this mystery, it is unlikely to be resolved, due to the passage of time. In addition, storage of the samples likely occurred before the Select Agents Program was established, at a time when biosafety standards were very different from today.

The Blue Ribbon Panel identified several key factors that contributed to the smallpox virus incident: There was a lack of individual responsibility for infectious materials in the FDA occupied space where the vials were found. There were also numerous missed opportunities to find the samples prior to 2014, particularly in the 1980's when all smallpox virus samples were required to be either destroyed or sent to CDC, and again in 2003 when laws governing the possession of regulated pathogens, called "select agents," were implemented. In addition, a lack of policies for dealing with abandoned research materials and for regular inventory of potentially hazardous biological materials were major contributors to the occurrence of this incident.

The panel assessed the response to the incident as appropriate and thorough, with excellent inter-agency cooperation (including the FBI) to manage a highly unusual situation. However, the Panel noted several specific problematic issues relating to the immediate response after discovery of the smallpox virus and other samples. In particular, the Panel determined that given the potentially hazardous nature of the abandoned samples, there are significant concerns about how they were packaged and transferred between buildings on the NIH campus. Following the discovery by an FDA official, it was decided by NIH that the samples should be immediately transferred to a secure high-containment Biosafety Level 3 laboratory. The samples, in their original boxes, were packaged into a larger cardboard box, and then hand-carried to the secure NIH laboratory. No negative consequences occurred — there were no infections or injuries — but packaging and transport of the samples were conducted in ways that presented both biosafety and security risks. Other concerns identified by the panel included inadequate chain-of-custody and logging of events directly after the discovery of the vials, and the use of cardboard in cold-storage rooms. Although secondary to the issues associated with this event, cardboard containers can contribute to mold and unsanitary conditions.

The Panel assessed efforts pursued by NIH following the incident that were intended to improve biosafety and biosecurity procedures and minimize the likelihood of such occurrences in the future. It was determined that most of the factors and causative issues have been addressed by NIH's subsequent efforts and policy revisions and are detailed in the report. However, there are several remaining issues requiring attention.

The Blue Ribbon Panel offers to NIH the following observations and recommendations. First, with regard to specific, detailed steps NIH should take to remedy remaining gaps in biosafety policies and procedures, the BRP recommends:

- Revise several specific biosafety policies and procedures, as detailed in the report.
- Rapidly finish the on-going space audit to ensure responsibility and oversight of all research materials is assigned to individuals by name, and updated as required by personnel changes.
- Ensure that any shared research space arrangements have clear written agreements with responsibilities well defined.
- The BRP noted that NIH policies and procedures use terms that are not in general use; such as “High consequence pathogens,” “and “potentially infectious materials. These categories need to be defined carefully or eliminated when not clearly necessary.

Second, regarding more general approaches to improving biosafety and biosecurity at NIH, the BRP considers the following to be important considerations:

- Effective and complete implementation of current policies, procedures, guidance and practices on an on-going basis over time will be critical to ensuring safety and security surrounding pathogen research at NIH.
- The importance of leadership at the highest levels and continuous efforts to develop and maintain a culture of safety and responsibility among research staff cannot be overemphasized.
- There would be significant benefits to having consistent biosafety and biosecurity policies across the Department of Health Human Services (HHS) and the entire USG; ideally, insofar as possible, these should be harmonized with efforts by governments and international institutions as well. The BRP recommends continuing on-going efforts to address these issues.
- Response plans coordinated and exercised with agencies outside of HHS, including the Federal Bureau of Investigation, the Environmental Protection Agency and others, as needed, remain important.
- The variola virus incident illustrates how changes in infectious disease epidemiology and biosafety practices over time can radically alter a situation from “standard lab practice” to a potential major public health event.

The Blue Ribbon Panel concludes its effort with the observation that the smallpox virus incident illustrates how biosafety practices and laboratory management need to be continually evaluated. There was a time that research with smallpox virus could be conducted in relatively routine containment settings because the virus presented no extraordinary danger to the US population, as most everyone was vaccinated. As other infectious diseases are eradicated or controlled in the future, similar situations to the events of 2014 may arise — for example, with polio virus, which is currently close to eradication. Research samples and collections not

previously considered a significant biosecurity concern, need to be routinely re-evaluated to ensure proper biosafety and handling so that public health and safety are not compromised.

1. BACKGROUND

In July 2014, Food and Drug Administration (FDA) employees discovered twelve cardboard boxes containing over 300 vials of infectious agents and other materials in an FDA cold room located in a building on the National Institutes of Health (NIH) Bethesda campus that FDA had occupied for almost 50 years. These boxes included six vials that, based on vial labels, were suspected to contain variola virus, the causative agent of smallpox. All six vials were later shown by the Centers for Disease Control and Prevention (CDC) to contain viable variola virus. The boxes had been overlooked for many years and contained samples of a variety of pathogenic microorganisms and other biological materials that had not been stored in accordance with current biosafety standards, and some, categorized as select agents and toxins, that were not properly registered with the Federal Select Agent Program. The Select Agent Program, which came into force in 1997 is jointly administered by the CDC and the United States Department of Agriculture (USDA); the Program regulates use, storage and transfer of a group of human, animal and plant pathogens and toxins which have the potential to pose a severe threat to public, animal or plant health or to animal or plant products. This group of pathogens and toxins is referred to as select agents and toxins. Variola virus and some of the other agents that were also found among the 327 samples in the cardboard boxes in the cold room were select agents. Variola virus, in particular, is also subject to international agreements restricting its use and storage to only two laboratories in the world (one is the CDC in Atlanta, the other is the State Research Center of Virology and Biotechnology (VECTOR) in Russia). The discovery of the smallpox virus vials was one of several laboratory safety incidents at federal facilities about the same time that prompted the White House to direct federal departments and agencies to search their laboratories for improperly stored select agents and toxins. In addition, the White House called on agencies to review biosafety and biosecurity policies and procedures, and to make improvements, as necessary.

A number of other reviews of the smallpox virus discovery incident have been completed prior to this one. These include investigations by the Federal Bureau of Investigation (FBI) jointly with the CDC, by the Government Accountability Office (GAO), as well as by Congress. The FDA has also conducted its own internal review. For summaries of these reviews and links to the reports, see Appendix E.

This report is the result of an external review of the 2014 incident and related information by a Blue Ribbon Panel (BRP) of biosafety and smallpox experts appointed by the NIH. The review was initiated by NIH in response to Congressional interest and as part of on-going activities. The BRP was constituted as a Working Group of the National Science Advisory Board for Biosecurity (NSABB). The NSABB is a federal advisory committee that addresses issues related to biosecurity and dual use research at the request of the United States Government (USG). The BRP was charged with reviewing the incident and subsequent responses to substantiate that NIH has taken the steps necessary to avoid incidents like this in the future and to help ensure NIH is being fully compliant with all applicable requirements including laws, regulations, policies, practices, guidance, guidelines, and international treaties. Further, NIH must be a responsible steward of infectious agents, particularly those that are on the Federal Select Agents and Toxins List.

2. Blue Ribbon Panel Workplan

To address its charge, the BRP sought answers to the following questions:

1) What happened, both during the time immediately around the discovery of the vials and during times leading up to discovery of the vials?

2) Why did oversight systems that should have prevented such an occurrence fail to discover the samples before 2014?

3) Are current NIH procedures and policies, including revisions and changes since the incident, appropriate and likely to prevent such events in the future?

The BRP approached its work in phases: it gathered and analyzed relevant data, including the previously completed reviews of the incident and new information developed during its own investigations; it developed findings, conclusions and recommendations; it prepared a draft report; it presented the draft report to the NSABB; and then conveyed the final version to the NIH director. These tasks occurred over the period of August 2016 through May 2017, and involved multiple teleconferences and a day-long in person meeting which included inspection of the laboratories and buildings involved in the incident. The BRP also interviewed key individuals involved in the discovery and response, either in person or by teleconference.

The BRP roster is in Appendix A. A detailed description of the BRP Charge and Workplan is in Appendix B.

3. Historical Context

Because the events that led to finding the samples in 2014 began about 50 to 60 years ago, when the samples were likely stored in the cold room, it is important to provide some brief historical context about smallpox and about the evolution of biosafety standards over that time period.

3.1. Smallpox

Smallpox, caused by variola virus, was a scourge to humanity throughout history and is referenced as early as ancient Egyptian times. Development of an effective vaccine in the 19th century reduced the impact of smallpox in western countries, and then-- due to a massive global surveillance and vaccination campaign by the World Health Organization (WHO) in collaboration with many countries beginning in 1966 -- it was eliminated globally in the late 1970s, with the last community acquired case occurring in Ethiopia in 1977, although there was a laboratory-acquired infection in the 1980s. In 1980 WHO declared the disease eradicated, an unprecedented public health achievement. Vaccination of civilians ended in the United States (US) in 1972 and in most other countries in the 1980s. Following eradication, the WHO called for identifying remaining stocks of the virus and either destroying them or consolidating them in two highly secured WHO Collaborating Center Repositories. The remaining acknowledged

research stocks of variola virus are securely housed in the US at the CDC, Atlanta and in Russia, at State Research Center of Virology and Biotechnology, also known as VECTOR in Koltsovo, Oblast Novosibirsk; possession anywhere else in the US is illegal (18 USC § 175C). All live variola virus research at the Centers is reviewed and approved annually by an international expert committee of the WHO.

Prior to the eradication of smallpox, possession of, and research with variola virus was not regulated in any unique way, and current biosafety concerns over a now eradicated disease were not necessarily applicable because widespread vaccination of most citizens reduced the risk of epidemic disease in the US. The biosafety standards at the time the FDA samples were likely placed in the cold room in the late 1960s or early 1970s (see below) would have resulted in variola virus studies being conducted under conditions similar to what is now Biosafety Level-2 (BSL2), although BSL designations and specific descriptions of containment facilities and practices did not exist then. In light of this history, it is important to note that researchers working on variola virus in a laboratory in the 1960s would not have had the same biosafety and biosecurity concerns that exist today because the disease threat then was very different, with virtually the entire US population immune as a result of being vaccinated. In 2017, most US civilians would be susceptible to smallpox, with few under the age of 45 ever having been immunized against smallpox even once.

3.2. Evolution of Biosafety Standards

Although work with infectious agents and other hazardous biological materials is now extensively regulated by several US agencies (and some state and local governments), there were essentially no federal biosafety standards before 1970, and work with infectious agents was conducted using microbiological practices that were primarily taught informally and not extensively codified. The American Biological Safety Association was officially founded in 1984; however, microbiologists working in the government and other organizations had been meeting informally since the 1960s to discuss safety issues. Standards and containment features evolved as information about the causes of laboratory acquired infections developed, and understanding of disease threats changed with time. Safe and productive infectious disease research was conducted in government, academic, clinical and industrial laboratories in the US for many years before significant regulations and guidelines were in effect.

