Historical Background Related to BWC, Select Agents and Toxins, High Containment Labs, DURC and GOF

This paper discusses policy events and pathogens, including: (1) prohibitions of bioweapons and biological warfare; (2) high containment laboratories, research with pathogens and biosafety; (3) Select Agent Regulations; (4) Dual Use Research of Concern (DURC); (5) Gain of Function (GOF) research.

Biowarfare and Biological Weapons Prohibitions

In 1925 the Geneva Convention established a prohibition on chemical and biological warfare, following the use of chemical weapons during World War 1. The prohibition is a no-first-use agreement and in kind retaliation or offensive biological research and development was not banned by the protocol.

In 1969 President Nixon declared a unilateral end to the offensive biological weapons program of the United States. All offensive development was halted and stockpiles of biological weapons were to be destroyed.

In 1972 the Biological and Toxin Weapons Convention (BWC) was enacted as an international agreement. The United States became a signatory to the Convention which prohibits the development, production and stockpiling of biological and toxin weapons. There is no international agreement about research on pathogens, including those that might be used as biological weapons because of the dual use nature of the research. The BWC does not prohibit defensive research. Issues related to compliance with the obligations and verification of the BWC remain unresolved.

In 1989 the US passed the Biological Weapons Act which is the implementing legislation in the US. This law established the Biological Weapons statute which is Chapter 10, Title 18 of the US Code. This statute establishes criminal laws related to the development, manufacture, transfer or possession of a biological agent (not just a select agent), toxin or delivery system for use as a weapon. The BWC has country signatories who meet every few years to develop confidence building measures. There will be a meeting this August where gain of function (GOF) research likely will be discussed. GOF research aimed at vaccine development or better surveillance is not prohibited by the BWC. The use of GOF research results for the development of a biological weapon would be prohibited by the BWC. Because offensive and defensive research are not recognizable, the dual use dilemma results.
In 2004 the United Nations Security Council adopted Resolution 1540 to prevent terrorists from acquiring biological weapons. Under this Resolution States are required to: (1) refrain from providing any form of support to non-State actors that attempt to develop, acquire, manufacture, possess, transport, transfer biological weapons and their means of delivery; (2) in accordance with their national procedures, shall adopt and enforce appropriate effective laws which prohibit any non-State actor to manufacture, acquire, possess, develop, transport, transfer or use biological weapons and their means of delivery, in particular for terrorist purposes, as well as attempts to engage in any of the foregoing activities, participate in them as an accomplice, assist or finance them; (3) take and enforce effective measures to establish domestic controls to prevent the proliferation of biological weapons and their means of delivery, including by establishing appropriate controls over related materials and to this end shall: (4) develop and maintain appropriate effective measures to account for and secure such items in production, use, storage or transport; and (5) develop and maintain appropriate effective physical protection measures to protect those biological agents.

Work with Pathogens and High Containment Laboratories

For work on pathogens in general there are guidelines to ensure biosafety. In 1974, the CDC published Classification of Etiologic Agents on the Basis of Hazard. This report introduced the concept for establishing ascending levels of containment that correspond to risks associated with handling infectious microorganisms that present similar hazardous characteristics. Human pathogens were grouped into four classes according to mode of transmission and the severity of disease they caused. A fifth class included non-indigenous animal pathogens whose entry into the United States was restricted by USDA policy.

In 1976 NIH first published the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines). The NIH Guidelines describe in detail the microbiological practices, equipment, and facility safeguards that correspond to four ascending levels of physical containment and established criteria for assigning experiments to a containment level based on an assessment of potential hazards of this emerging technology. The NIH Guidelines establish safety guidelines for research with recombinant DNA and infectious diseases and required NIH funded institutions to have Biosafety Officers and Institutional Biosafety Committees (IBCs). The IBCs operate at the institutional level and examine research protocols, expertise, potential hazard and containment plans. Many institutions assign IBCs broader responsibility for overseeing research with pathogens and recombinant infectious agents.

The NIH Recombinant DNA Advisory Committee (RAC) provides expert advice on issues related to the Guidelines and changes are published for comment in the Federal Register. The NIH Office of Biotechnology Activities provides resources and training on the role and responsibility of IBCs. The NIH RDNA Guidelines and the Select Agent regulations specify reporting requirements for significant problems, violations, and research related accidents and illnesses. The HHS CDC and USDA APHIS administer the select agents and toxins regulations for facilities that possess, use or transfer them.
In 1984 the first edition of the *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) manual was published by the NIH, CDC and USDA. Now in its 5th Edition the BMBL provides the safety guidelines for working with microorganisms. The BMBL describes the appropriate containment levels for pathogenic microorganisms. The BMBL does not have the force of regulation and the document is considered a work in progress that changes over time based on new information.

Biosafety level 2 (BSL-2) is appropriate for handling moderate-risk agents that cause human disease of varying severity by ingestion or through percutaneous or mucous membrane exposure. Biosafety level 3 (BSL-3) is appropriate for agents with a known potential for aerosol transmission, for agents that may cause serious and potentially lethal infections and that are indigenous or exotic in origin. Exotic agents that pose a high individual risk of life-threatening disease by infectious aerosols and for which no treatment is available are restricted to high containment laboratories that meet biosafety level 4 (BSL-4) standards.

