Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
US federal oversight of biological materials and the IBC

Deborah Howard

Chapter Outline

Introduction 23
The early days of recombinant DNA research 24
Components of an IBC 26
Regulatory agencies and oversight 28
National institutes of health, environmental protection agency, and federal drug administration 29
IBC oversight of the SAP 29
Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism (USA PATRIOT Act) Act of 2001 30
U.S. Congress. Public Health Security and Bioterrorism Preparedness and Response Act of 2002 30
National Research Council (NRC) 31
National Science Advisory Board for Biosecurity (NSABB) 31
NSABB – US policy for oversight of life sciences DURC 2012 and how it affects IBCs 32
Seven experiments of DURC 32
2012 – Current events on dual use research 33
2012 US policy for oversight of life sciences DURC 35
The policy for institutional DURC oversight 35
October 2014, US Government announces moratorium on gain of function research 36
Conclusion 37
References 39

Introduction

Research in life sciences in the last century has provided advances in agriculture and industrial development while transforming the practice of medicine. In the field of biopharmaceutical products, major breakthroughs have been made including human recombinant insulin for the treatment of diabetes, a vaccine against hepatitis B, and medicines for cancer therapy, arthritis, multiple sclerosis, and cystic fibrosis [1].

Life science refers to the study of living organisms including, microbes, human beings, animals, fungi, and plants. It includes the fields of biology, aerobiology,
agricultural science, plant science, animal science, bioinformatics, genomics, proteomics, synthetic biology, environmental science, public health, modeling, engineering of living systems, and many other types of scientific study [1].

Better understanding of the principles of genetics, biochemistry, and the structure of DNA, as well as the discovery of gene-splicing technology have greatly advanced biological or life sciences. The discovery of genetic engineering was a major accomplishment for the scientific community. Genetic engineering allows for the modification and transfer of genetic material from one organism to another including from one species to another. These scientific advances are directly attributable to the sharing of knowledge among scientists and people with ideas moving freely between universities, government agencies, and private industry [1].

The early days of recombinant DNA research

In the late 1960s, biochemists and molecular biologists made remarkable progress in the study of DNA, RNA, and enzymes that are part of the replication process. These scientific advances caused the public and scientific community anxiety regarding the potential hazards of these cutting edge discoveries. If viruses could be made in the laboratory, there was concern for what could happen if they were pathogenic to humans or animals. Public fears about this new technology at the time were fed by Michael Crichton’s book *The Andromeda Strain* [2].

Recombinant DNA (rDNA) technology is the insertion of genetic material from one organism into the genome of another organism. This genetic material is then replicated and expressed by the receiving organism. The invention of rDNA technology is largely attributed to Drs Paul Berg, Herbert Boyer, and Stanley Cohen; however, many other scientists have also made important contributions to this field of science [3].

Paul Berg was a biochemist at Stanford University who was interested in the genetics of microbes. He wondered if it was possible to insert foreign genes into a virus, causing it to become a vector that would carry those genes to new cells. In 1971, Berg conducted a groundbreaking, controversial, gene-splicing experiment that involved splicing Simian Virus 40 (SV40) with an *Escherichia coli* restriction enzyme. Berg’s gene-splicing experiment resulted in the insertion of the restriction enzyme into virus-infected cells. This was the first man-made rDNA; as such experiments were eventually referred to in the research field [3]. This experiment eventually led to the inception of the federal regulation of rDNA.

In 1972, Herbert Boyer from the University of California at San Francisco, in collaboration with Stanley Cohen from Stanford University, advanced the development of modern biotechnology by inserting rDNA into bacteria where it would replicate naturally [3]. These experiments led to the breakthrough synthetic development of somatostatin, the hormone that plays a major role in regulating growth hormone and the hormone insulin that enables cells to absorb glucose from the blood [3].

Berg did not immediately move forward in his research inserting the rDNA into another organism because of the public concern over the possible risk of such experiments [3]. Berg’s experiment was considered controversial because SV40 is a monkey virus that can transform human as well as nonhuman primate cells into a cancerous...
state. Because of the perceived risks, Berg postponed his research and, to begin the process of evaluating the potential hazards, he organized a conference to discuss biohazards in biological research in January 1973 at the Asilomar Conference Center in Pacific Grove, California. This was the first conference that focused on laboratory safety and design to protect laboratorians handling rDNA. Following this meeting, the National Institutes of Health (NIH) and National Institute of Medicine (NIM) were asked to appoint a committee to study this new technology. Subsequently, a Recombinant DNA Advisory Committee (RAC) was set up by the NIH at the request of the scientific community to review recombinant experiments [2].