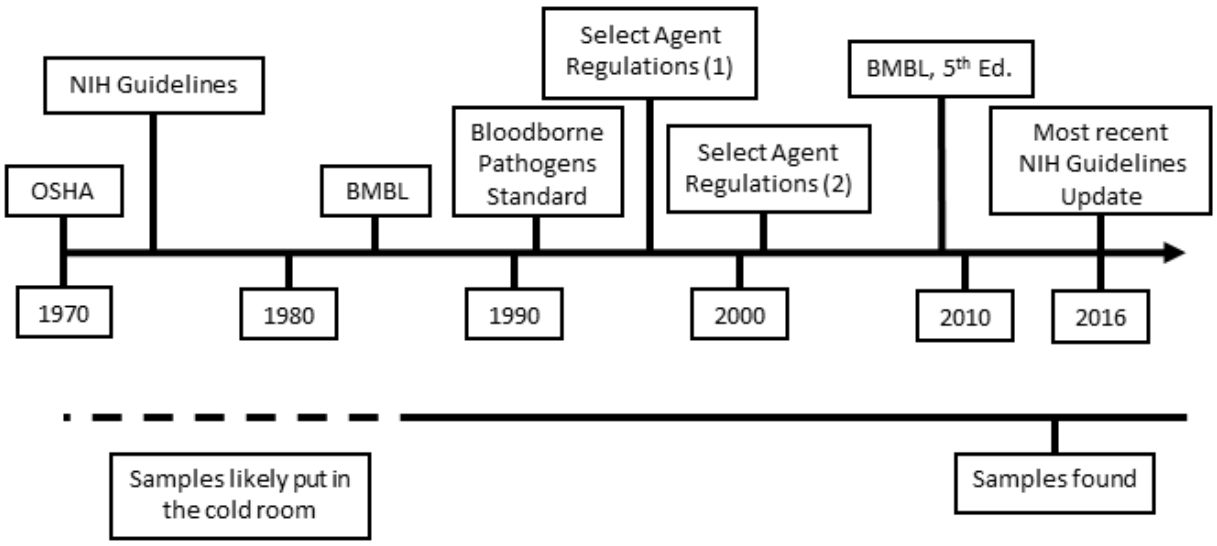
Federal oversight of work with infectious agents began in 1970 and continues to be expanded and modified. First, the Occupational Health and Safety Act (OSHA) of 1970 provided broad standards for safety in work places, including protection from blood-borne pathogens (29 CFR 1910.1030, promulgated in 1991). After the advent of recombinant DNA technology, safety concerns led to establishment of the Recombinant DNA Advisory Committee in 1974, and development of the *NIH Recombinant DNA Research Guidelines* (rDNA Guidelines) in 1976, which defined biosafety levels (BSL) for such work. Other concerns about the risks associated with work on pathogens led to the development of the NIH/CDC guidance document *Biosafety in Microbiological and Biomedical Laboratories* (BMBL), first published in 1984, with periodic new editions; the BMBL defined biosafety levels and standards for working with various agents. Both the rDNA Guidelines (now called *NIH Guidelines for Research Involving Recombinant or*

Synthetic Nucleic Acid Molecules) and the BMBL have been widely adopted and are now the standard of practice in the US and in many other countries.

Passage of the Antiterrorism and Effective Death Penalty Act of 1996 led to the establishment of the first Select Agents Regulations which initially covered only transfer of certain dangerous microbiological materials designated select agents and toxins. Following the anthrax attacks of 2001 and passage of the USA Patriot Act (2001) and the Public Health Security and Bioterrorism preparedness and Response Act (2002), the Regulations were expanded to include possession, use and transfer of select agents and toxins, and now regulate many aspects of such work, including registration, storage and inventory.

While possession of unregistered select agents and toxins, including variola virus, is a serious matter today, in the time period between 1950 and 1980 no law, regulation, or guidance would have made it illegal or absolutely prohibited. Work with variola virus would have been conducted using the biosafety standards of the time, and storage of virus samples as part of a laboratory culture collection would have been common practice.

A timeline illustrating key events in development of biosafety standards and regulation is shown below.



4. Earlier Events of Interest and Relevance to Understanding the Incident

Prior to the 2014 incident, there were several other occurrences at NIH involving failure to comply with the Select Agents Regulations that came to the attention of the CDC Division of Select Agents and Toxins (DSAT) and/or the Department of Health and Human Services (HHS)

Office of the Inspector General (HHS OIG). In 2008, discrepancies were noted in the inventory for a historical collection of *Burkholderia pseudomaleii* samples; in addition, the appropriateness of storing the samples in paper envelopes was questioned. In 2011, a restricted experiment involving antibiotic resistant *Yersinia pestis* specimens (the causative agent of plague) was conducted at the NIH Rocky Mountain Laboratories without proper prior approval by the CDC Select Agent Program. In 2012, there was a major incident involving several samples of *Bacillus anthracis* (the causative agent of anthrax) in unregistered spaces, unsecured samples of *B. anthracis*, and unapproved personnel having access to *B. anthracis* samples. These events resulted in an investigator losing authorization to conduct select agent work and NIH being put under a performance improvement plan by CDC-DSAT; the conditions of the plan have since been satisfied. The *B. anthracis* incident did set in motion a search for other anthrax materials in laboratories that had worked with the agent, and a more general search for anthrax or other select agents and toxins in other NIH laboratory areas, but none was found at that time. Other CDC-DSAT inspection reports indicated a variety of deviations from requirements over the years, many administrative, but some involving biological materials.

Also in the period around 2014, there were significant incidents at other federal laboratories involving select agents and toxins. At CDC, in separate incidents, live samples of influenza virus and Ebola virus were transferred within CDC and to other agencies in ways that violated Select Agents Regulations. In 2015 it was disclosed that the US Army Dugway Proving Ground (the nation's leading test center for chemical and biological defense) shipped presumed fully inactivated reference samples that were not properly inactivated, and thus contained live material, to government and commercial laboratories over a period of several years.

5. FINDINGS

The BRP first reviewed all of the reports from previously conducted investigations relating to the smallpox virus incident to gather facts surrounding the incident. In addition, new or corroborating information was obtained from interviews and discussions with individuals who were involved in or familiar with the incident, or who might have background historical information. A number of important NIH and other biosafety and biosecurity policies, procedures, and guidance were examined, and the BRP also conducted a site visit to Buildings 29A and 13 on the NIH campus, the sites where the variola virus samples were discovered and then stored, respectively.

5.1. Description of the Incident

Building 29A on the NIH Bethesda campus was built and occupied by NIH staff in 1968. As a result of a major organizational realignment that transferred responsibilities and personnel from NIH to FDA, between 1972 and 2014 the FDA leased the building from NIH for research purposes; the building was occupied solely by FDA personnel. NIH was responsible for biosafety oversight in the building, including select agents and toxins, and the FDA was responsible for implementation of biosafety policies in the laboratories they occupied. In 2014, all FDA staff members in Building 29A were preparing to move to new agency facilities, not on NIH property;

many people, including contractors, were in Building 29A engaged in activities relating to the move.

Late on the morning of July 1, 2014, while cleaning out a cold room in preparation for the move, an FDA researcher in Building 29A found several apparently abandoned cardboard boxes that contained 327 old biological samples; these included some that were labeled in a manner indicating that they possibly contained smallpox virus (variola major and Alastrim, a weakened virus, also known as variola minor) as well as a variety of other select agent and non-select agent microbial samples and biological materials. The cold room was not registered with the NIH Select Agent Program, and the researchers were not conducting research with select agents and toxins or authorized to possess them. That afternoon, the researchers who found the samples notified a senior FDA staff member who then contacted the Director of the NIH Division of Occupational Health and Safety (DOHS) who was also the select agent responsible official (RO). In response to direction from the NIH RO to bring the samples to DOHS in Building 13, the senior FDA official and an FDA staff researcher packed the found samples/boxes into a larger box (in a manner that did not meet acceptable biosafety standards), and then the FDA official transported the samples by walking the larger box from Building 29A to Building 13, a distance of about 2 blocks. The FDA official and the NIH RO met at Building 13 and possession of the materials was transferred to NIH; the materials were secured in the DOHS select agent registered BSL3 laboratory.

What followed was an extremely rapid and thorough inter-agency response. On July 1, the NIH RO notified the FBI and the CDC Select Agent Program. On July 2, FBI agents came to Building 13 and took charge of the incident and building security, although they did not enter the BSL3 laboratory, room 3W84, containing the samples; the FBI was present during the subsequent events of July 2 to 9. CDC staff arrived on July 7 and, jointly, the FBI and CDC conducted an investigation. As part of these events, the found samples were examined and inventoried by FBI and CDC in the BSL3 laboratory; 16 samples (those that appeared to be variola virus and several other select agents) were transported in accordance with regulations by air by the FBI to CDC for analysis. Also at that time, 32 samples of no apparent value were destroyed at NIH, and the remaining 279 samples accompanied by the FBI, were securely transferred to the National Biodefense Analysis and Countermeasures Center (NBACC, a division of the Department of Homeland Security (DHS) at Ft. Detrick, Maryland). Later 163 of these samples were destroyed at the NBACC and the remaining, non-variola pathogens and samples, were transferred appropriately to CDC, the US Army Medical Research Institute of Infectious Diseases (USAMRIID) and the National Biological Threat Characterization Center (NBTCC, a component of NBACC) for research purposes. Within a few days of the incident, CDC staff in Atlanta tested the presumed variola virus samples in their BSL4 facility and confirmed the presence of live virus in all six of them. Early in 2015, all of the discovered variola virus samples were destroyed at CDC with WHO oversight.

By July 9, 2014 the incident was over at NIH, and none of the found samples remained there. Secure transport of the samples, by various modes of transportation, from NIH to other destinations was provided by the FBI. Decisions regarding their destinations were made primarily by DHS and National Security Council (NSC) staff on a basis of who might have scientific need or interest for them.

More details about these events, timelines, and ultimate disposition of the samples are in Appendix C. and D.

5.2. United States Government and NIH Evaluation and Response to the Incident

Immediately following the incident, NIH and several other agencies of the USG launched robust efforts aimed at understanding what happened, why it happened, and how to remedy the underlying causes. Since this was one of several biosafety lapses at government laboratories around that time (discussed above in section 4.), there was considerable attention to and commitment throughout the government to bolster biosafety and biosecurity. Not all of these efforts are discussed here, only those most relevant to the smallpox virus incident at NIH.

The immediate follow up response by USG and NIH included the following:

On July 10, 2014, the Director of NIH issued a memorandum, "Potentially Hazardous Biological Materials Management Plan, Phase 1" followed on July 11 by an email to all staff calling for the "NIH Clean Sweep". This initiated a mandatory, comprehensive lab-by-lab examination of all biological materials stored in all refrigerators, freezers, cold rooms, and storage areas in all NIH owned or leased facilities to search for potentially hazardous biological materials (PHBM), including select agents and toxins. Biological materials were to be either well-labeled and inventoried suitably or destroyed, as appropriate; any unregistered select agents or toxins were to be reported to DOHS for proper disposition. Also announced was a new requirement to inventory, in a centralized NIH database system, all human pathogens that require BSL2 or higher containment as well as toxins and some other biological materials. The Clean Sweep commenced immediately and was completed by September 30, 2014. Millions of samples were examined, and eleven previously unrecognized select agent or toxin samples were found.

On August 18, 2014, a joint memorandum "Enhancing Biosafety and Biosecurity in the United States" was issued by Lisa Monaco, Assistant to the President for Homeland Security, and Counterterrorism and John Holdren, Assistant to the President for Science and Technology. The memorandum called for all federal agencies and departments that work with infectious agents to take immediate steps to enhance safety and security for their work with infectious agents. This was to include a "Safety Stand-Down" during which biosafety and biosecurity best practices would be emphasized, inventories would be conducted, and a survey of all infectious materials would be conducted; extramural facilities that receive federal funding were encouraged to conduct similar activities. The memorandum also called for longer term efforts to strengthen biosafety and biosecurity systems, both in the US and through international activities.

On February 2, 2015, NIH released its "Potentially Hazardous Biological Materials Management Plan, Phase 2" which outlined plans for policy review and revisions, if needed, changes to the NIH Table of Penalties (actions that may be taken against employees for policy violations), and establishment of clear responsibilities for biosafety at all levels in NIH. Implementation of this plan led to many changes in NIH biosafety and biosecurity policies and guidance; these are discussed in detail below in section 5.3.

On October 29, 2015 Monaco and Holdren issued "Next Steps to Enhance Biosafety and Biosecurity in the United States." The memorandum accompanied the release of reports from the Federal Experts Security Advisory Committee (FESAP) and the Fast Track Action Committee on Select Agents Regulations (FTAC-SAR) which contain a broad range of recommendations to be implemented across the government and other US institutions that conduct work with pathogens. These efforts continue today, and are aimed at coordinating biosafety and biosecurity efforts across the government and throughout the US.