Laboratories with BSL 3 and 4 capacity are designed to maximize the safety of laboratory staff and minimize potential pathogen escape from the laboratory. These laboratories follow biosafety procedures to protect personnel working in the laboratory and the outside community. High containment laboratories are subject to federal laws, regulations and voluntary standards to maximize safety and security for work with dangerous agents. The NIH which has funded additional research laboratories built to BSL 3 and 4 standards, has terms of award for construction, and research grants that include a requirement for compliance with the BMBL standards.

In February 2013 the RAC recommended additional enhancements for research on mammalian transmissible HPAI H5N1 virus to supplement the biosafety requirements for HPAI H5N1 that are already delineated in the NIH guidelines. The enhancements include changes to the facility and biosafety equipment and practices.

The ASM has testified before Congress, the Interagency Task Force on Optimizing Biosafety, has filed an amicus curiae describing safety features of high containment laboratories, and participated in numerous congressional and government policy discussions regarding biosafety and biosecurity issues. A listing of ASM statements is provided separately, including recommendations to improve biosafety. The ASM position has been that oversight and guidance are essential and that a strength of the current oversight is that NIH, CDC and APHIS have scientific and public health expertise and are knowledgeable and committed to the protection of public health and safety. After considerable deliberation in the 1980s and 90s Congress decided that NIH, CDC and USDA (plant and animal pathogens) should have responsibility for recombinant DNA research oversight and regulation of etiologic agents and select agents and toxins because these agencies have scientific and public health expertise and have access to the broader scientific and public health communities. In 2002 the Department of Homeland Security was established and was given a role with respect to risk assessment of select agents and toxins for purposes of developing countermeasures.
Much but not all of the research in BSL 3 and 4 facilities involves select agents and toxins. Local IBCs oversee research involving all pathogens studies in high containment labs and bloodborne pathogen regulations and CLIA regulations also cover work with pathogens.

Work with dangerous pathogens is performed on a daily basis in US and international laboratories and has been since the inception of the field of microbiology in the late 1800s. Public health laboratories, research laboratories and commercial facilities regularly work with a range of potentially deadly human and animal pathogens. This research is aimed at the protection of human and animal health. There also is extensive work on plant pathogens aimed at preventing blights and adverse ecological impacts.

Researchers funded by the USG daily work to discover diagnostics that can identify the pathogens that cause specific diseases, therapeutics that can diminish the impact of those diseases, and vaccines that can reduce the incidence of infectious diseases. Clinical laboratories isolate pathogens from ill patients every day, many of which potentially cause deadly diseases, so that appropriate treatments can be instituted. Even in the United States the agents that cause plague and anthrax are sometimes isolated. The only pathogens that have been eliminated and are no longer isolated anywhere in the world are the viruses that cause smallpox and Rinderpest.

Besides the constraints of the Select Agent Regulations for specific pathogens described below there are additional restrictions regarding pathogenic microorganisms. The shipment of infectious agents is regulated by the DOT (interstate), the Department of Commerce (exports), the CDC (imports) and the USDA virus, serum toxin act, and IATA for international shipments.

In 1936 the US Congress restricted FMD virus to offshore labs. It has been restricted to Plum Island since then. A new DHS laboratory is being constructed to replace Plum Island.

After the eradication of smallpox in the mid-1980s the possession and conduct of research on live variola has been restricted. The World Health Organization (WHO) Advisory Committee on Variola Virus Research (ACVVR), which was established in 1999, oversees all research using live variola virus. Repositories of live Variola virus are currently maintained only at two WHO collaborating centres: the Centers for Disease Control and Prevention, Atlanta, United States of America, and the State Research Center of Virology and Biotechnology VECTOR laboratory, Novosibirsk, the Russian Federation.

The National Institutes of Health is a major funding source for academic research on pathogenic microorganisms. NIH funding for infectious disease research was expanded following the 2001 anthrax bioterrorism attacks to increase preparedness against biothreat agents. Funding to protect against bioterrorism increased from 25 million in 2001 to 1.7 billion by 2003 and remains at about that level in 2014. The NIH program was initially
designed to foster basic research on microbes with bioterrorism potential, and the specific and non-specific host defense mechanisms against these agents plus applied/translational research for the ultimate production of new/improved diagnostics, vaccines, and therapies. Besides using the increased funds for studies on biothreat agents, the NIH has leveraged the programs so as to fund studies on a broad spectrum of emerging and reemerging infectious diseases including influenza, SARS, MERS, TB, Ebola, antibiotic resistant bacteria, etc. Today the NIH has an integrated program on emerging and reemerging infectious diseases that includes funding for basic pathogenesis studies on both naturally occurring diseases and those that might be intentionally introduced.

Select Agent Regulations

In 1995 an incident in the US involving unlawful acquisition of plague by mail order prompted the Department of Justice to testify before Congress that there were no controls on biological agents. At the time, there were no requirements for work or transfer with agents and toxins eventually to become known as “select”. The ASM testified at the hearing which examined the lack of controls on the transfer of highly dangerous agents.

In 1996, Congress passed the Antiterrorism and Effective Death Penalty Act of 1996 (Public Law 104–132, April 24, 1996). Section 511 of the Act required the Secretary of Health and Human Services (HHS) to issue regulations to govern the transport of certain biological agents and toxins with the potential to pose a severe threat to public health and safety. Section 511 resulted in regulations for the transfer of 36 select agents and toxins. The regulations went into effect in 1997.