The RAC is a federal advisory committee that provides recommendations to the NIH director as they relate to basic and clinical research involving recombinant or synthetic nucleic molecules. All RAC proceedings and reports since 1999 are posted on the NIH’s Office of Biotechnology Activities (OBA) website, publicly available to the scientific and lay communities alike, and thereby promoting transparency and accessibility to basic and clinical research involving recombinant or synthetic nucleic acid molecules [4].

OBA is the governing body that oversees rDNA research and the RAC. OBA promotes science, safety, and ethics in the advancement of public policies in three different areas: Biomedical Technology Assessment, Biosafety, and Biosecurity. The office is tasked with developing policies related to (i) conduct of clinical trials when using recombinant and synthetic nucleic acids at an institution receiving NIH funding, (ii) biosafety for those receiving NIH funds, (iii) biosecurity, including oversight of dual-use research of concern (DURC) for those institutions receiving NIH funding, and (iv) registration of new stem cell lines for institutions receiving NIH funding. OBA also updates and interprets biosafety policies under the NIH guidelines involving research with recombinant and synthetic nucleic acids. Their input is critical for emerging governmental policies, such as the recently published regulations for DURC [5].

As a result of rDNA research advances and safety concerns, in 1975 Berg organized another and more in-depth conference at Asilomar focused on establishing voluntary guidelines to ensure the safety of working with rDNA. It was a three-and-a-half-day meeting attended by both scientists and members of the press. Approximately 150 of the leaders in this emerging field debated the risks of cloning, manipulating foreign genes and their expression in bacteria. At the end of this meeting, a series of resolutions that set forth guidelines for physical and biological containment procedures was given to the newly established NIH RAC. RAC became the governing body for the implementation of the guidelines. The public participated in the design of the guidelines through open hearings, and the guidelines were given strength by linking compliance with federal funds for any such research. The NIH guidelines established roles and responsibilities for institutions including implementing policies for the safe conduct of research subject to the NIH Guidelines and establishing an Institutional Biosafety Committee (IBC) to oversee rDNA research at the local level in individual laboratories [6].

It is interesting to note the experiments that were prohibited under the Asilomar Guidelines in 1975 are still regulated in the latest 2013 edition of the NIH Guidelines [7], and therefore, by IBCs at the local level. The experiments prohibited at the Asilomar conference were the following: (i) transfer of drug resistance traits not found in nature that would affect control of disease, (ii) deliberate formulation of rDNAs containing genes for the biosynthesis of toxins of very high toxicity, (iii) deliberate
creation of rDNAs that can increase virulence or host range, (iv) release of rDNAs into the environment, and (v) large-scale experiments – more than 10 liters of culture. Even in 1975, the participants at the Asilomar conference recognized these experiments could be used for malevolent or dual-use purposes in life science research [6].

In the most recent edition of the NIH Guidelines, the most regulated rDNA experiment is still the transfer of drug-resistant traits that would affect the control of disease. In order to conduct this experiment, the IBC must request the OBA to make a determination regarding whether an experiment involving the deliberate transfer of a drug-resistant trait falls under NIH Guidelines Section III-A-1-a and therefore requires RAC review and NIH Director approval before experiments can begin [7].

IBCs were federally mandated in the NIH Guidelines for Research Involving Recombinant DNA Molecules for institutions that receive federal funds to conduct rDNA research. At the local level, IBCs are the foundation of oversight for research involving recombinant and synthetic nucleic acids. The IBC’s primary responsibility is to safeguard protection of the personnel, public, and environment as it pertains to rDNA technology experiments [8].

In March 2013, the NIH Guidelines were updated to include synthetic nucleic acid molecules. This change was implemented for two reasons: (i) Recognition of the correct biosafety containment level of an agent is important regardless of the technology used to generate the agent (i.e., recombinant or synthetic methods). (ii) The National Science Advisory Board for Biosecurity (NSABB) recommended that the US Government partner with the scientific community to ensure that current biosafety guidelines are appropriate, adequate, and easily understood with respect to working with synthetic nucleic acids [7].

The new language of the Section I-A of the NIH Guidelines states “The purpose of the NIH guidelines is to specify the practices for constructing and handling: i) recombinant nucleic acid molecules, ii) synthetic nucleic acid molecules, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, and iii) cells, organisms and viruses containing such molecules.” Within the NIH Guidelines, the term “recombinant DNA molecules” has been changed to “recombinant or synthetic nucleic acid molecules” to include research with recombinant and synthetic nucleic acids [7].