Several investigations focused specifically on the smallpox virus incident were launched in 2014, and reports were subsequently issued:

- The CDC and FBI jointly conducted a site visit and investigation July 7-9, 2014; a letter report to NIH was issued on August 8, 2014.
- Between July 7 and August 1, 2014, CDC personnel in Atlanta analyzed the 6 samples labeled variola virus and Alastrim and confirmed the presence of live variola virus; they provided the results of their studies to other involved government agencies.
- An External Laboratory Safety Workgroup (ELSW) of the Advisory Committee to the Director of CDC (ACD-CDC) was charged by the Secretary of HHS to review the NIH biosafety program and its practices, in addition to other tasks. The ACD-CDC issued a report on its findings May 4, 2015.
- A congressional investigation began shortly after the event, and a memorandum report was issued April 19, 2016.
- The Government Accountability Office (GAO) conducted a more general review of high-containment laboratories and issued a report on March 21, 2016 (GAO-16-305).
- The FDA conducted an internal review of the incident in 2016 and the report was released in December 2016.

The BRP found these investigations and reports to be collectively comprehensive and helpful to its tasks. Brief summaries of these investigations and reports with links to supporting documents are in Appendix E.

5.3. Biosafety Policy at NIH

The NIH DOHS resides organizationally within the Office of the Director of NIH and, thus, reports to the highest level of leadership within the NIH; DOHS has broad supervisory responsibilities for all programs involving handling and management of potentially infectious material. As such the NIH DOHS is responsible for oversight of biosafety policies, practices, and procedures at all NIH facilities, working to ensure their implementation together with the Institute and Center Directors, Institute and Center Scientific Directors and laboratory principal investigators (PIs). Specifically, DOHS provides executive leadership in development, promulgation, and implementation of occupational safety and health policies, standards, and procedures for NIH, including periodic facility inspections, inventories, training, and audits. DOHS manages the NIH Select Agent Program. The NIH Occupational Safety and Health Committee and the NIH Institutional Biosafety Committee (IBC) provide advice and recommendations about laboratory safety to senior NIH leadership; the IBC reviews research projects involving recombinant DNA, pathogenic microorganisms and those presenting

potential dual-use research of concern (DURC), although review of some low-risk research may be delegated to the NIH Biosafety Officer. Institute Directors, Scientific Directors and Institute and Center Safety and Health Committees have significant responsibility for ensuring that policies, standards, and procedures are implemented throughout their Institute and that training and a culture of safety are being supported. Many responsibilities, such as site-specific training and implementation of lab-specific requirements fall to individual employees, supervisors and ultimately, principal investigators. Employees may face penalties for failure to comply with established research safety policies.

Relevant training, technical assistance, program audits and inventory controls, are also important aspects of an effective biosafety program. NIH has established mandatory biosafety training for all laboratory personnel as well as an extensive menu of additional specific training opportunities appropriate for various types of work and risks. DOHS staff provide technical assistance and consultation to researchers in addition to fulfilling their oversight responsibilities such as inspections and audits. Institutes and Centers also have responsibilities for ensuring completion of appropriate training and for compliance.

Current NIH Policy Documents

Links to specific documents are in Appendix F. Table 1. below summarizes key policies.

NIH official policies, are made available as "Manual Chapters (MC)." Several MC relate to occupational health and safety. In addition, there are site specific policies and procedures for particular laboratories. MC relating to the BRP tasks are:

- Chapter 1340 – "NIH Occupational Safety and Health Management," revised 3/10/16; provides an overarching description of the scope and objectives of the Occupational Safety and Health Management Program at NIH and defines the responsibilities of various NIH personnel. It includes descriptions of several NIH-wide safety committees and states the requirement for use of appropriate personal protective equipment (PPE);
- Chapter 1340-1 – "Permits for the Import, Transfer, or Export of Biological Materials," revised 6/7/16; describes the requirements and responsibilities regarding import, transfer or export of biological materials including select agents and toxins. It states the need to package and transport materials appropriately, according to federal standards, but covers primarily movements into or out of NIH;
- Chapter 3035 – "Working Safely with Potentially Hazardous Biological Materials," revised 7/31/15; this is a critical document that governs storage and conduct of work of potentially hazardous biological materials (PHBM) in the NIH research environment; PHBM includes recombinant and synthetic nucleic acid molecules; toxins and poisons; human/animal/plant pathogens that require BSL 2 containment or higher; and human and non-human primate blood, tissues, and body fluids, including primary human cell cultures; and select agents and toxins. The NIH policy for movement (transport and packaging) of infectious or potentially infectious materials within an NIH site or building is described; this generally aligns with federal regulations, although is in excess of the minimum required. This chapter also discusses DURC, and includes several revisions and additions in response to the 2014 incident;

- Chapter 3037 – "NIH Biological Surety Program," issued 7/31/15; describes responsibilities, policies and procedures for certification of personnel who work in BSL3 and 4 laboratories at NIH, including BSL3 and 4 animal laboratories. It covers primarily personnel reliability and to a limited extent biosafety; it does not encompass physical security or agent accountability.

Other Important NIH Documents

- "Guidelines and Policies for the Conduct of Research in the Intramural Program at NIH," 5th ed., 2016 (a document issued by the NIH Intramural Program); the sections about Biospecimen Storage and Tracking (p. 19), Health and Safety (p. 21), and Research Material Management and Research with High-Consequence Pathogens (p. 23) are most pertinent; it also covers DURC. These Guidelines apply to all researchers at all NIH facilities;
- Potentially Hazardous Biological Materials Management Plan I and II (July 2014 and February 2015), describe NIH's response plans immediately following the July 2014 incident;
- Annual reminder email (select agent email) about use and possession of select agents and toxins which is sent to all researchers; standard operating procedure (SOP) 902 "Intra-Entity Transfer of Discovered Select Agents" which describes what DOHS staff are to do if unregistered select agents or toxins are found;
- Pathogen registration forms, biological materials inventory forms, and laboratory inspection forms that are used by DOHS and investigators.

Other Relevant Policies

In addition to NIH-specific policies, practices and procedures, research at NIH is, of course, subject to a variety of federal regulations, policies and guidance including, but not limited to:

- The Federal Select Agents Regulations;
- *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules;*
- *Biosafety in Microbiological and Biomedical Laboratories, 5th edition;*
- Federal and institutional life science Dual-Use Research of Concern Policies;
- HHS Framework for oversight of certain research involving highly pathogenic H5N1 and low pathogenicity H7N9 avian influenza viruses;
- Export Controls.
- Department of Transportation Regulations about transport of dangerous materials, including infectious agents.
- The Occupational Safety and Health Administration standards.

These are described in Appendix H.

Table 1. Summary of Relevant NIH Biosafety Policies and Guidance in Place in 2014 and Status in 2017

Policy or Guidance	Topics Covered, as of 2017	Status Relative to 2014
Manual Chapter 1340, "NIH Occupational Safety and Health Management"	Outlines overall safety responsibilities at NIH; Describes NIH-wide safety committees; Includes a requirement to use personal protective equipment (PPE)	PPE requirement was not in place
Manual Chapter 1340-1, "Permits for the Import, Transfer, or Export of Biological Materials"	Import, transfer or export of biological materials (including select agents and toxins (SA)); covers the need to safely transport biological materials in appropriate containers.	In place in 2014; minor changes were made to add more specificity regarding responsibilities
Manual Chapter 3035, "Working Safely with Potentially Hazardous Biological Materials (PHBM)"	Use and storage of PHBM; DURC; Responsibility for shared spaces; Prevention of abandoned materials; Requirements for work with SA; Required training; PHBM inventory requirement; Registration of work involving rDNA and PHBM; Proper transport of biological materials within NIH; Use of PPE.	The 2014 version was revised substantially in 2015 to address critical areas and shortcomings raised by the variola virus incident (see section 5.4. below)
Manual Chapter 3037, "NIH Biological Surety Program"	Defines laboratory spaces that are subject to the NIH Biological Surety Program and the requirements for approval of persons to work in them	The program was operational in 2014, but the Manual Chapter was put in place in 2015.
Guidelines and Policies for the Conduct of Research in the Intramural Program at NIH	Care and use of research materials; Research with dangerous pathogens, including SA; Human biospecimen storage and tracking; DURC; Storage of biological materials and inventory requirements; Non-needed materials; Health and safety and training	Existing version was revised after the incident to reflect the changes in MC 3035.

Policy or Guidance	Topics Covered, as of 2017	Status Relative to 2014
Potentially Hazardous Biological Materials Management Plan 1 and 2	Lays out plans to implement: • Clean sweep for PHBM; • Inventory of PHBM; • Review and revision of biosafety policies; • Establishment of clear responsibilities and penalties; • Establishment of culture of responsibility; • Check out procedures for departing scientists.	Written in 2014 after the incident to enhance biosafety and biosecurity and to improve policies
Inventory requirement	Spreadsheet of data to be recorded for all PHBM	In 2014 inventory required only for SA
Annual SA reminder (email) and SOP 902, "Intra-Entity Transfer of Discovered Select Agents"	Describes generally what is covered by the NIH and CDC SA Programs and what to do if SA are discovered.	Neither was in place in 2014, although NIH SA Program was operational
Registration of pathogens and rDNA	Defines data to be provided to IBC and updated annually	In place in 2014, but projects were not reviewed annually

Links to the documents in this table may be found in Appendix F.

5.4. Policy Changes and Steps Taken Since the Incident

As established in the Potentially Hazardous Biological Materials Management Plan, parts 1 and 2, relevant NIH policies, procedures and guidance have been reviewed, and many needed changes have been made:

- Chapter 1340 was changed to define responsibilities more specifically and add statements about the requirement for all personal to use appropriate personal protective equipment;
- Chapter 1340-1 was changed to include more specificity regarding responsibilities, particularly requiring principal investigators to include information about any permits acquired when they submit their biological materials registrations and to emphasize the need for proper transport and packaging of biological materials;
- Chapter 3035 was changed to include:
    - Annual review of required registrations for projects with recombinant or synthetic nucleic acid molecules or PHBM with the NIH IBC (registration approval of some sort has been in place for many years, but projects were not reviewed regularly after initial approval);
    - Institute and Center Scientific Directors are required to assign responsibility for all shared spaces and are required to have policies to prevent abandoned materials;
    - Required inventory of PHBM; required inventory of biological materials in long-term storage;
    - Required annual review of projects for DURC; previously projects were only reviewed at the beginning;
    - Required submission of any permits obtained to be included with annual registrations;
    - Requirement that laboratory supervisors ensure that the annual inventory of potentially hazardous biological materials is conducted.
- Chapter 3037 which covers the NIH Biological Surety Program was issued for the first time in 2016, although the program had been operating since 2009;
- Centralized reporting to DOHS for biosafety activities at all NIH sites was implemented to ensure consistency across all of NIH; previously some remote sites operated largely independently;
- The Biorisk Management Branch in DOHS was created; it provides oversight of research with pathogens that require BSL3 containment and select agents and toxins, and manages the biosurety program;
- An NIH-wide centralized inventory system for all PHBM was implemented with required annual updates;
- New requirements for exempt quantities of select toxins were implemented; all toxins must be registered and logs must be kept;
- New and updated SOPs were developed, such as SOP 902 “Intra-Entity Transfer of Discovered Select Agents” which discusses procedures to follow upon discovery of unregistered select agents and toxins;

- The guidance about cardboard was clarified in the laboratory inspection checklist to specify that spaces are to be "free of unused, discarded or damaged cardboard";
- Guidelines and Policies for the Conduct of Research in the Intramural Research Program at NIH was updated by NIH Institute and Center Scientific Directors to be consistent with new NIH-wide mandates;
- A clean sweep of all NIH laboratory spaces and all biological materials was conducted in 2014 to examine all biological materials, find any unregistered select agents and toxins and to dispose of abandoned and unwanted items of all types;
- Increased implementation responsibilities for Institute and Center Scientific Directors were added;
- An annual email reminding investigators about their responsibilities with regard to select agents and toxins is sent by DOHS.