The HHS Secretary delegated authority to regulate select agents and toxins to the Centers for Disease Control and Prevention (CDC). To ensure that the transfer of these agents was carried out only by and between responsible parties, CDC required that laboratories transferring select agents be registered and report each transfer. The list included some agents that could affect both humans and animals (for example, Bacillus anthracis and Francisella tularensis), but did not include those affecting only animals and plants. In drawing up the list, groups of experts from inside and outside the government focused on agents and toxins that had been weaponized by the United States and biological weapons programs prior to the advent of the BWC or those that were considered to have the greatest potential for weaponization. The legislative language says the Secretary shall by regulation establish and maintain a list of each biological agent and toxin that has the potential to pose a severe threat to public health and safety.

Like the Biological Weapons Act of 1989, the 1996 law said that individuals and groups with legitimate objectives should continue to have access to such agents for clinical and research purposes. ASM supported this insertion of this language.

In 1998 the Clinton Administration expressed concern that the possession of a biological agent is not a crime under federal law, even if the possessor is a felon, fugitive from justice or has no scientific training. In 1998, Janet Reno, then Attorney General, testified that mere possession of a biological agent is not a crime under federal law unless there is
proof that it is intended as a weapon, notwithstanding the existence of factors such as lack of scientific training, mental instability, or felony record. In 2000 the Clinton Administration drafted a bill and Congress introduced legislation to regulate possession of select agents. The bill was introduced as the 21st Century Crime bill in 2000. The bill was under discussion in Congress in September of 2001. Many of its provisions were picked up as legislation was introduced following the anthrax incidents.

In the wake of the terrorist attacks of September 11, 2001, and the *Bacillus anthracis* mailings in October of 2001, Congress passed legislation that substantially expanded the scope of the Select Agent Program. The *USA PATRIOT* Act of 2001 (Public Law 107–56, October 26, 2001), Section 817 expanded and amended Chapter 10 Title 18 of criminal law prohibiting the knowing possession of a biological agent, toxin or delivery system of a type or in a quantity that under the circumstances is not reasonably justified by a prophylactic, protective, bona fide research or other peaceful purpose. The language exempted naturally occurring agents.

The ASM was involved with the Congress in inserting language protecting research and exempting naturally occurring agent. The Act also made it a criminal offense for restricted persons to possess select agents and toxins and barred aliens from countries designated as supporting terrorism from possession within the US.

The 2002 Public Health Security and Bioterrorism Preparedness and Response Act added two new criminal offenses to the BW statute for knowingly unregistered for possession and knowingly transferring a select agent to an unregistered person.

In 2004, the Intelligence Reform and Terrorism Prevention Act imposed stiff penalties on the possession of terror weapons including smallpox and amended the law for variola virus later clarified by the Department of Justice to mean the agent that causes smallpox. Section 6906 of the 2004 law makes it a crime to knowingly produce, engineer, synthesize, acquire transfer directly or indirectly receive, possess, import, export, or use or possess and threaten to use variola virus. Work conducted by or under the authority of the HHS is exempted. The DOJ stated that the law does not apply to orthopoxviruses. Legislation has been introduced in Congress to codify the WHO requirements for the distribution, handling and synthesis of variola virus DNA to prevent reengineering of the live virus from DNA fragments or parts of the variola virus genome.

In June of 2002, Congress passed the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Public Law 107–188, June 12, 2002). The Act required registration for possession of select agents and toxins and expanded the list to include plant and animal and overlap agents. The law required the implementation of safeguards and security requirements and that registered facilities control access to select agents and toxins and clear the names of persons with access with the Department of Justice using criminal, immigration and national security databases available to the federal government to ensure that no restricted persons have access. The Act also gave the U.S. Department of Agriculture (USDA), through its Animal and Plant Health Inspection Service (APHIS), the authority to regulate the possession, use, and transfer of BSAT materials that relate to plant and animal health and products, complementing the
authority granted to CDC for human pathogens. The regulation of select agents and toxins is thus a shared federal responsibility involving HHS/CDC, USDA/APHIS, and the Department of Justice (DOJ). The Bioterrorism Act has been implemented through a series of regulations; the final regulations—42 CFR 73 (human pathogens), 9 CFR 121 (animal pathogens), and 7 CFR 331 (plant pathogens)—became effective in the spring of 2005.

The intent of the legislation was to ensure that personnel with access to select agents be cleared by the FBI and have the appropriate training and skills to handle dangerous pathogens on the list of select agents and toxins and that entities doing work with select agents and toxins have appropriate facilities in which to contain and dispose of these agents. Congress was careful to use the word “reasonable” regulations for safety, security, personnel screening, access controls, incident response requirements and inspections. The legislation called for regulations commensurate with the risk.

The ASM was extensively involved in the development of the select agents and toxins legislation and regulations and worked closely with Congress and policymakers in the Executive Branch and the agencies. The ASM has commented on all the changes that have been proposed and made to the regulations since 1996 including changes to the list of agents and toxins that are regulated.

In 2009 the Interagency Task Force on Select Agents and Toxins asked the ASM to convene a meeting at ASM to discuss revising and stratifying the list of select agents and toxins.