**Components of an IBC**

According to the NIH Guidelines an IBC has to consist of no less than five members with the applicable recombinant or synthetic nucleic acid molecule technology and be able to evaluate the safety of recombinant or synthetic nucleic acid molecule research and recognize any potential risk to public health or the environment. At least two members must be community members not associated with the institution. If the institution conducts plant or animal research, experts specializing in this field must be represented on the committee. If the institution produces large-scale recombinant research material (>10L) or works at high containment levels (such as biosafety level 3 or 4), a Biological Safety Officer (BSO) must be appointed and serve on the IBC. The role of the BSO is to develop emergency plans for handling accidental spills and personnel
US federal oversight of biological materials and the IBC

contamination with recombinant or synthetic DNA, and they must report any recombinant or synthetic nucleic acid problems, violations, and research-related injuries or illnesses to the IBC. In addition, the BSO advises on security and offers technical advice to the Principal Investigators and IBC on safety procedures. The committee must have expertise in biological safety, containment, risk assessment, applicable law, and knowledge of institutional policies. As previously mentioned, the NIH Guidelines require at least two community members to be on the committee. Community members on the IBC are an important component, because they bring an outside perspective with respect to health and the protection of the environment. Community members are usually representatives from local public health or environmental authorities, and are frequently members with laboratory, medical, occupational, or environmental experience. The community members represent the concerns of the local population. When experiments contain topics that fall outside the knowledge of the IBC committee, it is appropriate to seek ad hoc members with appropriate additional expertise. IBCs are required to register with the OBA and file an annual online update. The update must identify the Chairman and contain contact information and biographical sketches for all members. The BSO can be the chairman of the committee if they have the relevant scientific background to evaluate the research protocols [8].

While the IBC was originally formed to review research with rDNA for conformity with the NIH guidelines, the committee was also tasked with conducting risk assessments to protect the environment and public health. When the NIH guidelines were established, the IBC evaluated containment levels using the NIH Guidelines as a guidance tool [2]. Assessing the adequacy of the facilities, reviewing standard operating procedures (SOP) and training were also under the original responsibilities of the IBC [5]. Other roles assigned to the IBC are the enforcement of institutional and investigator compliance along with serious adverse event (SAE) reporting to regulatory bodies such as the RAC and local oversight such as the Institutional Review Board and the Institutional Animal Care and Use Committee (IACUC). As the NIH regulations have evolved, IBCs were also given the role of reviewing human gene therapy protocols to certify compliance with Appendix M of the NIH Guidelines verifying that participants were not enrolled in a clinical trial until the appropriate approvals had been obtained [7]. In many cases, smaller institutions without the committee expertise to review human gene therapy protocols have to resort to hiring an outside IBC for this purpose.

All human gene transfer clinical trials occurring at or sponsored by institutions receiving NIH funds for research with recombinant or synthetic nucleic acid molecules have to be submitted to OBA for review by the RAC. RAC review must be completed before local IBC or IRB review. SAEs from human gene protocols were also given to the IBCs to oversee, as previously stated [8]. An SAE is any detrimental outcome associated with the use of a medical or biological product administered to a patient. In the case of an adverse event being reported and reviewed by the IBC, the incident has to involve recombinant or synthetic nucleic acid molecules. The event is “serious” and is required to be reported to FDA when the patient outcome is death, disability or permanent damage, life threatening, or hospitalization as a result. Emergency room visits that do not result in hospital admission should also be documented and evaluated by the IBC to determine whether it is an adverse event [9].
The role of the IBC has evolved in the last 30 years to review much more than rDNA projects. Many IBCs are now charged with reviewing the use of select agents and toxins, bloodborne pathogens, xenotransplantation, DURC, nanotechnology, and synthetic nucleic acid research. Some IBC oversight also includes reviewing policies and procedures and facility review for containment. With the new personnel suitability requirements of the Federal Select Agent Program (SAP), some institutions working with select agents are now requiring their IBCs to review biosecurity and personnel suitability plans before institutions adopt them. The increase in regulatory burden has significantly increased the workload for this committee of volunteers. Research projects involving recombinant and synthetic nucleic acid molecules at institutions have increased significantly in the last 15 or so years. The budget for the NIH has more than doubled from $13.7 billion in 1998 to $31.3 billion in 2014. Due to world events, IBCs have had to expand their oversight responsibilities to include biodefense and emerging infectious disease research review. New technological capabilities are also of concern to IBCs, such as the genomic synthesis of viruses (e.g., polio), reconstructing organisms (e.g., the 1918 pandemic influenza strain), and novel gene therapy protocols. The ease of rDNA techniques and access to necessary materials (along with the ability to purchase genetics elements off the internet) has increased the need for tighter oversight and restrictions on the publication of life science research.

Since the 1990s, the debate about the possible control or censorship of research in life science research has intensified. The timeline for concern began with the terrorist attacks on September 11, 2001 and the anthrax letters in the United States mail the following week. These events were followed by the 2001 report in the *Journal of Virology* regarding a re-engineered mousepox virus intended to sterilize mouse populations that unexpectedly produced a much more virulent virus. In *Science* in 2002, researchers reported they reconstructed poliovirus from chemically synthesized oligonucleotides linked together and transfected into cells. That same year in *Proceedings from the National Academy of Sciences*, researchers reported on the modification of the immune response under the influence of a virulence gene from vaccinia (vaccine strain for smallpox), including information on how to increase viral virulence. All of these DURC experiments raised fears about their potential for bioterrorism.