6. ANALYSIS

6.1. Contributing Factors and Problem Issues

The BRP was charged with determining the causes or factors responsible for the 2014 smallpox virus incident and with noting other issues of concern that might become apparent as a result of its review. Information was gathered from other investigations of the incident, interviews with pertinent current and former NIH and FDA staff and others who might have useful knowledge of the incident or how the samples came to be in the cold room, analysis of background documents and materials, review of NIH policy, procedure and guidance documents and a site visit to Buildings 29A and 13. After discussing the information collected, the BRP identified the issues discussed below as having contributed, to varying degrees, to the 2014 incident. No single issue was solely responsible, and the list does not attempt to apportion responsibility quantitatively in any way. Several of these issues overlap, but are discussed separately for clarity. In addition, while the BRP deemed the USG response to the incident commendable, the panel identified some specific concerns related to the immediate incident response and to the clarity or scope of several NIH policy/procedure documents.

- Lack of responsibility for infectious materials in shared space. The cold room where the samples were found was shared space with access provided from a common corridor. Several investigators and their staff used the room over the years, but neither FDA nor NIH had policies in place that assigned full responsibility for the space and its contents to any one individual. NIH conducted safety inspections in the building, including the cold room, and FDA was responsible for the research in the building and assigned laboratory space to individual investigators. Investigators knew who to contact in an emergency, but the presence of the abandoned samples did not cause any concern or raise alarms, other than as related to cardboard storage (see below). Thus, materials were able to remain for many years ignored and unaccounted.

- Failure to find all variola virus samples in the 1980s. By the mid-1980s all variola virus samples throughout the world were to have been destroyed or conveyed to the CDC in the

US or a repository in the then USSR. There are no known records that document how the identification and disposition of possible variola virus samples in NIH laboratories was managed at the time, and no one who was interviewed for this report has direct knowledge. It is not clear how investigators who might have had variola virus samples were notified about the mandate to divest their samples, what materials might have been found and either destroyed or transferred to CDC, or who at NIH monitored the process. In the mid-twentieth century, biosafety practices were less stringent than today, and it is possible that the process was informal and not systematic. It is also possible that the owner(s) of the samples were no longer working in Building 29A or for NIH/FDA in 1980 and, thus, could not have complied even if clear guidance was given.

- Failure to account for all select agents in 2003. In 2003 NIH filed its first Select Agents Registration, which included work on influenza virus by FDA in Building 29A. Prior to 2003 only transfer of select agents and toxins between laboratories was regulated; possession and use were not covered until the new Regulations became effective. There is limited documentation about how implementation of the expanded Select Agents Regulations was conducted at NIH. Based on existing evidence it appears that all NIH investigators were notified of the requirement to report their holdings of select agents and toxins, and detailed plans were developed to become compliant with the Patriot Act of 2001. It appears that a substantial effort to register select agent and toxin inventories took place throughout NIH. However, the emphasis seems to have been placed primarily, if not solely, on investigators who were known to be working with select agents and toxins. Investigators who did not knowingly possess select agents and toxins may have been unaware of any new reporting or registration requirements. There was no established campus-wide verification of pathogen inventories at that time. Since the variola virus and other samples found with them were not known to exist by NIH or FDA researchers or by NIH DOHS staff in 2003, they escaped scrutiny and remained unregistered and improperly stored. The possibility of agents in historic collections with long absent owners did not receive attention.

- Lack of complete, regular inventory of potentially hazardous biological materials. Prior to 2014, there were no policies in place at NIH and/or FDA to require inventories of biological materials unless they were select agents or toxins. Other microbial agents and some human-derived materials, including some of the materials found in the cold room, are potentially hazardous, but no policies were in place to account for them on a regular basis. Since the Select Agents Regulations are based upon a list of specific pathogenic microorganisms and toxins, agents not included on the list were not subject to routine inspections and inventories and received less oversight, although now NIH policies on inventories have changed. Prior to 2014, the NIH IBC reviewed protocols involving various infectious agents, and would likely have recognized proposed work involving select agents and toxins or other highly pathogenic agents not previously known to be at NIH, but stored materials, not being actively studied, were not subject to this review and would not have been noticed.

- Lack of policy for abandoned materials. When investigators leave laboratories, it is common for them to leave behind biological samples, records, and other materials for possible future use by other researchers. Prior to 2014 there were no clear policies at NIH and/or FDA about responsibility for and oversight of abandoned materials; each laboratory would have dealt with such materials in their own way, and a need for storage space would likely have been the impetus for clearing out old items. Unneeded and possibly hazardous biological materials could easily accumulate, particularly in shared space. Thus, the variola virus and other specimens were able to remain unrecognized in the Building 29A cold room for many years. This was compounded by the lack of specific, assigned responsibility for all materials in the cold room.

- History of NIH lapses following implementation of the Select Agents Regulations. In 2008, an inspection by CDC-DSAT found inventory discrepancies and raised questions about the containers used for storage of a historical collection of *Burkholderia* samples from the NIH Clinical Center. In 2011 a researcher at Rocky Mountain Laboratories (an NIH facility) conducted an unapproved, restricted experiment with antibiotic-resistant *Yersinia pestis*. In 2012 several investigators were found to have unaccounted *Bacillus anthracis* samples in unregistered spaces, and several people with access to the samples were not registered with the NIH and Federal Select Agent Programs. This series of incidents alerted NIH leadership to the need to strengthen oversight of select agents and toxins, particularly inventories. Although significant efforts were undertaken to identify all select agent and toxin materials on site at NIH facilities, the 2012 survey did not apply to all investigators and all laboratory spaces. The NIH Select Agent Program in 2012 focused on the incident involving the release from select agent registered space but did not find other unaccounted select agents and toxins on the campus. A CDC-DSAT investigation in 2012, at the time of the anthrax incident, identified numerous violations of Select Agents Regulations. NIH was put on a performance improvement plan by CDC-DSAT in 2012 (which has since been removed). Although these earlier incidents do not directly relate to the 2014 smallpox virus incident, they point to possible systemic problems regarding biosafety and biosecurity that were not fully addressed until after 2014. In addition, if these events had induced a completely thorough search for select agents and toxins, the samples in the cold room and others might have been found before 2014.

- Missed opportunities to find the samples before 2014. The previously mentioned incidents involving select agents and toxins in NIH laboratories in 2008, 2011, and 2012 alerted NIH officials that NIH was not fully compliant with the Select Agents Regulations. Although efforts were made to find unaccounted materials in unregistered spaces, the effort focused on investigators known to have worked with select agents and toxins. In addition, in 2012 all investigators were required to attest that they did not have unregistered materials in unregistered space; however, this attestation involved the self-reporting of known samples. The 2012 effort to find select agents and toxins would not have found materials that were abandoned or forgotten. A more comprehensive effort to ensure full compliance with Select Agents Regulations might have led to the discovery of the smallpox virus samples at the time of one of these incidents. In addition, the samples found in the cold room were more

than likely at NIH at the time of the original select agent registration in 2003, and should have been identified at that time as well.

- Lack of clarity regarding responsibilities between NIH and FDA. The relationship between NIH and FDA regarding Building 29A was complex. FDA was responsible for its personnel in the building (there were no NIH staff in Building 29A) and overall oversight of the research being conducted. NIH was responsible, through Interagency Agreements, for oversight of safety in the building, including the oversight of any select agent and toxin work, and the conduct of periodic biosafety inspections. However, FDA also had responsibility to ensure that its research was conducted according to applicable regulations, policies, etc. The cold room was inspected on a regular basis by NIH and concerns regarding storage of cardboard in the cold room were noted, but never completely resolved. Despite all of this, the cardboard boxes containing the variola virus and other samples escaped attention by both NIH and FDA.

- Improper transfer of materials at the time of the incident. When the samples in the cold room were discovered and reported to the NIH RO, it was decided that the FDA senior official should bring them to the secure DOHS BSL3 laboratory in Building 13 where they could be securely stored, given that contractors and others were working throughout Building 29A preparing for the move. The samples, in their original boxes, were packaged into a larger cardboard box, and then hand-carried from Building 29A to Building 13 where NIH took custody. This procedure was not compliant with the NIH policy in MC 3035 which call for securing the material in place and waiting for DOHS to arrive and determine a course of action. In addition, transport of select agents and toxins as well as other pathogens is regulated and appropriate packaging materials required for transport are well-defined; NIH policies describe appropriate procedures. These requirements were not followed. Although nothing untoward happened—no one was infected or injured-- the transport and packaging was conducted in a way that presented both biosafety and security risks.

- Inadequate chain-of-custody and log of events. Until NIH took possession of the samples in Building 13, no written record was made as the events of July 1 took place and the samples were not secured at all times. Having such a record would have facilitated understanding exactly what took place, when it occurred, and who was involved. Apparently, FDA staff were unaware of this practice, and NIH biosafety guidance at the time was not clear or did not require strict chain-of-custody and detailed time logs as events unfolded.

- Cardboard in cold rooms. Although having cardboard in cold rooms did not directly contribute to the smallpox virus incident, it was noted as a problem area in the House Energy & Commerce Committee report. Cardboard, particularly if it gets wet, can contribute to mold problems, unsanitary conditions and put other materials at risk. The NIH policy about cardboard in cold rooms was not clear in 2014; the laboratory inspection checklist mentioned cardboard, but did not make it clear what is and is not acceptable. If there had been a clear policy, the abandoned boxes might have been noticed earlier.

6.2. Assessment of Current Policies and Recent Changes with Regard to the Contributing Factors and Problem Issues

The BRP was charged with determining whether the current NIH biosafety policies, practices, procedures and oversight systems adequately address problems and gaps identified as a result of investigations of the 2014 incident; the BRP was asked to determine if the changes that have been implemented by NIH will eliminate or greatly reduce the possibility of these factors contributing to problems now and in the future. Table 2. below summarizes this analysis.

- Lack of responsibility for infectious materials in shared space.
  Positive steps: A requirement that a single individual be identified as the responsible party for all materials in each shared space at all NIH facilities was added to Manual Chapter 3035 and should mitigate this contributing factor. Inclusion of this requirement in the NIH Intramural Program Guidelines, with increased accountability of Institute and Center Scientific Directors for fulfilling the requirement, should assist effective implementation. While ongoing implementation and accountability for this matter lies with the Institutes and Centers, in an effort to provide centralized oversight, DOHS has begun a "space audit" that will list all laboratory spaces and indicate a responsible person for each.
  Remaining Gaps: The NIH-wide space audit is incomplete, and should be completed as soon as possible; it should also be updated periodically, particularly when investigators responsible for spaces leave.

- Failure to find all variola virus samples in the 1980s. NIH efforts to consolidate variola virus samples around 1980 are poorly documented, so the reason(s) the variola virus samples were undiscovered is unknown. The clean sweep, conducted in 2014 should have identified any remaining unaccounted select agents and toxins, including variola virus; there is every reason to think that new variola virus samples could not enter NIH unnoticed because of its prohibition in the current national and international status regarding select agents and toxins and variola virus.

- Failure to account for all select agents and toxins in 2003.
  Positive steps: The clean sweep conducted in 2014 should have identified any previously unaccounted select agents and toxins. Increased attention to select agent matters, starting at the highest levels of NIH, creation of the Biorisk Management Branch to monitor select agents and toxins as well as other pathogens that require BSL3 containment, increased accountability of Scientific Directors and principal investigators with regard to select agents and toxins, frequent inspections and serious penalties for failure to comply with regulations, policies and guidance should greatly reduce, but not totally eliminate, the possibility that there will be deviations from Select Agents Regulations at NIH in the future. The required annual biosafety refresher training, an obligation of all research personnel, covers awareness of select agents and toxins and regulatory requirements. An email is sent annually pointing out investigators' responsibilities with regard to select agents and toxins. The number of investigators registered with the NIH Select Agent Program is relatively

small, and DOHS staff are in frequent communication with PIs authorized to work with select agents and toxins.
Remaining Gaps: The annual select agent email is not detailed enough regarding actions to be taken if select agents and toxins are discovered in laboratories. Currently the email makes it clear that researchers should contact the RO immediately, but does not discuss in detail the process of securing the material, creating a time log, or ensuring a proper chain-of-custody.