In 2012, the CDC and APHIS published final changes following the release of 2010 Executive Order 13546 (working through existing statutory authorities) which directed a subset of the select agent and toxin list as Tier 1, a category that presents the greatest risk of deliberate misuse with the greatest potential for mass casualties or devastating effects to the economy, critical infrastructure or public confidence. There are 8 HHS Tier 1 select agents and toxins: Ebola, F. tularensis, Marburg, variola major and minor, Yersinia, Bot nerutoxin and neurotoxin producing species of Clostridium, B. anthracis Burkholderia mallei, and Burkholderia pseudomallei. Based on their significant public health risk, SARS Cov, Lujo and Chapare virus were added to the list. Some agents were removed including herpes B, Clostridium perfringens, epsilon toxin, Coccidioides posadasii, and C. immitis, E. Eencephalitis (S American type).

It should be noted that in constructing the select agent and toxin list there is a public process for adding and deleting an agent and for determining safety. New agents have been added to the list using criteria in the legislation.

In 2005, there was concern about the reconstructed 1918 influenza virus. HHS proposed that it be added to the list of select agents. The SAT regulation is the only federal regulation that controls by regulation the safe handling of a new infectious agent that could pose a serious threat. The criteria specified in the legislation includes: degree of contagiousness, method of transfer, availability and effectiveness of drugs and immunizations and any other criteria, including needs of children and vulnerable...
populations. CDC looks at genetic material and there are exemptions and exclusions in the regulations. The legislation and regulations have been careful not to impede diagnostic testing and response to outbreaks.

One of the issues with using a broad definition of pathogens to cover future developments and not a list is that all labs and pathogens would be regulated. Regulations cannot be written for future developments, scenarios and the unknown. The conditions for work with select agents are subject to regulatory control but the research is not restricted, nor is it considered legitimate or not legitimate. There is a section in the regulations, 73.10c for restricted experiments; currently, they are the same ones that are in the RDNA guidelines.

According to the CDC, as of July 1, 2014, there are 324 entities registered with Federal Select Agent Program for possession, use, or transfer of select agents and toxins (284 are registered with CDC and 40 are registered with APHIS). These include the following types of laboratories: Government (non-Federal, state and local laboratories) 34%; Academic 30%; Government (Federal) 15%; Commercial (publicly owned) 15%; and Private (privately owned) 6%. There are 1131 of BSL-3 laboratories maintained by 255 entities registered with the Federal Select Agent Program (not all registered entities have a BSL-3 laboratory. There are currently 11,034 individuals with authorized access to these laboratories.

The ASM has sent numerous alerts to members urging compliance with all the SAT regulations and to act responsibly and ethically to make certain that biosafety and biosecurity are ensured when working with dangerous pathogens regardless of whether they are designated as select agents.

Dual Use Research

While the Select Agent Regulations sought to protect a limited number of pathogens from being acquired by those who might misuse them to do harm, these Regulations did not attempt to limit the distribution of scientific knowledge. Shortly after the anthrax attacks of 2001, however, concern was expressed that the knowledge generated from research in the life sciences could be misused to do harm. Advances in the life sciences, especially in molecular biology and informatics, and the potential for misuse of scientific research raise the possibility that an act of terrorism could involve biological agents or that science could be misused for biowarfare. As stated in a 2006 report of the National Research Council: “For millennia, every major new technology has been used for hostile purposes, and most experts believe it naive to think that the extraordinary growth in the life sciences and its associated technologies might not similarly be exploited for destructive purposes...as with all scientific revolutions, there is a potential dark side to the advancing power and global spread of these technologies.” The potential for the misuse of legitimate scientific knowledge to do harm has become known as the "dual-use" dilemma.

To illustrate this dual use dilemma, in 2001 at the time of the anthrax attacks, the American Society for Microbiology (ASM) had posted information about anthrax at its
was aimed at advancing the science that could help develop diagnostics, therapeutics, and vaccines for medical uses. Questions, however, were raised about whether this information should be deleted because of its potential misuse. The ASM took the position that “The principle right now is one of openness in science--if someone wants to publish a legitimate research paper we’re not going to be the censor.” (Ronald Atlas--President elect ASM 2001). Arthur Caplan, a bioethicist at the University of Pennsylvania took the opposite position and was quoted as saying: “We have to get away from the ethos that knowledge is good, knowledge should be publicly available, that information will liberate us...Information will kill us in the techno-terrorist age, and I think it's nuts to put that stuff on Web sites.”

In response to the controversy the ASM asked the National Academies to address the question of scientific publishing in an age of terrorism. The National Academies together with the Center for International Strategic Studies convened a symposium that discussed the dual use dilemma and what should be published. The Symposium did not reach any conclusions.

The ASM subsequently convened a meeting of editors and publishers to address this matter. That group issued a statement that said: (1) “…there is information that, although we cannot now capture it with lists or definitions, presents enough risk of use by terrorists that it should not be published.” (2) “The integrity of science must be maintained--Science is too important to jeopardize it.” (3) “Editors and scientists will act responsibly without government intervention.” (4) “Each field is different and needs specific ethical practices to protect against its misuse.” And (5) “We will constrain information we consider could do harm.”

The Interacademy Panel representing the world’s national academies issued the following statement on biosecurity: “In recent decades scientific research has created new and unexpected knowledge and technologies that offer unprecedented opportunities to improve human and animal health and environmental conditions. But some science and technology can be used for destructive purposes as well as for constructive purposes. Scientists have a special responsibility when it comes to problems of "dual use" and the misuse of science and technology.” This suggests that there is “forbidden knowledge” and that some information in the life sciences should be classified or shared on a limited basis.