Due to the threat of bioterrorism, over the years Congress has passed legislation requiring US Government agencies to promulgate rules and regulations to regulate life science research to protect public health and enhance national security. When new laws and regulations are disseminated, an established body that understands the science must have oversight to assure proper implementation. Over the years, this burden of oversight has, by default, fallen to the IBC at the institutional level.

**Regulatory agencies and oversight**

The regulatory structure for life sciences research has evolved over the last five decades. Responsibility for regulation in the fields of biotechnology research in life sciences in the United States now falls under the jurisdiction of several federal agencies. Over the years various biological incidents including mishandling, releases, illnesses, and accidents have occurred throughout the world. The most recent incidents in 2014 at the CDC include the mishandling of the bacteria anthrax, the Ebola, and
the H5N1 viruses. These events have forced the CDC to change the agency’s overall safety culture as well as develop and implement stronger oversight measures in order to restore the public’s confidence in the CDC [13]. Over the years, as a direct result of public pressure, federal agencies have responded to these incidents by publishing additional guidelines and regulations to control the use and to monitor access to the biotechnology. IBCs have been required to adopt and adhere to these regulations and guidelines in order to conduct research at their institutions.

**National institutes of health, environmental protection agency, and federal drug administration**

The NIH and other national and international agencies support the publication of federally funded, fundamental research. Fundamental research is defined as basic and applied research in the areas of science and engineering where the resulting information is intended to be published and shared broadly within the scientific community with no governmental restrictions [14]. The technology used during the research is publicly available and may even be a part of the published information [14].

The NIH is the original governing regulatory agency for rDNA and the driving force behind implementing the IBC committee at the local level to oversee rDNA research at an institution. Standards and procedures are set for all NIH-funded research involving rDNA, which the IBC must adopt and follow. Research involving human gene therapy is a special subcategory under the NIH guidelines. Both the NIH and FDA are required to review the research protocols before the initiation of the research. If recombinant material will be released to the environment for crop improvement or other environmental applications, involvement of the Environment Protection Agency (EPA) is also required. Human research and environmental release have added to the administrative and reporting requirement burden on the IBC as they must also review the protocols at a local level to ensure compliance with biosafety and containment requirements [8].

**IBC oversight of the SAP**

Biological Select Agents and Toxins (BSAT) are agents and toxins determined by the Federal Government to have the “potential to pose a severe threat to public health and safety and animal or plant health and products” [15]. To advance scientific knowledge regarding biological agents and toxins while increasing knowledge of biological countermeasures, academic, commercial, and government institutions have been authorized by the US Government to perform research using these agents [16]. The oversight of the SAP has fallen to the IBC at many organizations. Some IBCs are now required to review SOPs accident and illness reports along with incidents involving theft, loss or release of BSAT agents and ensure the facilities will contain the agent with no release outside of the laboratory. Although not required by the select agent regulations, the annual review of biosecurity plans involving the inventory and security of select agents has also fallen under the purview of the IBC at some institutions.
No government program for the oversight of BSAT existed in the United States before 1996. In that year, Congress passed the Antiterrorism and Effective Death Penalty Act following an incident involving a person without a research need that ordered plague strains from a supplier of biological agents. After the arrest, government officials realized they had no legal right to charge the individual with a crime other than mail fraud [17]. The Act authorized the Secretary of the Department of Human and Health Services (DHHS) to regulate the transfer of BSATs harmful to humans. DHHS requested the CDC to develop regulations that would manage BSAT to protect the public without hindering scientific research. As a result, the CDC was designated as the agency within DHHS responsible for enforcing this regulation [17].

Select agent oversight is a shared federal responsibility between the DHHS, US Department of Agriculture (USDA) and Department of Justice (DOJ). Congress authorizes DHHS to regulate the possession, use and transfer of BSAT. The Secretary of DHHS assigned this authority to the CDC. Congress provided USDA/APHIS the authority to regulate BSAT that pose a severe threat to animal and plant health and/or products respectively, while the DOJ is responsible for conducting background checks (aka Security Risk Assessments) of individuals that have access to laboratories performing BSAT research [16].

**Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism (USA PATRIOT Act) Act of 2001**

In 2001, Congress bolstered the SAP by passing the *Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism (USA PATRIOT ACT) Act of 2001* [18]. This expanded the regulations by restricting the shipping, possession, and receipt of BSAT. The USA PATRIOT Act established requirements for the appropriate use of BSAT. It also identified individuals who should be restricted from working with these agents and imposes criminal and civil penalties for the inappropriate use of BSAT [17]. As a direct result of implementing the PATRIOT Act, as it pertains to BSAT rDNA research, it provided more authority to the IBC and the BSO on the oversight of the BSAT program.