- Lack of complete, regular inventory of potentially hazardous biological materials (PHBM).
  Positive steps: In 2014 NIH defined, for its internal use, a new category of biological materials called PHBM which includes recombinant and synthetic nucleic acid molecules; toxins and poisons; human/animal/plant pathogens that require BSL 2 containment or higher; and human and non-human primate blood, tissues, and body fluids, including primary human cell cultures; and select agents and toxins. NIH also established a PHBM inventory requirement, for all laboratories with annual updates. This categorization exceeds Select Agents Regulations or BMBL requirements and is intended to provide greatly enhanced oversight at NIH for work involving pathogens and other possibly hazardous/regulated materials. Combined with other policies already mentioned, the inventory requirement should reduce, but not totally eliminate, the probability of unaccounted possibly hazardous/regulated materials.
  Remaining Gaps: None noted.

- Lack of policy for abandoned materials.
  Positive steps: Establishment of the requirement in MC 3035 that Scientific Directors put systems in place to prevent any biological materials (PHBM and other) from being abandoned or left behind without clear ownership, also mentioned in the Intramural Research Guidelines, should greatly reduce, but not totally eliminate, the probability of unaccounted hazardous biological materials. Materials in laboratories that have been registered with the NIH IBC (those working on rDNA or BSL2 or higher pathogens) must be accounted for when investigators leave the NIH, and Institute and Center safety committees are responsible for non-IBC laboratories.
  Remaining Gaps: None noted.

- History of lapses in following the Select Agents Regulations.
  Positive steps: Extremely broad efforts at NIH since 2014 (see section 5.4.), in particular establishment of the Biorisk Management Branch within DOHS, have raised awareness among researchers about the requirements with regard to possession, use and transfer of select agents and toxins. These efforts along with increased accountability for failure to comply should greatly reduce, but not totally eliminate, the probability of future select agent and toxin lapses. Institute and Center Scientific Directors are responsible for what takes place in their Institutes and Centers with regard to select agents and toxins.
  Remaining Gaps: None noted.

- Missed opportunities to find the samples before 2014.
  Positive steps: The 2014 clean sweep, the requirement for biological materials inventories, the designation of responsibility for materials in shared space, and the requirement for materials to be transferred or destroyed when investigators leave should greatly reduce, but not totally eliminate, the possibility of finding previously undiscovered historical materials in the future.
  Remaining Gaps: None noted.

- Some lack of clarity regarding responsibilities between NIH and FDA. The interagency agreements that were in place before 2014 did not give specific personnel clear responsibility for biosafety with regard the contents of the cold room. Since FDA no longer occupies any space at NIH facilities, this factor is no longer relevant as related to FDA and the 2014 incident. However, any arrangements that involve shared facilities within or external to NIH should be based on clear, written agreements about responsibilities.

- Improper packaging and transport of samples during the incident.
  Positive steps. Requirements for transport and packaging of infectious biological materials are defined in Department of Transportation Regulations, Occupational Safety and Health Administration Regulations and in NIH policies; in addition, the Select Agents Regulations govern transfers of select agents and toxins. The requirements have not changed recently; NIH describes its internal guidance about packaging and transport in MC 1040-1, in MC 3035, in the annual select agent email and in SOP 902; and education efforts for researchers about this issue have been increased.
  Remaining Gaps: The annual select agent email, SOP 902 and MC 3035, should be reviewed to make individual investigators thoroughly aware of their responsibilities with regard to packaging and transport of biological materials (both in and out of NIH and internally on the campus), particularly if select agents or toxins are discovered. These documents should also indicate clearly the division of responsibilities between investigators and DOHS staff.

- Inadequate chain-of-custody and time logs.
  Positive steps: The desirability of a time log to be recorded as an incident progresses and the necessity for a complete chain-of-custody were raised during interviews conducted by the BRP, but were not noted in previous investigations of the smallpox virus incident. Since this is a new observation, the BRP has not seen evidence that NIH has addressed it previously, but now that it has been identified, positive steps can be taken.
  Remaining Gaps: SOP 902, the annual select agent email, and an appropriate manual chapter should be revised to address this issue and make sure individual investigators understand what to do.

- Cardboard in cold rooms.
  Positive steps: The annual laboratory inspection form has been modified to clarify that cold rooms must be free of unused, discarded, or damaged cardboard, although cardboard is permitted.
  Remaining Gaps: None noted.

Table 2. Contributing Factors and Problem Issues: Summary of Analysis

Contributing Factor or Problem Issue	Situation Before 2014 Incident	Current Situation	Remaining Gaps and Comments
Lack of responsibility for infectious materials in shared spaces	No specific policies for NIH or FDA	Manual Chapter 3035, page 13 requires Institute and Center (IC) SDs to implement procedures that make one person responsible for any shared space; this is also stated in the Guidelines for Intramural Research; ICs are responsible, but DOHS is conducting a space audit that will list spaces with responsible persons	The planned NIH space audit must be completed as soon as possible to be sure ICs are compliant; the list must be updated on a regular basis, and when there are personnel changes
Failure to find all variola virus samples in the 1980s	Not Applicable (NA)	NA	No longer relevant; what was done at that time is not known; the 2014 clean sweep should have found any additional variola virus materials at NIH
Failure to account for all select agents and toxins (SA) in 2003 (variola in particular) when NIH's initial SA registration was done	The NIH SA Program existed to manage compliance with the SA Regulations	The clean sweep should have found any unknown SA samples; Manual Chapter 3035 covers SA; Biorisk Management Branch established to monitor SA compliance; Annual memo to all investigators about SA; Annual required safety training covers SA; Scientific Directors (SD) responsible for compliance in ICs	The annual SA email is not detailed enough about what to do if SA are discovered, particularly regarding what researchers should do about securing the material, creating a time log, and maintaining chain-of-custody.

Contributing Factor or Problem Issue	Situation Before 2014 Incident	Current Situation	Remaining Gaps and Comments
Lack of complete, regular inventory of Potentially Hazardous Biological Materials (PHBM)	No policy except for SA	Required inventory of PHBM, updated annually, is described in MC3035, Guidelines for NIH Intramural Research, and on DOHS website (available to investigators); Inventory is spot checked during annual inspection for IBC registered laboratories; ICs and PIs are responsible for implementing inventories	None noted.
Lack of policy for abandoned materials	No policy	Manual Chapter 3035, page 13 requires IC SDs to implement procedures to prevent all research materials from being abandoned or ownerless; requirement is covered in Intramural Guidelines; IBC registrations must be cancelled when investigators leave and materials must be accounted for; implementation for non-IBC laboratories is done by IC safety committees	None noted.
History of lapses in following the SA Regulations at NIH (including unauthorized access to SA)	NIH SA Program existed	Biorisk Management Branch was established to focus on SA; Annual safety training and email alert all investigators about SA; the SA program is small and known SA investigators understand their responsibilities	None noted.

Contributing Factor or Problem Issue	Situation Before 2014 Incident	Current Situation	Remaining Gaps and Comments
Missed opportunities to find the samples before 2014	No complete clean sweep was ever done, and biosafety incidents were handled on an *ad hoc* basis	Clean sweep was conducted in 2014; Required inventories; Single person responsibility for shared spaces; Transfer of materials when investigators leave	Responsibilities of all parties for all aspects of implementation need to be clearly defined. Space audit must be completed.
Some lack of clarity regarding responsibilities between NIH and FDA.	Interagency agreements were in place, but not precise	No FDA presence at NIH now	No longer relevant for this incident/. However, future "sharing" arrangements need to be well-defined, with clear responsibilities
Improper packaging and transport of found materials from Bl. 29A to Bl. 13 on day of incident	Requirements were covered in Manual Chapter 1340-1, in MC 3035 and in SA Regulations;	NIH policy was not changed, although the annual SA email and SOP 902 were added to give increased emphasis to this issue	As discussed above, the annual SA email and SOP 902 are not detailed enough, particularly regarding what researchers should do about reporting the incident to DOHS, securing the material, creating a time log, and maintaining chain-of-custody if SA are discovered
Inadequate chain-of-custody records and time log records for the incident	No specific NIH policy or guidance	Chain-of-custody responsibilities for DOHS staff is covered in SOP 902, but researcher responsibilities are not covered in detail in any policy or guidance	All researchers must to understand their responsibilities and need better guidance; as discussed above, SOP 902 and the annual SA email are not detailed enough about what to do in this regard.
Cardboard in cold rooms	No policy; inspection checklist was vague	Checklist was revised to define that cold rooms must be free of unused, discarded, or damaged cardboard	None noted.

7. CONCLUSIONS

Based on the results of its own investigations, as well as the others conducted after the incident, the BRP believes that what happened during and leading up to the 2014 smallpox (variola) virus incident is as well-documented as possible. The BRP found no evidence that any significant information has been overlooked. However, records from earlier times are sparse, and information about the origin or ownership of the samples was not found, despite extensive efforts by NIH, FDA and FBI to do so. In addition, the factors that contributed to the incident have been clearly recognized by the BRP and in the other reports. In this report, eight such contributing factors have been identified (section 6.1.). Most directly relevant were the lack of clear responsibility for the materials in the cold room, the lack of policies to prevent abandoned materials, the lack of regular inventory and examination of infectious materials, and missed opportunities to have found the samples earlier. The BRP notes that while historical biosafety problems may be clear now when regarded in hindsight, they were nevertheless not so obvious in the evolving biosafety and regulatory environment of the last 40 years.

The BRP observed several problems related to the incident response at NIH. Most notably, the samples were not transported from Building 29A to Building 13 in a manner that is compliant with NIH policy and current best standards of biosafety. The decision to move the samples is understandable in light of the upheaval and lack of security in Building 29A at the time of the incident, but perhaps biosecurity concerns in this case were given priority over proper biosafety measures. An alternative approach would have been to immediately place guards to control access to room 3C16 in Building 29A until the NIH DOHS could implement a packaging and transport plan consistent with NIH biosafety policy. As a result of the manner in which the materials were transported, individuals may have been placed at undue risk by hastily moving the material when they were first discovered. Fortunately, no human infections or other problems resulted from this action. In addition, adequate chain-of-custody records and detailed time logs were not kept while events were unfolding during the initial hours after the samples were discovered. Subsequent movement of the samples to CDC and other facilities was handled in accordance with all relevant regulations and, because of the unique biosecurity aspects of smallpox virus, accompanied by the FBI.

The incident response involved NIH, CDC, FBI, and FDA personnel, with coordination through HHS, DHS, and NSC. Overall, with the exceptions noted above, the BRP believes that the response during the period between July 1 and 9 was appropriate, thorough, and effectively handled a highly unusual situation without further complications. There was excellent interagency coordination and a thorough investigation by CDC and FBI during the incident. The response was rapid, and effective. The discovery was communicated to NIH leadership and other federal authorities appropriately. It should be noted that while both the biosafety and biosecurity aspects of the response were considered, the immediate actions may have allowed the security components to dominate over the safety aspects -- as demonstrated by the hasty

packaging and transfer of the samples on the day of their discovery. This is hopefully an instructive anomaly due to the unusual place smallpox virus occupies as a potential bioweapon among the select agents and toxins.

The follow-up response within the government was USG-wide and led to important biosafety changes and efforts that are still on-going. Immediately following the incident, clean sweeps and safety stand-downs, along with reviews of policies and practices were instituted. Government labs were put on notice that biosafety and biosecurity would be subject to ongoing scrutiny at the highest levels. The Monaco-Holdren memoranda also led to the appointment of the Federal Experts Security Advisory Panel and the Fast Track Action Committee that were charged with identifying needs and gaps and making recommendations to strengthen biosafety and security for select agents and toxins within the US, and to foster collaboration and cooperation broadly within the USG. The international aspect of the subject was also acknowledged; it would be desirable to have harmonized policies and approaches across all countries conducting this type of research. Subsequently, HHS has created the Health and Human Services Biosafety and Biosecurity Council which issued a HHS Coordinating Framework for Biosafety and Biosecurity, with the goal of establishing a consistent approach across agencies; this was followed by individual agency frameworks, including one for NIH.