The US National Academies convened a committee chaired by Gerry Fink to address the dual use dilemma and to propose a system for oversight of life sciences research and communication that could reduce the threat of misuse of scientific knowledge. The “Fink Committee” issued a report entitled: Biotechnology Research in an Age of Terrorism: Confronting the Dual Use Dilemma. The report embraced the principle that government regulations work best when areas of concern can be objectively defined and that one of the defining characteristics of potential dual use research in biotechnology is the inability to establish “bright lines” around the areas of concern—hence the need for self-regulation and extensive consultation between those trying to define the sphere of concern and those
in the research community who can help figure out what should appropriately be constrained.

The Fink Committee defined dual use research as: “Research that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied by others to pose a threat to public health and safety, agricultural crops and other plants, animals, the environment, or materiel.” It called for the development of an architecture to help protect the life sciences scientific community against the potential misuse of such research. It proposed a bottom up approach aimed at helping reduce the threat of misuse of the life sciences while protecting scientific enquiry and communication to the maximum extent possible. The aim was to build upon the previous 1982 NAS Corson report that dealt with the physical sciences.

For the near term the Committee considered microbial pathogens and toxins as the primary threat. The Committee identified seven classes of “experiments of concern” that illustrate the types of endeavors or discoveries that will require review and discussion by informed members of the scientific and medical community before they are undertaken or, if carried out, before they are published in full detail. These classes were process rather than organism based. Research in these seven areas was not to be categorically prohibited. According to the recommendation of the Fink Committee, these seven classes of experiment “that will require review and discussion … before they are undertaken or, if carried out, before they are published…” The criteria included experiments that would demonstrate how to render treatment or detection measures ineffective, increase the pathogenicity, transmissibility or host range of a pathogen, or make it easier to develop a biological agent into a weapon of mass destruction. The Fink Committee also foresaw that future advances in the biomedical sciences might require a few additional criteria to determine, for example, whether an experiment would ease access to dangerous pathogens.

To help develop and oversee the governance of research that might readily be misused the Fink Committee recommended the creation of a National Science Advisory Board for Biodefense (NSABB) within the Department of Health and Human Services to provide advice, guidance, and leadership for the system of review and oversight we are proposing. The Committee was to be composed of scientists and security experts. The Committee envisaged that the NSABB would act like the RAC and provide the necessary guidance to protect science and the public.

The US Government accepted the recommendation to establish the NSABB but renamed it the National Science Advisory Board for Biosecurity. Although the US government established the National Science Advisory Board for Biosecurity (NSABB) in 2003, its first meeting was in June 2005 after two years of preparations. The newly formed NSABB reworded the definition of dual use research, calling it Dual Use Research of Concern (DURC). The criteria put forth by the NSABB in 2007 for DURC was: Research that likely could: (1) Enhance the harmful consequences of a biological agent or toxin; (2) Disrupt immunity or the effectiveness of an immunization without clinical and/or
agricultural justification; (3) Confer to a biological agent or toxin, resistance to clinically and/or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitate their ability to evade detection methodologies; (4) Increase the stability, transmissibility, or the ability to disseminate a biological agent or toxin; (5) Alter the host range or tropism of a biological agent or toxin; (6) Enhance the susceptibility of a host population; or (7) Generate a novel pathogenic agent or toxin or reconstitute an eradicated or extinct biological agent.

Although the Fink Committee had envisaged that the NSABB would work in a way analogous to the Recombinant Advisory Committee (RAC), i.e. that it would consider specific cases of potential DURC and make recommendations that would set precedent and offer guidance to the community, the committee was not initially tasked with doing specific reviews. Thus, much of the work performed by the NSABB was abstract and not readily applicable to specific research of concern.

In 2005 a research team from the US Armed Forces Institute of Pathology submitted a paper for publication in Science giving the sequence of the influenza virus that had caused the 1918 pandemic called the Spanish Flu. Just one day before Science went to press with the Spanish influenza paper, the US Department of Homeland Security ordered a review of the publication by the NSABB. Members were polled and approved the paper within a day. Clearly a thorough review of risks and benefits could not have been done in such a short time, so the scientific basis for the NSABB's approval remains obscure. The only concrete step the NSABB took was to suggest the addition—in a ‘note added in proof’ to the Science paper—of information on public-health benefits of the reconstructed Spanish influenza virus. Instead of critically assessing the benefits, the NSABB provided an ex post justification of the project.

In 2011, the NSABB again would face the question of specific publication of research results—this time involving research that showed which mutations might make the avian influenza virus H5N1 transmissible from human to human. The gain of function research (GOF) funded by the National Institutes of Health had been conducted in the Netherlands by Ron Fouchier and in Wisconsin by Yoshihiro Kawaoka. Fouchier's team used a combination of genetic engineering and serial infection of ferrets to develop a mutant H5N1 virus that could spread among the animals without direct contact. Kawaoka's group used a slightly different approach and created an H5N1-H1N1 chimera virus that was likewise capable of airborne spread in ferrets.

Shortly before the two studies were to be published, the NSABB considered whether publishing the full details of the studies could lead to the release of a dangerous virus. The journals (Science and Nature) and the authors agreed to postpone publication pending the recommendation of the NSABB. The board recommended in December 2011 that key details be stripped from the papers before publication. But after the authors provided additional information and made some clarifications in their manuscripts, the board in March 2012 consented to publication of the full versions of both, although the vote on Fouchier's report was not unanimous. Kawaoka's study was published in May
2012 and Fouchier's followed in June. Since then, several other influenza GOF studies have been published without review by the NSABB.