**U.S. Congress. Public Health Security and Bioterrorism Preparedness and Response Act of 2002**

In 2002, Congress passed another act called the *Public Health Security and Bioterrorism Preparedness and Response Act* [19] which significantly improved oversight of BSAT. This act strengthened the regulatory authority of DHHS under the Antiterrorism and Effective Death Penalty Act of 1996 by requiring a security risk assessment be conducted for individuals having access to BSAT and granted similar regulatory authority to USDA/APHIS for BSAT that present a significant threat to
animal or plant health and/or products. It also required coordination and agreement between DHHS and USDA/APHIS on program activities such as the development of regulations, reporting forms, and approval of changes to regulated laboratories’ registrations and inspection process for BSAT regulated by both agencies [17].

Over the years, the Bioterrorism Act has been augmented through a series of additional regulations. The DHHS published an interim final rule, the “Possession, Use, and Transfer of Select Agents and Toxins” Interim Final Rule (42 CFR 73, 9 CFR 121, and 7 CFR 331) (effective on February 7, 2003), which implemented the relevant provisions of the Bioterrorism Act. These rules became effective on April 18, 2005. On October 20, 2005, DHHS established an Interim Final Rule adding reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments to the DHHS select agent list. These regulations are referred to as the “Select Agent Regulations.” The regulations were recently updated and implemented on October 5, 2012 [20].

**National Research Council (NRC)**

The NRC is an operating arm of the United States National Academies with the mission of improving government decision making and public policy. Their goal is to increase public understanding while educating and disseminating information in the fields of science, engineering, technology, and health. The council publishes independent expert reports to inform the US policy-making process. Their objective is to improve the lives of people around the world [21]. The NRC’s “Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology” published the book, *Biotechnology Research – An Age of Terrorism: Confronting the Dual Use Dilemma* in 2004. This was the first report that specifically addressed national security and life sciences. In the biosafety community, this book is referred to as the “Fink Report” named after the Chairman of the report Gerald R. Fink [22]. The Fink Report contains seven recommendations to ensure responsible oversight for biotechnology research with potential bioterrorism applications. One of the recommendations was to create the NSABB within the Department of Health and Human Services to educate scientists and advise the government on the oversight of “dual use of concern research” [1]. When first published, the “Fink Report” was distributed by the institutions receiving NIH funding to IBC Chairs, administrators and BSOs to review. The book and its contents were discussed at IBCs around the nation. The book indicated the landscape of oversight for life science research was changing, and the IBC would likely take an active role in the oversight of “DURC” as it pertains to rDNA and life science research.

**National Science Advisory Board for Biosecurity (NSABB)**

Following the publication of the “Fink Report,” the Secretary of the DHHS created the NSABB in 2004. The NSABB responsibilities carried out many of the recommendations suggested by the National Academies. The NSABB is an oversight committee tasked with proposing a framework for the identification, review, conduct, and
communication of life sciences research with dual use potential. Their role is to consider both the protection of national security while promoting life science research. The group advocates the free and open exchange of information in the life sciences area. Their aim to address dual use concerns is to raise awareness of the issues while strengthening the scientific culture within the research community by increasing understanding and fostering responsibility. The NSABB recommends strategies and has developed tools for researchers to assist in communicating results of research with dual use concerns [23].

NSABB – US policy for oversight of life sciences DURC 2012 and how it affects IBCs

In the language of the Department of Commerce (DOC) or International Traffic and Arms (ITAR) regulations, dual use refers to technology intended for civil end use while also having a military (or terrorism) application. Technology encompasses more than just a product, it also includes how to produce and use the product [14]. In the life sciences field, the definition of dual use is “biological research with a legitimate scientific goal that could be misused by rogue states, terrorist organizations, or individuals to pose a biological threat to public health or national security” [22].

Dual use potential is inherent in life sciences research. However, research with a smaller subset of BSAT organisms – currently 15 in number – is considered to have a higher likelihood for providing knowledge, technology, or end products that can be used to threaten public health or national security including the greatest risk of deliberate misuse. These agents combined with the seven categories of experiments of concern are currently considered “DURC” [24].

Seven experiments of DURC

The NSABB has identified seven categories of research that fall under the category of DURC. These research projects warrant close scrutiny to the potential nefarious application of the research by the investigator or others when being designed, conducted, and published [24].