After the incident, NIH responded rapidly and broadly to address the underlying causes, and responded to the issues raised in the FBI-CDC report and, later, to those in the reports by the CDC-ACD, the House Energy and Commerce Committee and the GAO. Within days of the incident, the Potentially Hazardous Biological Materials Management Plan 1, and later 2, were established to provide overall direction from the NIH Director's Office. Efforts to fulfill these plans and address the issues that led to the incident have been extensive, as noted in Section 5.4. As discussed in section 6.2., the BRP believes these efforts have largely addressed the issues and gaps that existed in 2014. NIH has gone beyond the minimum necessary response with policies such as the Potentially Hazardous Biological Materials Inventory that mandates actions which are not required federally. A few gaps do remain, however, especially related to the assigned specific responsibility in each laboratory for ensuring these new policies are implemented appropriately. As evidence of improvement, there have not been any select agent and toxin related problems noted at NIH since 2014, with formal DSAT inspections required, at a minimum, every three years. While it is impossible to reduce biosafety and biosecurity risks completely, the current situation at NIH has greatly reduced their probability and addressed most of the systemic faults that previously existed.

Finally, it is important to mention the impact of changes in biosafety oversight over the last 60 years and their relation to this incident, which is a product of another era. The material in question was stored prior to the Select Agents Regulations being established and likely pre-dated the eradication of smallpox and the consolidation of variola virus strains into international repositories. Despite extensive efforts by the BRP, NIH, CDC, FBI and FDA to find out, it was not possible to discover who was responsible for the placement of the material in the cold room and why the samples were not found when WHO issued its request to all countries and laboratories to destroy their smallpox virus samples or send them to one of the

two repositories. However, there is no indication that there was malicious intent on the part of anyone associated with the storage of the viruses.

8. RECOMMENDATIONS

First, with regard to specific, detailed steps NIH should take to remedy remaining gaps in biosafety and biosecurity policies and procedures, the BRP recommends that NIH:

- Revise several policies and procedures as detailed in section 6.2.; this includes updating and improving the annual select agent email and SOP 902, with additions to MC 3035 and perhaps others as needed to clarify person-specific responsibilities for each policy and procedure, and provide more detailed direction.
- Rapidly complete the on-going space audit (see Section 6.2, first bullet); make sure that there is a plan for periodic updates to the data collected by this audit, and implementation oversight, particularly when there are personnel changes.
- Ensure any shared research space arrangements, including interagency, inter-institute, inter-center, intra-center and others have clear written agreements detailing well-defined responsibilities.
- The BRP noted that NIH policies and procedures refer to several categories of infectious agents in addition to select agents and toxins; this includes “potentially hazardous biological materials” and “high consequence pathogens”, “potentially infectious materials” terms that are not in general use. The use of non-standard terms can be confusing, and such categories need to be defined carefully and eliminated when no longer necessary.

Second, regarding more general approaches to improving biosafety and biosecurity at NIH, the BRP considers the following important:

- Effective and complete implementation of current policies, procedures, guidance and practices on an on-going basis over time will be critical to ensuring safety and security surrounding pathogen research at NIH. This implementation presents challenges in such a large and diverse agency, where responsibilities for biosafety and biosecurity are distributed throughout the organization, including centrally at DOHS and locally with the Institutes and Centers. In addition, training and ensuring that newly hired staff are acclimated and engaged with the culture of safety and security and associated responsibilities is critical. Implementation is more likely to be achieved if specific individuals are named as responsible, from the level of the NIH Director to the individual researcher, and a clear chain of reporting is established.
- The importance of leadership at the highest levels and continuous efforts to develop and maintain a culture of safety and responsible actions cannot be overemphasized. Progress is evident, but it is essential to guard against complacency and loss of attention as time goes on. NIH should take advantage of best-practices and ideas from other organizations with successful programs. The NIH Director should be regularly updated on the results of audits carried out by DOHS and on any external inspections or reviews.

- There are significant benefits to having consistent biosafety and biosecurity policies across HHS and the entire USG-- and ideally harmonized with international institutions as well. The BRP recognizes that there are on-going efforts in the government and encourages all levels of the government to work together to ensure that specific responsibilities and logistics are well-defined and that policies are consistent from one agency to another.
- It is vital to create and routinely exercise response plans with agencies outside of HHS, including FBI, EPA and others as needed to ensure well-rehearsed and effective interagency response to any biosafety and biosecurity incidents.
- The variola virus incident illustrates how changes in infectious disease epidemiology and biosafety/biosecurity practices over time can radically alter a situation from "standard lab practice" to a major potential public health or media event. As other pathogens are eradicated, particularly if mass vaccination practices change, a similar situation may be repeated with another infectious agent considered by current standards as only moderately risky. The possible presence of samples judged today as relatively benign in historical and personal collections needs to be considered and, with the perspective of the smallpox virus incident, argues for institutional for oversight and attention beyond the individual laboratory or investigator level.

9. APPENDICES

Appendix A. BRP Roster

Blue Ribbon Panel to Review the 2014

Variola Virus Incident on the NIH Campus

Kenneth Bernard, M.D. (Chair)
RADM, U.S. Public Health Service (Ret.)
Former Special Assistant to the President for Biodefense, Homeland Security Council, White House
Former Special Adviser for Health and Security on the National Security Council

David R. Franz, D.V.M., Ph.D.
Former Commander, United States Army Medical Research Institute for Infectious Diseases (USAMRIID)
Professor for the Department of Diagnostic Medicine and Pathobiology
College of Veterinary Medicine
Kansas State University

Gigi Kwik Gronvall, Ph.D.
Senior Associate
UPMC Center for Health Security
Associate Professor, University of Pittsburgh School of Medicine and Graduate School of Public Health

Debra Hunt, Dr.P.H., CBSP
Director of Biological Safety
Assistant Professor, Division of Occupational Medicine, Department of Community and Family Medicine, Duke University
Responsible Official for Duke Select Agent Program
Duke University / Duke Medicine

Joseph Kanabrocki, Ph.D., NRCM(SM)
Associate Vice President for Research Safety
Professor of Microbiology
University of Chicago

James W. LeDuc, Ph.D.
Director, Galveston National Laboratory and Professor, Department of Microbiology and Immunology
University of Texas Medical Branch

Melissa A. Morland, MS, CBSP, RBP
Biosafety Officer
Environmental Health and Safety
University of Maryland
Past-President, American Biological Safety Association (ABSA) International

Appendix B. BRP Charge and Workplan

Blue Ribbon Panel to Review the 2014 Variola Virus Incident on the NIH Campus

Tasks and Work Plan

Background

In July 2014, Food and Drug Administration (FDA) employees discovered twelve boxes containing over 300 vials of infectious agents and other materials– including six vials of variola virus, the causative agent of smallpox – in an FDA cold room located in a building on the NIH Bethesda campus that FDA had occupied for years. These boxes had been overlooked for many years and contained samples of infectious agents that had not been properly registered with the Federal Select Agent Program; in addition, the samples were not stored in accordance with current biosafety standards. Variola major virus, in particular, is also subject to international agreements restricting its use and storage to only two laboratories in the world (one of which is the Centers for Disease Control and Prevention [CDC] in Atlanta). The discovery of the smallpox virus vials was one of three laboratory incidents at federal facilities that prompted the White House to direct federal agencies to search their laboratories for improperly stored select agents and toxins. In addition, the White House called on federal agencies to review biosafety and biosecurity policies and procedures, and to make improvements when necessary.

The discovery of samples of variola virus has also been investigated by the FBI and CDC Select Agent Program, Government Accountability Office (GAO), as well as by Congress, and the FDA is also conducting its own review. In its investigation of the smallpox virus incident, the House of Representatives Committee on Energy and Commerce Subcommittee on Oversight and Investigations identified other biosafety lapses at NIH over the last few years, including failures to properly store and register other select agents and toxins. The Committee has described "a pattern of recurring issues" that may have contributed to the delay in discovering the variola virus vials. They also note "systemic, cultural, and behavioral factors that may need to be addressed in addition to the policy changes and oversight efforts being implemented by Federal agencies."

NIH will conduct an internal review of the events leading to the discovery of the vials of variola virus in order to ensure it has taken the steps necessary to be fully compliant with all applicable requirements including laws, regulations, policies, practices, guidance, guidelines, and international treaties and be responsible stewards of infectious agents so that laboratory workers and the public are protected, and similar incidents are prevented from occurring in the future.

Charge

The NIH will conduct an internal review to determine how vials of variola virus came to be improperly stored and were subsequently overlooked for many years on the NIH Bethesda campus. Understanding the cause(s) of this incident will allow NIH to determine whether its current policies and procedures will prevent similar incidents in the future, or whether additional policies or procedures should be implemented. To accomplish this review, NIH will

establish a Blue Ribbon Panel of external subject matter experts, which will be constituted as a Working Group of the National Science Advisory Board for Biosecurity (NSABB).

The Blue Ribbon Panel is charged with the following:

- Determine the cause, or causes, that led to the unauthorized possession and storage of six vials of variola virus on the NIH campus.
- Review and document, to the extent possible, what happened during the days immediately around the discovery of the variola virus samples.
- Review and document, to the extent possible, any relevant details of other events that occurred at earlier times that may inform the investigation.
- Determine why the variola virus vials were not discovered until 2014, many years after their initial storage.
- Identify any systemic issues that may have contributed to the unauthorized possession and storage of variola virus and to the delay in its discovery.
- Issue a report detailing its findings.

Tasks

To address its charge, the BRP will seek answers to the following questions.

1) What happened, both during the time immediately around the incident and during times leading up to the discovery of the vials?

- How and when did the vials come to be in the cold room?
- Who put them there?
- How were the vials discovered?
- Exactly what happened upon discovery?
- What was done with the samples after discovery?
- Were there other incidents relating to select agents and toxins occurring at NIH prior to the variola incident that may be relevant? If so, what happened and what was the outcome?
- When NIH filed its Select Agents Registration in 2003, what occurred with respect to identifying and registering pathogens that were subject to the regulations?
- What has happened since to ensure compliance with the Select Agent Regulations?

2) Why did oversight systems that should have prevented such an occurrence fail?

- Who should have been responsible for the samples?
- Why were the samples not discovered earlier?
- What oversight policies and procedures were in place in 2014 and at earlier times regarding possession and storage of infectious agents and select agents and toxins in particular?
- Were there deficiencies in these procedures, practices, etc. in 2014 and earlier?

- How did the divided responsibilities between FDA and NIH influence the situation?

3) Are current NIH procedures and policies, including revisions since the incident, appropriate and likely to prevent such events in the future?

- What enhancements to NIH policies and procedures have been put in place since 2014?
- Are they being implemented fully and effectively?
- Will they help to prevent issues similar to the smallpox virus incident from occurring again?
- What additional measures, if any, might be needed?

Work Plan

Phase I. Gather information and analyze.

There are a large number of relevant documents as well as several reports of investigations relating to the variola incident. NIH/OSP staff is compiling these materials and will make them (and/or summaries) available to the BRP. With input from the BRP, staff will also interview individuals likely to have relevant information and provide the BRP with information acquired. The BRP will provide input into this work plan and staff activities, including helping to identify input sources and methods for performing this review. The BRP may conduct a site visit to the NIH campus and meet with/receive briefings from any individuals with information pertaining to the incident.

Phase II. Develop findings.

The BRP will analyze the information collected in Phase I and identify the key issues that were responsible for the problem. These will be assembled into findings.

Phase III. Draft a report.