In 2013 the editors of the *Journal of Infectious Diseases* faced the dilemma of what to do about a request from authors of a manuscript on a new strain of botulism causing bacteria that they be allowed to withhold some critical information so that the study information not be misused. The request was based on the fact that there was no known antitoxin for the newly discovered toxin. The journal permitted the redaction of information that is normally considered essential for publication. This may have offered protection against misuse but it also may have been a setback for discovering countermeasures for this toxin; it also meant that the results could not be confirmed by others since omitting details meant the studies could not be repeated. As pointed out following the decision to redact information from this journal publication by Arutro Cassadeval and coauthors in a 2013 editorial in the journal *mBio*: “The publication of scientific information that derives from dual use research of concern (DURC) poses major problems for journals because it brings into conflict the benefits of free access to data and the need to prevent misuse of that information by others.”

In March 2012 the USG issued a policy for the oversight of DURC research of concern which was implemented in August of 2013. The policy established a federal review of USG funded or conducted research with certain high consequence pathogens and toxins for their potential to be DURC in order to mitigate risks and to collect information to inform oversight. The USG has sought to preserve the benefits of research while minimizing risk of misuse of the research. The policy applied to 15 listed pathogens and toxins (the Tier 1 list) and takes into consideration risky categories of experimentation.

In February 2013 the USG requested comments on a proposed USG policy for institutional oversight of life sciences dual use research of concern which established certain categories of life sciences research at institutions that accept federal funding for such research. The policy also focused on the 15 microorganisms and toxins of most concern as possible high consequence agents and restricted DURC consideration to the 7 categories of research activities of most concern.

The institutional policy is not yet final. It seems clear that the USG in restricting DURC to Tier 1 agents involving risky experiments, sought to limit the impact of the policies on research.

**Gain of Function Research**

The research that increased the transmissibility of H5N1 and other avian flu viruses in mammals not only raised DURC questions related to the dissemination of the research knowledge gained from the studies, but also raised serious questions as to whether such research was safe and ethical. While the debate about whether the research results should be published raged in 2012 the broader question as to whether the research should have been performed at all led the research community to declare a temporary self-imposed moratorium on continuing GOF research on influenza viruses. This voluntary pause on
any research involving highly pathogenic avian influenza H5N1 viruses leading to the generation of viruses that are more transmissible in mammals was supposed to last 60 days during the winter of 2012. But it went on well beyond that. In the summer of 2012, the U.S. Government proposed an indefinite continuation of the moratorium on gain-of-function studies with H5N1 viruses that could affect mammalian virulence and transmissibility until a consensus emerged on what type of experiments should be done and the level of containment that should be imposed. The research community adhered to this request.

On December 17 and 18, 2012 the National Institutes of Health organized an international consultative workshop on Gain-of-Function Research on Highly Pathogenic Avian Influenza H5N1 Viruses. Although some thought that this would be the first step leading to a broader dialog on the ethics and safety of such research the US Government indicated that it would issue a framework for overseeing approval of future GOF research that would ensure that the short term benefits outweighed the risk.

In February 2013 the HHS published a Framework to guide funding decisions on proposals for research anticipated to generate HPAI H5N1 viruses that are transmissible among mammals by respiratory droplets which outlined a review process that takes into account benefits and biosafety and biosecurity risks and mitigation of risk pertinent to the proposed research. In February 2013 HHS also finalized changes to the RDNA Guidelines for research with HPAI H5N1. The ASM provided comments on both policies and recommended changes in the funding Framework.

It is not clear how the Framework has worked. What is clear is that the research resumed and expanded to other viruses, including H7N9 and H1N1, and that the controversy about the ethics and safety of such research intensified as the results of each new study was revealed.

Marc Lipsitch has argued that experiments that render H5N1 more contagious in mammals are too risky and that other research approaches can unlock the mysteries of flu transmissibility without risking the release of a potential pandemic virus. Rich Roberts has argued that such GOF research is unethical. In July 2014 Lipsitch led a group of researchers known as the Cambridge Group to issue a consensus statement which held that "Laboratory creation of highly transmissible, novel strains of dangerous viruses, especially but not limited to influenza, poses substantially increased risks." The Cambridge Group has proposed a pause in such research. Others including the Royal Society have called for a new moratorium on GOF research.

In opposition to the Cambridge Group which is seeking to limit research on dangerous microorganisms, Vincent Racaniello has organized a group called Scientists for Science which points to the benefits that can be gained by GOF research and other research on potentially dangerous pathogens. This group is calling for a neutral party such as the National Academies of Science or the American Society for Microbiology to foster a discourse on GOF function research.
The ASM is supportive of efforts that would lead to defining the sphere of concern regarding GOF function research and a process for oversight that takes into account the benefits and the potential risks.
Links to ASM Statements and Testimony

Biological Weapons Legislation

October 9, 2001 - Biological Weapons Control Testimony: Recommendations for Federal Funding of Public Health Activities
On October 9, 2001, Dr. Michael Osterholm, Director of Center for Disease Research and Policy, University of Minnesota, and Chair of the PSAB Committee on Public Health, testified before the Senate Committee on Health, Education, Labor, and Pensions, for a hearing on Effective Responses to the Threat of Bioterrorism. His testimony described the budget recommendations of a Working Group on Bioterrorism Preparedness, including the American Society for Microbiology, for public and private laboratories, hospitals, and federal, state and local public health agencies to effectively recognize and respond to the threat of bioterrorism.