These include research with the ability to initiate the following:

1. Enhance the harmful consequences of the agent/toxin (e.g., experiments designed to make seasonal flu as virulent as the pandemic 1918 influenza virus).
2. Disrupt immunity to or the effectiveness of an immunization against the agent/toxin without clinical or agricultural justification (e.g., inserting an immunosuppressive cytokine into a viral genome to make the immune response less effective).
3. Confer agent/toxin resistance to clinically or agriculturally useful prophylactic or therapeutic interventions against that agent/toxin or facilitates their ability to evade detection methodologies (e.g., altering the sensitivity of the bacterium Yersinia pestis (plague) to doxycycline, the antibiotic used to treat plague infections).
4. Increase the stability, transmissibility, or ability to disseminate the agent or toxin (e.g., genetically modifying a pathogenic thermophilic bacterial strain to grow at ambient temperatures).

5. Alter the host range or tropism of the agent/toxin (e.g., altering a mosquito-transmitted virus so that it is transmissible via a new species of mosquito).

6. Enhance the susceptibility of a host population to the agent/toxin (e.g., modification of a pathogen to allow it to evade a crucial host immune response).

7. Generate or reconstituting an eradicated or extinct agent/toxin (e.g., 2005 reconstruction of the 1918 pandemic influenza virus) [24].

2012 – Current events on dual use research

In late 2011, two federally funded research groups led by Drs Ron Fouchier (Erasmus Medical Centre, Rotterdam, Netherlands) and Yoshihiro Kawaoka (University of Tokyo, Japan and University of Wisconsin-Madison, United States) submitted manuscripts detailing methods for increasing human-to-human transmissibility of H5N1 avian influenza virus (bird flu). These experiments are referred to as “gain-of-function” research because the experiments alter the pathogens in ways that give them features or functions not found in nature or in the wild. Both groups genetically modified highly pathogenic, avian influenza H5N1 viruses, some through re-assortment with the H1N1 (swine) influenza virus (Kawaoka experiment), directed mutation (Fouchier), and virus passage experiments (Fouchier). The resulting viral mutants could be transmitted via aerosol among ferrets, a model for influenza transmission in human beings [25]. The submission of these two manuscripts to the scientific journals Nature and Science caused pandemonium in the scientific community and resulted in an unprecedented recommendation from NSABB to suspend the publication of the research.

In the United States, NSABB requested the methods used to enable transmission of the H5N1 virus from mammal to mammal and the results of the experiment be redacted before the articles were released to the public. NSABB feared that the exact details of the scientific methods used and the mutations involved could pose a significant biosafety risk. In the Netherlands, the Dutch government delayed the release of the paper by Dr Fouchier as authorities believed the work may have violated export control rules, related to dual use, and government-regulated technology [26]. The NSABB also recommended a 60-day moratorium on all similar research while the potential risks were assessed. Leading influenza scientists around the world agreed to the moratorium. The World Health Organization (WHO) did not agree with the recommendation of NSABB to redact information in the articles before publication. They believed that widely sharing the results of the articles would provide significant public health and scientific value [27]; however, the WHO did agree to the moratorium until the risks could be further evaluated [28].

Science and Nature both agreed to the NSABB recommendation to redact the information, with the understanding the information would be made available to researchers and organizations with a legitimate reason for access, including governments of countries with endemic H5N1, influenza research institutions around the
world and pharmaceutical companies. The research groups agreed to these conditions, although members of the groups, along with others in the broader scientific community, viewed the proposal as censorship [25]. The WHO did not support making the information available only to certain groups citing that it would be too difficult and time-consuming to develop a mechanism for distribution and to determine those that would have access to the redacted information [27].

The recommendation to postpone publication and redact details of the methods used to mutate the virus to enable aerosol transmission in mammals sparked fierce debate among the scientific community, government agencies, non-governmental organizations, and biosafety specialists who all presented valid data to support the benefits and risks of such research. In the process of evaluating the potential risks and benefits of these research articles, it became clear that it is vital to assess research with DURC potential before the initiation of the project as well as before the results are submitted for publication [23]. It is interesting to note that in March 2012, the US DHHS reconvened the NSABB to review the revised manuscripts of Kawaoka and Fouchier regarding the transmissibility of A/H5N1 influenza virus in ferrets. After reviewing, NSABB decided that the revised manuscripts should be communicated in full [29].

The H5N1 dilemma highlighted a challenge for the scientific community and regulatory agencies at the intersection of two important concepts: scientific discovery and societal responsibility. Scientists must look at their research from two different points of view: adherence to accepted standards of scientific practice in both conducting and reporting research and the social consequences of applying research findings. This idea raises two important questions:

1. How much of a researcher’s methods must be accessible in order to assess the integrity of the findings?
2. What is the scientist’s responsibility to society at large when the research has dual use applications [30]?