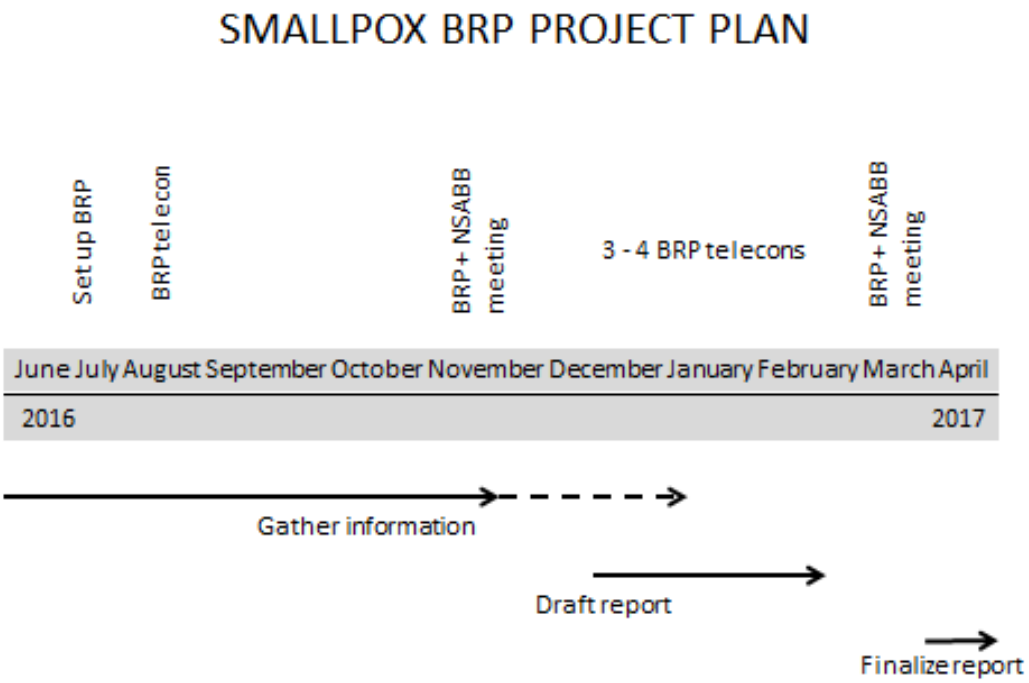
The findings and other information will be synthesized into a draft report that addresses the various aspects of the BRP charge.

Phase IV. Finalize report.

The BRP will present a draft report at a public meeting of the NSABB. The report will be discussed NSABB will ultimately vote to accept the report, which will then be conveyed to the NIH Director and other relevant officials.

Project Timeline

Date	Venue	Tasks
8/18/2016	BRP telecon	Introductions, review charge
10/28/2016	BRP telecon	Discuss progress, plans, review and discuss "Facts" document, prepare for in person meeting.
11/3/2016	BRP meeting, Bethesda, MD	Discuss progress; conduct site visit; hear presentations by agencies; review "facts" of the incident, discuss factors that contributed to the incident
11/4/16	NSABB telecon	Update NSABB on progress
12/21/2016	BRP telecon	Discuss historical context; discussion with FDA
1/5/2017	BRP telecon	Discussion with FBI; discussion current NIH policies;
1/30/2017	BRP telecon	First discussion of draft report, recommendations and conclusions
3/16/2017	BRP telecon	Discussion of draft report
May 11, 2017	NSABB meeting	BRP presented its report to NSABB
May 2017	Submit report	Report submitted by NSABB to NIH leadership



[Originally prepared August 2016; updated at the time of this report.**]**

Appendix C. Detailed Description of Events and Timelines

1968. Construction of Building 29A was completed on the NIH Bethesda campus and the building was occupied by the NIH Division of Biological Standards. Staff moved from other buildings on campus to the new building.

1972. The Division of Biological Standards, with its personnel, was transferred to FDA and became the Bureau of Biologics, which remained in Building 29A, although no records about this have been found.

1992. A Senior Investigator, Center for Drug Evaluation and Research (CDER)/FDA) began using the cold storage room on NIH's campus, which was a shared space (3C16 in building 29A) in 1992 and used it until 2014 when the FDA's CDER moved to the White Oak Campus. This person recalls that the cold room was occupied and not empty when he began using it.

2002. Office of Biotechnology Products (formally the Bureau of Biologics) was realigned from the FDA's CBER (Center for Biologics Evaluation and Research) to CDER.

The relationship between FDA and NIH involved FDA leasing the entire space in Building 29A from NIH; NIH's Division of Occupational Health and Safety (DOHS) was responsible for biosafety oversight in the building, including inspections. The NIH Institutional Biosafety Committee (IBC) reviewed FDA work conducted at Building 29A. Any select agent and toxin work was conducted under the NIH Select Agent Program. FDA was responsible for management of personnel and the research conducted and ensuring that biosafety policies and procedures were being implemented at the local level. There was select agent work conducted by FDA personnel in the building at some times, but not after 2012.

2014. FDA was preparing for its move from Building 29A to new facilities not on the NIH campus. Materials were being packed and moved, and the building was in a state of disruption.

July 1, 2014. The collection of 327 sealed glass vials of pathogens and biological materials was discovered. A detailed timeline of the day's events:

Time	Event
11:30-12:30pm	The FDA Senior Researcher (SR) is working in cold storage room 3C16 in building 29A, preparing for the physical laboratory move from the NIH campus to the FDA White Oak Campus.
~12:30pm	SR investigates the contents of 12 brown cardboard boxes, which he does not own, located on a shelf in the back left corner of the cold room and discovers glass vials with typed labels. One vial of lyophilized material had a typed label that stated "variola."
~1:00pm	SR informs the Director, Division of Viral Products (DDVP) CBER/FDA.

Time	Event
~1:30pm	They finish their investigation of the boxes, leave them in the cold room and go to the office of DDVP's supervisor, Associate Director of Research (ADR) CBER/FDA who was not in the office. DDVP emails ADR indicating that he would like to have a discussion upon her return
~4:30pm-5:00pm	ADR emails DDVP indicating that she has returned to her office and is available to talk.
~5:00pm	DDVP goes to the office of SR, the two then proceed to ADR's office and inform her of the aforementioned events leading to the discovery of the vials labeled "variola" and "Alastrim" as well as with the names of other pathogens that had been discovered.
~5:30pm	ADR contacts the Responsible Official (RO) and Director, DOHS, NIH. RO instructs ADR to transport the material to NIH's DOHS office on the third floor of building 13.
	RO informs NIH senior management and prepares to receive the samples.
~5:35pm	ADR contacts DDVP, and the two of them meet in the cold storage room 3C16. They do not open any boxes and place all 12 boxes into a larger cardboard box. The used lab coats and gloves are also placed into the larger box with the 12 smaller boxes. The larger box is sealed with clear packaging tape, and ADR alone hand-carries the material approximately 2 blocks to the NIH's DOHS office on the 3rd floor of building 13.
~5:50pm	ADR arrives and meets RO at the NIH's DOHS office. RO initiates a chain of custody form to document the transfer of the material from the FDA to NIH's DOHS. RO and ADR proceed to the biosafety level 2 laboratory, building 13, room 3W84. ADR remains outside of 3W84, but watches through the window as RO disarms and enters biosafety level 3 laboratory, 3W84B, and places the material in the biosafety cabinet within 3W84B.
	ADR walks back to her office in the building 29 complex and notifies her supervisor, at that time, Director, FDA's CBER.
~6:30pm	RO makes contact with the FBI.
6:35pm	RO calls and notifies director of the CDC's Division of Select Agents and Toxins (DSAT).

July 2, 2016. The FBI arrived on the Bethesda campus and stationed armed agents in Building 13 but did not enter the BSL3 laboratory. They played a critical role in the initial response to the incident.

July 7-9, 2014. According to access logs provided by NIH, no personnel accessed the BSL3 laboratory 3W84B where the found materials were secured after 5:51 p.m. July 1, 2014 until

10:54 a.m. July 7, 2014 when the combined CDC Division of High-Consequence Pathogens and Pathology and FBI team started their joint site visit and investigation of the incident. They oversaw the photo documentation and preliminary inventory of the found materials, and FBI provided secure transportation of the samples to CDC and other agencies. It was noted that the integrity of one vial was compromised (labeled Nor. SPL. ANT – presumed to be Normal Spleen Antigen which is neither a pathogen nor a select agent or toxin). More specifically:

July 7, 2014. Of the 327 vials, 6 vials that were believed to contain variola virus along with 10 other vials (1 Russian spring summer encephalitis virus, 1 eastern equine encephalitis virus, 1 Q fever, and 9 unidentified) were transferred to CDC custody for confirmation and eventual destruction of smallpox under WHO supervision.

July 8, 2014. Of the remaining 311 vials, 32 were destroyed on the NIH's Bethesda Campus. This included 4 labeled "vaccinia WR" and 28 "NOR SPL ANT". The remaining 279 vials were transferred to the National Biodefense Analysis & Countermeasures Center (NBACC) where they were subsequently destroyed or transferred to other agencies, on a basis of who might have need or interest for them. These decisions were made primarily by Department of Homeland Security and National Security Council staff. As of July 8, no samples remained at NIH; the immediate incident response concluded July 9.

Aug. 4, 2014. 7 of the 279 vials were retained at National Biological Threat Characterization Center (NBTCC), a group within NBACC, for research purposes.

Jan. 13, 2015. 106 of the 279 vials were transferred to the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) for research purposes.

Jan. 15, 2015. 3 of the 279 vials were transferred to the CDC for research purposes.

Jan. 29, 2015. The remaining 163 of the 279 vials were destroyed.

Feb. 24, 2015. The 16 vials transferred to CDC on July 7, 2014, were destroyed by CDC under World Health Organization (WHO) observation.

A summary of which samples went to which agency or facility, and which were destroyed, may be found in Appendix D.

Appendix D. Disposition of Samples

Table 3. Summary of Disposition of the 327 Samples

Retained at NBACC for research purposes	7
Transferred to USAMRIID for research purposes	106
Transferred to CDC for research purposes	3
Transferred to CDC for destruction (including 6 variola virus vials)*	16
Destroyed at NIH	32
Destroyed at NBACC	163
Total	327

* All smallpox virus samples were destroyed under WHO oversight.

Appendix E. Summaries of Other Investigations

Summary of CDC-FBI Investigation/Report (Redacted Report)

A team of CDC (DSAT plus others) and FBI personnel were on the NIH campus from July 7 to 9, 2014. They looked into the discovery of the materials, how the material was secured prior to and after discovery, the security environment in relevant areas, and future actions needed. The team also conducted interviews. They inventoried the samples and transferred some to CDC-Atlanta, witnessed destruction of some at NIH and transferred some to NBACC. They assembled a detailed timeline of events. Significant findings include: the materials were in a location that did not meet the requirements of the Select Agents Regulations (SAR); there were no access logs or inventory of materials in the cold room; and there were "significant vulnerabilities with access control and accountably"; the materials were not properly packaged and transported from Building 29A to Building 13; and the select agent registration submitted by NIH did not include variola virus. The report concludes with an assessment of the root cause as "failure of past NIH and FDA actions to fully identify and account for material labeled as potentially select agents and toxins on the NIH Bethesda campus, specifically the failure to have oversight and accountability for material in a shared storage space".....”were (sic) ownership of the material is not clear or unknown." The report concludes with requests for further information from NIH and requests that certain actions be taken. The matter was referred to the HHS Inspector General, although no action has been taken by HHS.

Summary of the CDC Analysis of the Variola/Alastrim Samples

Within a few days of their discovery, the six presumed variola virus/Alastrim vials were analyzed for the presence of variola virus DNA and tested positive. Samples were studied in tissue culture, and viable virus was found. In addition, full genomic sequences were obtained for each of the samples. The samples labeled Lee and Kim are both identical to a previously known strain in the CDC collection; the samples labeled Yamada are very similar to a known strain; the 2 Alastrim samples were different from one another and have significant differences to all previously sequenced strains. Nothing associated with the samples indicates with any certainty their origin.