November 6, 2001 - Senate Judiciary Subcommittee on Technology, Terrorism and Government Information


June 25, 2002 - ASM Testimony on the Department of Homeland Security
Dr. Ronald Atlas, President of the American Society for Microbiology presented testimony before the House Energy and Commerce Subcommittee on Oversight and Investigations at a hearing to consider the creation of the Department of Homeland Security (DHS).

July 9, 2002 - ASM Testimony on the Department of Homeland Security
Dr. Gail Cassell, Chair of the Public and Scientific Affairs Board presented testimony on the establishment on the Department of Homeland Security.

ASM sent a letter to Representative W. J. "Billy" Tauzin (R-LA) to commend the bipartisan recommendations and provisions of the House Energy and Commerce Committee for the Department of Health and Human Services (DHHS) in HR 5005, which establishes the Department of Homeland Security (DHS).

ASM sent a letter to Representative Armey (R-TX) endorsing the recommendations and provisions of the House Energy and Commerce Committee Proposal on Homeland Security Legislation.
American Society for Microbiology

July 30, 2002 - Letter to Senator Joseph Lieberman (D-CT) Regarding Homeland Security Amendment

August 23, 2002 - ASM Recommendations on Biodefense Research Funded by the National Institute of Allergy and Infectious Diseases
ASM Sent a letter to the House Appropriations Subcommittee on Labor, Health and Human Services and Related Agencies Biodefense Research Supported by the NIAID.

September 24, 2002 - Letter to Senator Phil Gramm (R-TX) Regarding Homeland Security

On October 10, 2002 - ASM Testimony: Conducting Research During the War on Terrorism: Balancing Openness and Security
Dr. Ronald Atlas, President of ASM testified before the House Committee on Science at a hearing on "Conducting Research During the War on Terrorism: Balancing Openness and Security."

June 16, 2005 ASM Presentation at the Biological Weapons Convention Meeting, Geneva
The ASM presentation on the Professional Responsibilities of Scientists at the Biological Weapons Convention Meeting of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction in Geneva with comments from the International Union for Microbiological Societies.

November 4, 2005 - ASM Comments on the Biodefense and Pandemic Vaccine and Drug Development Act of 2005
The ASM sent a letter to the Senate Subcommittee on Bioterrorism and Public Health Preparedness commenting on Section 3, the Biomedical Advanced Research and Development Agency (BARDA), in the Biodefense and Pandemic Vaccine and Drug Development Act of 2005 (S. 1873)

December 5, 2005 - ASM Statement on Pandemic Influenza Plan
The ASM sent a letter to Michael O. Leavitt, Secretary of Health and Human Services commenting on the Pandemic Influenza Plan.


July 13, 2010 - ASM Comments on the WMD Prevention and Preparedness Act of 2010
ASM sent comments to the House Committee on Homeland Security commenting on the WMD Prevention and Preparedness Act of 2010 (HR 5498).
August 31, 2010 - ASM Invited to Testify before Federal Biosecurity Panel
The ASM Public and Scientific Affairs Board was invited to present comments on August 31 at
the meeting of the Federal Experts Security Advisory Panel (FESAP).

June 8, 2012 - ASM Supports Funding for BARDA
The ASM signed onto a letter sent to Congress supporting Biomedical Advanced Research and
Development Authority (BARDA) funding. The letter requested at least $547 million for Fiscal
Year (FY) 2013, the level requested by the Administration.

Select Agents

July 11, 2002 - Possession of a Select Agent
ASM submitted comments to the Centers for Disease Control and Prevention on the July 2,
Federal Register notice on proposed data collections for notification of possession of a select
agent.

July 23, 2002 - ASM Submits Points to Consider and Recommendations to the Centers for
Disease Control and Prevention Regarding Select Agents and Toxins
ASM submitted points to consider and recommendations for implementation of Title II, Enhancing
Controls and Dangerous Biological Agents and Toxins to the Centers for Disease Control and
Prevention.

September 13, 2002 - ASM Comments on CDC Revision to List of Select Agents and Toxins

January 31, 2003 - ASM Comments to the CDC on the Interim Final Rule on the Possession, Use
and Transfer of Select Agents and Toxins

February 15, 2003 - Statement of Journal Editors and Authors Group on Scientific Publishing and
Security

October 23, 2003 - ASM Letter on the Implementation of the Select Agent Rule
The ASM sent a letter to Ann Veneman, Secretary of the Department of Agriculture regarding
implementation of the Interim Final Rule 7 CFR Part 331; 9 CFR Part 121 Possession, Use and
Transfer of Biological Agents and Toxins.

December 19, 2005 - ASM Comments on Possession, Use, and Transfer of Select Agents and
Toxins—Reconstructed Replication Competent Forms of the 1918 Pandemic Influenza Virus
Containing Any Portion of the Coding Regions of All Eight Gene Segments
ASM commented on the interim final rule published in the October 20, 2005 Federal Registered
on the reconstructed replication competent forms of the 1918 pandemic influenza virus containing
any portion of the coding regions of all eight gene segments.

September 8, 2009 - ASM Comments on the Proposed Addition of SARS-CoV to the List of
Select Agents and Toxin
ASM commented on the proposal to add SARS associated Coronavirus (SARS-CoV) to the list of HHS select agents and toxins, published in the July 13, 2009, Federal Register, Vo. 74, No. 132.