The intervention of national and international government parties into the publication process reinvigorated the debate over the role of government in regulating science and the relationships between science and society. In the past, science was mostly investigations of testable hypotheses to include practical applications of new knowledge. Today, scientists often find themselves subject (at least in part) to the interests of a myriad of stakeholders – both individuals and of the commons – who see scientific results as part of a larger goal whether it be profit, funding, patients seeking a cure, politicians seeking votes or the global community seeking assurance that the science is safe. As a result, many biosafety, scientific, and government groups are demanding accountability from the scientific community. Determining the level of regulation that meets the needs of the majority of stakeholders is a balancing act that will require ongoing and open negotiation among all interested parties [30]. It has been a challenge for the government to respond to the H5N1 influenza controversy as they balance increasing public pressure for greater government oversight of scientific research with the need to support researchers in preparing for another pandemic.
2012 US policy for oversight of life sciences DURC

As a direct outcome of the H5N1 experiments, the NIH Office of Science Policy (OSP) published in March 2012, the *U.S. Policy for Oversight of Life Sciences Dual Use Research of Concern*. The policy’s purpose was to promote transparency, awareness, and accountability from the inception of research through the publication of research results to protect public health. The dual use policy was not intended to restrict science but rather to support public health and national security while minimizing the risk of misuse of the technologies, by-products, information, and knowledge resulting from the research [24].

The 2012 policy was designed “to establish regular review of US Government funded or conducted research with certain high consequence pathogens and toxins for its potential DURC” [24]. The policy identified a well-defined subset of 15 of the higher-risk pathogens and toxins on the CDC BSAT list and required funding agencies to identify all federally funded research involving these agents within 60 days. Within 90 days, the agencies were required to report all instances of research involving the 15 agents that could be considered dual use. Furthermore, the funding agency, institution and lead scientists of studies found to have dual use risks were required to create risk mitigation plans. Plans could include modification of scientific methodology, relocating research to a more secure laboratory, and altering the communication of the research to the public and scientific community [24].

Previously, research executed at the NIH and CDC was reviewed for potential dual use. The 2012 policy applied this same standard to all research funded by the NIH or CDC. Dual use evaluations were now to be performed for all current and future studies for the 15 Tier I BSAT pathogens [24].

As previously discussed, the March 2012, DURC policy outlined a process for routine federal review of life science projects to identify DURC, assess the research for possible risks and benefits and methods to mitigate the risks. When the policy was promulgated in 2012, roles and responsibilities were not well defined by the USG in the document. It was assumed by many that the IBC would take the lead on the issues as they relate to DURC research because the committee has recognized knowledge of the research being conducted by investigators and because of its members’ many years of experience evaluating research involving rDNA, performing risk assessments, and assigning bio-containment levels.

The policy for institutional DURC oversight

Following the 2012 DURC policy, the *United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern* was officially proposed on February 21, 2013 by the OSP; this policy was published in September 2014 and became effective in September 2015 [31]. The 2014 Oversight Policy and the March 2012 DURC Policy are harmonized to accentuate a culture
Ensuring National Biosecurity

of responsibility to maintain the integrity of science and prevent its misuse. The 2012 policy describes the responsibilities of the federal agencies while the 2014 policy formally describes the roles and responsibilities of institutions and principal investigators conducting research that meets the criteria in the 2012 DURC policy. Of particular significance, 2014 policy reassigns the burden back to the Principal Investigator to initially identify their project as DURC. Further, the institution is required to establish an Institutional Review Entity (IRE). The IRE can be a committee established to review dual use research, an extant committee such as an IBC with the addition of ad hoc members to meet the established requirements of the committee, or an externally administered committee to review dual use research [31]. The IRE must be set up for the sole purpose of conducting review of research for dual use potential. The IRE must meet several criteria including that the group must be composed of at least five members and empowered by the institution to ensure it can execute the relevant requirements of the Policy for DURC Oversight. The members must have knowledge to assess the dual use potential of the range of relevant life science research conducted at a research facility. In addition, the committee must have individuals with knowledge of relevant US Government policies and understanding of risk assessment. The panel must also be conversant in risk management, biosafety, and biosecurity. The IRE is responsible for communications with the US Government funding agencies regarding mitigation plans and will have ongoing oversight of the project [31]. Not surprisingly, the requirements for the IRE align with the established mandates for an IBC. In most circumstances and at the majority of establishments, the IBC is the logical choice for the review and oversight of DURC at the institutional level. However, putting the burden of DURC review on the IBC increases the workload and regulatory burden on an already overtaxed committee that is not compensated for their time and effort. Some institutions may decide to set up a new committee or if they do not have in-house expertise on their IBC they may be forced to use an externally administered committee, such as an IBC, for the purpose of reviewing DURC protocols.