Summary of the CDC-ACD ELSW Report
https://www.nih.gov/sites/default/files/research-training/acd-cdc-report-2015.pdf

In July 2014, the CDC-Advisory Committee to the Director established the External Laboratory Safety Workgroup (ELSW). HHS Secretary Burwell charged the group with reviewing laboratory safety practices at NIH and FDA, in addition to CDC. The ELSW conducted a four-day site visit to NIH in February 2015. Their report results from discussions, review of documents, and visits to laboratories. Major findings: The NIH DOHS is a model for other institutions and agencies, and NIH leadership is committed to laboratory safety. Governance structures and committees support a culture of responsibility and accountability. Risk assessment of protocols is done by the IBC and the BSO; this process could be improved. The DOHS director and staff were highly

praised. The Occupational Medicine program is very strong. Reporting of incidents is non-punitive to encourage reporting. Minor suggestions for improvement were made.

Summary of GAO-16-305: High-containment laboratories, comprehensive and up-to-date policies and stronger oversight mechanisms needed to improve safety
https://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/documents/201603GAO.pdf

GAO did this study for Congress in response to safety lapses at federal laboratories in 2014 and 2015. It examines the extent to which agencies have comprehensive and up-to-date policies for biosafety, how they oversee laboratories, and how well recommendations from laboratory safety reviews have been implemented; 15 agencies at 8 departments were assessed. The report also reviewed the 2014 smallpox virus incident. GAO identified 6 key elements of a comprehensive biosafety/biosecurity policy framework: incident reporting; roles and responsibilities; training; inventory control; inspections; adherence to the BMBL. NIH was found to have policies in place for all key elements, although not all policies were up to date. NIH was found to be using inspections to oversee management of hazardous biological agents, but the results were not reported to senior agency and department officials, which GAO considers important. NIH has made progress in implementing recommendations intended to help strengthen its policies and oversight for high-containment laboratories. GAO made recommendations to the Secretary of HHS, and NIH has made changes in response to these. Finally, the GAO report reviewed the 2014 smallpox virus incident, and reached the same conclusions as previous reports; it notes that NIH has made changes to address concerns.

Summary of the House Energy and Commerce Committee Memorandum Report
https://osp.od.nih.gov/wp-content/uploads/BRP-House-EC-Report.pdf

Staff from the Committee investigated the incident and gathered information by written requests and in interviews. They also relied on the CDC-FBI investigation. The report reviewed the details of the smallpox virus incident as well as several related biosafety incidents at federal facilities. In particular, NIH had select agent biosafety events involving the causative agents of plague in 2011 and anthrax in 2012 which ultimately resulted in NIH being placed on a Performance Improvement Plan by CDC-DSAT. There was also an inventory problem involving *Burkholderia* samples in 2008. Major findings of the report: NIH and FDA failed to include smallpox virus in their Select Agent Program Registration in 2003; NIH failed to account for *Bacillus anthracis* spores in an unregistered space in 2012; efforts by NIH to uncover undeclared and unregistered select and toxins agents prior to 2014 were incomplete; the issue of cardboard in the cold room was noted, but not addressed effectively; NIH has a history of questionable handling of historical collections; there are concerns about CDC-DSAT's oversight of NIH compliance with the Federal Select Agent Program; and the HHS Office of Inspector General did not take timely action with respect to CDC referrals concerning the NIH. The report indicates that there are issues that require further investigation including: failure to conduct comprehensive inventories; failure to account for regulated select agents and toxins; failure to

restrict unauthorized access to select agents and toxins; poor enforcement by the Federal Select Agent Program as applied to federal laboratories. The report concludes that there has been a "pattern of recurring issues, of complacency and a lax culture of safety".

Summary of the FDA Internal Investigation and Report
https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM532877.pdf

This investigation was conducted in 2016 and a draft report was provided to NIH staff in September 2016. In addition to reviewing previous reports and existing materials, the FDA interviewed several of its staff with direct knowledge about the incident. The report contains a general description of the incident and a detailed timeline, both of which agree with other reports. Key findings highlighted the following problems that led to the vials not being discovered earlier: lack of security and inventory control of abandoned biological materials; no single individual responsible for the shared cold room storage area; neither FDA nor NIH conducted a complete inventory of all laboratories at the time smallpox was eradicated and all variola virus samples were to be consolidated at CDC; failure to follow Select Agents Regulations for packaging and transporting the samples from building 29A to building 13 (by FDA); delay between discovery of the vials and the notification of appropriate officials (by FDA); and not following best practices to prevent mold growth in the cold storage area. The report outlines corrective actions for FDA and progress taken to date on their implementation.

Appendix F. Biosafety Policies at NIH.

The following links provide access to the various policies discussed in Section 5.3 and Table 1.

Manual Chapter 1340
https://policymanual.nih.gov/1340

Manual Chapter 1340-1
https://policymanual.nih.gov/1340-1

Manual Chapter 3035
https://policymanual.nih.gov/3035

Manual Chapter 3037
https://policymanual.nih.gov/3037

Guidelines and Policies for the Conduct of Research in the Intramural Program at NIH
https://oir.nih.gov/sites/default/files/uploads/sourcebook/documents/ethical_conduct/guidelines-conduct_research.pdf

Potentially Hazardous Biological Materials Management Plan, Parts 1 and 2
https://osp.od.nih.gov/wp-content/uploads/BRP-Hazaradous-Material-Phase-I-Phase-II.pdf

Annual select agent email
https://osp.od.nih.gov/wp-content/uploads/Annual-Notification_-Possession-of-Select-Agents.pdf

SOP 902
https://osp.od.nih.gov/wp-content/uploads/SOP-5-20-16.pdf

PHBM inventory requirement
https://osp.od.nih.gov/wp-content/uploads/BRP-Inventory-Worksheet.xlsx

Registration of pathogens and rDNA research
https://osp.od.nih.gov/wp-content/uploads/BRP-registration-form.pdf

Appendix G. Key Biosafety/Biosecurity Policies of the United States Government

Oversight Measure	Risks Addressed	Description of Oversight	Analysis
Biosafety in Microbiological and Biomedical Laboratories (BMBL), 5th Edition (December 2009) http://www.cdc.gov/biosafety/publications/bmbl5/index.htm	Biosafety risks	**Applies to:** Life sciences research involving infectious microorganisms or hazardous biological materials **Description:** General biosafety practices and biological containment for various classifications (risk groups) of microorganisms and etiological agents	BMBL includes summary statements and biocontainment guidance for research involving many pathogens. BMBL is a guidance document and generally considered the authoritative reference for laboratory biosafety but it is not a regulatory document; compliance is voluntary.
NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (April 2016) http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines	Biosafety risks	**Applies to:** Basic or clinical life sciences research that involves recombinant or synthetic nucleic acid molecules and is conducted at an institution receiving NIH funding for any such research **Description:** Describes roles and responsibilities of institutions and investigators in safely conducting research. Requires institutional review by an IBC with a focus on the concepts of risk assessment, risk group classification of agents, physical and biological containment levels, practices, personal protective equipment, and occupational health. Advised by the NIH Recombinant DNA Advisory Committee.	NIH Guidelines are often used as a model of biosafety guidance by the broader scientific community but compliance is required only by institutions receiving funding from the NIH; compliance may be required as a term and conditions of award by other federal agencies. The scope is limited to research involving recombinant or synthetic nucleic acids. Some IBCs also review and approve non-recombinant pathogen research; however, not all institutions require their IBCs to do so.

Oversight Measure	Risks Addressed	Description of Oversight	Analysis
HHS and USDA Select Agent Program (as of July 2014) http://www.selectagents.gov/regulations.html	Biosecurity (physical and personnel) and biosafety risks	**Applies to:** Biological agents and toxins that have the potential to pose a severe threat to public health and safety, based on a set of criteria. **Description:** Regulates the possession, use, and transfer of select agents and toxins. Overseen by the Federal Select Agent Program. Requires registration of individuals and entities; federal background investigations; federal review of restricted experiments; training; institutional compliance; etc.	Research with pathogens on the select agents and toxins list, is subject to oversight by the SAP. Researchers and institutions performing such studies must receive favorable security risk assessments by the FBI, register with the SAP, receive training on the proper procedures and practices for handling such agents, and abide by other aspects of the regulations. Certain experiments such as those conferring resistance to medical countermeasures would require additional review and approval prior to being conducted
USG Policy for Institutional Oversight of DURC (September 2014) http://www.phe.gov/s3/dualuse/Pages/InstitutionalOversight.aspx	Biosecurity risks, particularly involving misuse of research information, products, and technologies	**Applies to:** Life sciences research conducted at an institution receiving USG funding that involves any of 15 agents that pose the greatest risk of deliberate misuse with most significant potential for mass casualties or devastating effects.	The institutional DURC policy requires federally-funded institutions to establish a system for the identification and oversight of certain pathogen research anticipated to involve any of 7 experimental types. USG DURC policies only apply to research involving 15 pathogens. Institutions may review other studies for DURC potential but are not required to do so.
HHS Funding Framework for Certain GOF studies (August 2013) http://www.phe.gov/s3/dualuse/Pages/HHSh5n1Framework.aspx	Biosafety and biosecurity risks associated with certain GOF experiments involving certain influenza virus strains	**Applies to:** Gain-of-function studies that are reasonably anticipated to generate HPAI H5N1 viruses that are transmissible, and LPAI H7N9 viruses that have increased transmissibility, between mammals by respiratory droplets **Description:** Describes an HHS Department-level review pre-funding review and approval process for certain GOF studies.	Applies only to HHS agencies. Narrowly focused only on specific GOF studies (enhancing mammalian transmissibility) involving two avian influenza viruses; other GOF studies may raise concern and would not be required to be reviewed under this framework.

Oversight Measure	Risks Addressed	Description of Oversight	Analysis
USG Export Control Regulations http://www.bis.doc.gov/index.php/regulations/export-administration-regulations-ear		**Applies to:** Export or release of equipment, software and technology, chemicals, microorganisms, toxins, and other materials and information deemed dual use or strategically important to U.S. national security, economic, and/or foreign policy interests	Comprehensive set of federal regulations that control and restrict the export and release of sensitive equipment, software and technology; chemical, biological, and other materials and information as a means to promote national security interests and foreign policy objectives.
Occupations Safety and Health Administration Regulations https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=10051	Health and Safety risks	**Applies to:** health and safety in the workplace very broadly; most pertinent is sections describing requirements for working with infectious materials	Broad guidance to cover working with blood-borne pathogens and other infectious materials to prevent exposure and infection.
Department of Transportation Regulations https://www.gpo.gov/fdsys/pkg/CFR-2012-title49-vol2/xml/CFR-2012-title49-vol2-subtitleB-chapI-subchapC.xml	Health and safety risks and security of transporting hazardous materials	**Applies to:** transport and packaging of hazardous materials, including infectious agents and toxins. Contains detailed definitions and requirements for packaging and shipping of materials.	Applies only to transport "in commerce", and does not cover movement of infectious agents and toxins within an NIH facility.

10. Acronyms and Abbreviations

BRP	Blue Ribbon Panel
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BSO	Biological Safety Officer
CDC	Centers for Disease Control and Prevention (Atlanta, GA, US)
DHS	Department of Homeland Security
DOHS	Division of Occupational Health and Safety (NIH)
DSAT	CDC Division of Select Agents and Toxins
FBI	Federal Bureau of Investigation
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
IBC	Institutional biosafety committee
NIH	National Institutes of Health
NBACC	National Biodefense Analysis and Countermeasures Center
NBTCC	National Biological Threat Characterization Center
NSABB	National Science Advisory Board for Biosecurity
NSC	National Security Council
PHBM	Potentially hazardous biological materials
rDNA Guidelines	NIH Recombinant DNA Guidelines
RO	Responsible Official (for the Federal Select Agents Program)
SA	Select agent(s)
US	United States
USAMRIID	United States Army Medical Research Institute of Infectious Diseases
USDA	United States Department of Agriculture
USG	United States Government
WHO	World Health Organization