August 19, 2010 - ASM Comments on the Changes to the HHS List of Select Agents and Toxins
The ASM sent comments to the Centers for Disease Control and Prevention responding to the July 21, 2010 Federal Register Notice, "Public Health Security and Bioterrorism Preparedness and Response Act of 2002; Biennial Review and Republication of the Select Agent and Toxin List."

August 30, 2010 - ASM Comments on the Proposed Changes to the APHIS List of Select Agents and Toxins
The ASM sent comments to APHIS on the Federal Register notice, "Agricultural Bioterrorism Protection Act of 2002; Biennial Review and Republication of the Select Agent and Toxin List; Reorganization of the Select Agent and Toxin List."

December 1, 2011 - ASM Comments on Proposed Changes to the CDC List of Biological Agents and Toxins
The ASM sent comments to the Department of Health and Human Services (DHHS) on the October 3 Notice of Proposed Rulemaking which requested input on the proposed changes to the DHHS list of biological agents and toxins that have potential as severe threats to public health and safety.

December 1, 2011 - ASM Comments on Proposed Changes to the APHIS List of Biological Agents and Toxins
The ASM sent comments to the Animal and Plant Health Inspection Service (APHIS) on the October 3 Notice of Proposed Rulemaking which requested input on the proposed changes to the USDA list of biological agents and toxins that have potential as severe threats to public health and safety.

RDNA

June 6, 2007 - ASM Comments on Research Involving Recombinant DNA Molecules
The ASM sent comments to the National Institutes of Health Office of Biotechnology Activities about the Federal Register Notice, "Recombinant DNA Research: Proposed Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)."

April 9, 2009 - ASM Comments on Revisions to the NIH Guidelines for Research Involving Recombinant DNA Molecules
The American Society for Microbiology submitted comments on the proposed revisions to the NIH Guidelines for Research Involving Recombinant DNA Molecules, published in the March 4, 2009 Federal Register.
January 14, 2010 - ASM Comments on the Screening Framework Guidance for Synthetic Double-Stranded DNA Providers
The ASM submitted comments to the Department of Health and Human Services on the November 27, 2009 Federal Register notice on the Screening Framework Guidance for Synthetic Double-Stranded DNA Providers.

May 20, 2010 - ASM Statement on JVCI Paper on Synthesizing DNA Genome
March 25, 2013 - ASM Comments on NIH Recombinant DNA Molecules Guidelines
The ASM sent comments to the NIH's Office of Biotechnology Activities regarding changes to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

Laboratories/Biosafety

September 5, 2007 - ASM Files Amicus Brief on the Need and Safety of BSL 4 Laboratories in the US
The ASM filed an Amicus Curiae brief in August, which provided information about scientific matters related to the need and safety of Biosafety Level 4 laboratories.

October 4, 2007 – ASM Comments on Laboratory Biosafety
ASM sent a letter to the House Energy and Commerce Committee Subcommittee on Oversight and Investigations commenting on biosafety and biocontainment laboratories in the United States.

September 23, 2009 - ASM Testifies on Federal Oversight of High Containment Biolaboratories
Dr. Ronald Atlas, Cochair of the Public and Scientific Affairs Board Committee on Biodefense testified before the Committee on Energy and Commerce Subcommittee on Oversight and Investigations on Federal Oversight of High Containment Biolaboratories.

2006 - Survey for Determining the Location, Capacity, and Status of Existing and Operating BSL-3 Laboratory Facilities within the United States (2005)
In October 2004, the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH) partnered with the American Society of Microbiology (ASM) to conduct a brief survey of academic, biotechnology, and pharmaceutical facilities in the United States (US) on the location, capacity, and status of existing and operating US laboratory facilities that incorporate Biosafety Level 3 (BSL-3) containment.

Dual Use

October 20, 2010 – ASM Presentation before the NSABB Codes of Conduct Working Group
The ASM made a presentation before the National Science Advisory Board for Biosecurity on “Codes of Conduct and Dual Use Research.” The round table was titled, “Promoting Awareness and Responsibility in Dual Use Research: A Critical Assessment of the Role of Codes of Conduct.” Dr. Ronald Atlas, Co-chair of the Committee on Biodefense presented ASM’s comments.
March 27, 2013 - ASM Comments on Dual Use Research Policy
ASM sent comments to the Office of Science and Technology Policy regarding the February 22, 2013 United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern.

Influenza

December 14, 2012 - ASM Comments on Influenza Viruses Containing the Hemagglutinin from the Goose/Guangdong/1/96 Lineage
http://www.asm.org/index.php/publicpolicy-2/statements-testimony/137-policy/documents/statements-and-testimony/90970-12-14-12-h5n1
The ASM submitted comments in response to the Federal Register Notice, "Influenza Viruses Containing the Hemagglutinin from the Goose/Guangdong/1/96 Lineage."

January 7, 2013 - ASM Comments on Proposed Framework for Guiding HHS Funding Decisions about Highly Pathogenic Avian Influenza H5N1 Gain-of-Function Research
The ASM submitted comments to the National Institutes of Health on the Proposed Framework for Guiding HHS Funding Decisions about Highly Pathogenic Avian Influenza H5N1 Gain-of-Function Research.

FBI Notice

January 28, 2002 - FBI Asks for Help in Identifying Sender of Anthrax Bacillus
http://www.asm.org/index.php/component/content/article?id=1905