October 2014, US Government announces moratorium on gain of function research

In October 2014, the White House Office of Science and Technology Policy (OSTP) and DHHS made the announcement that they were going to review policies covering gain-of-function research projects. As noted earlier, this type research by Drs Ron Fouchier and Yoshihiro Kawaoka made world headlines in 2012 causing a moratorium on influenza research that lasted a year. Now, in the face of global threats like influenza, severe acute respiratory syndrome – Coronavirus (SARS-CoV), and Middle East respiratory syndrome – Coronavirus (MERS-CoV), which have killed many in Canada, the Middle East, and Asia, the US Government is, as of the time of
writing, instituting a halt to gain-of-function funding for experiments involving these three viruses [32].

NIH previously funded these projects at institutions in order to learn how the virus spreads, and enable scientists to assess the potential for a possible pandemic. NIH Director Francis Collins in a statement in October 2014 said these studies have biosafety and biosecurity risks that need further evaluation [32]. This moratorium has forced IBCs to re-evaluate existing protocols that include these organisms. If institutions don’t have previous permission from the NIH to work with MERS-CoV or SARS-CoV then they will not receive federal funding to do the work [33]. If however, the PI already has one or both of the viruses, then they can continue working with the pathogen(s). Principle investigators are currently working with their NIH/NIAID program officers to determine whether the proposed research/experiments can be continued, weighing the risks and potential gains of the scientific outcomes. Official letters are being issued from the funding agency outlining experiments/mutants/passage studies that can or cannot be performed. The risks and benefits of the research are to be evaluated by NSABB, the NRC, and outside experts. The NSABB will determine how this type of research fits into the federal rules and regulations [33].

Conclusion

Due to the breakthrough research of Drs Berg, Boyer, and Cohen in the early 1970s involving rDNA, the NIH Guidelines were developed and implemented. When the NIH Guidelines were initially published, they were the only guidance in place for the oversight of rDNA technology. The development of the Guidelines was a direct result of the Asilomar Conference in 1975 where researchers and the public discussed their trepidation of this new emerging science. At that time, local IBCs were established at institutions receiving funds from the NIH for research involving rDNA. The IBC was originally tasked with reviewing rDNA protocols using the strict guidelines instigated at the Asilomar Conference. As research evolved in the human subject’s field with recombinant gene therapy research, more IBC oversight was needed. Therefore, the IBC was tasked with reviewing human gene protocols for biosafety concerns and containment along with evaluation and mitigation of SAEs from human gene protocols. Currently, no human participant can be enrolled in a study without RAC, IBC, and IRB approval.

The Congress enacted the “Antiterrorism and Effective Death Penalty Act of 1996” into law, regulating shipment of pathogens after the illicit ordering and delivering of Y. pestis to an individual’s home was discovered that year. Before 1996 there was no oversight of BSAT. After 9/11, and the subsequent anthrax attacks, the threat of bioterrorism changed the landscape of regulations governing life science research. Post 9/11 in 2001, the US PATRIOT Act was passed to strengthen the BSAT program. When this regulation was passed, it required more oversight on the part of the BSO and IBC to review research rDNA protocols, SOPs, incidents and accidents, security and personnel reliability plans, and other documents to support the BSAT program.
In 2004, “Biotechnology Research – An Age of Terrorism: Confronting the Dual Use Dilemma” was published by the NRC and copies were provided to IBC Administrators, Chairs, and BSOs serving on the IBC. After discussing the book, IBCs around the country recognized that the federal oversight of life science research was changing in order to protect national security and public health. One of the recommendations from the 2004 book that came to fruition was the establishment of the NSABB within the Department of Health and Human Services to educate scientists and advise the government on the oversight of “dual use of concern research.” As a direct result of the 2011 gain of function H5N1 influenza experiments by Fouchier and Kawaoka, the Federal Government published the US Policy for the Oversight of Life Science Dual Use Research of Concern in March 2012. Although the roles and responsibilities were not established in this first policy, it was widely accepted that IBCs would take on the responsibility of this new regulation. In preparation of what was to come, many IBCs implemented new institutional practices at this time to support the emerging regulations.

In March 2013, the NIH Guidelines were revised to also address synthetic nucleic acid molecules. The modification of the NIH Guidelines was instituted to ensure containment was assessed and biosafety guidelines were appropriate for synthetic material research [7]. As a consequence, this change to the guidelines increased the workload of the IBC by requiring an update of institutional forms to include reporting of synthetic nucleic science for review, additional training, and alterations to institutional process.

In September 2014, the Policy for Institutional DURC Oversight was released by the US Government. In this document, institutional roles and responsibilities were more clearly defined to review and oversee DURC. Many established IBCs meet the necessary criteria outlined in the policy to review DURC. As a result, most institutions have given the review of DURC to the IBC.

Policymakers and stakeholders encounter difficult decisions in the attempt to balance the possible benefits of research against potential harm such as an accidental release, gain of function projects, or bioterrorism. This balancing act was recently demonstrated in October 2014 by the Federal Government as it imposed a moratorium on SARS-CoV, MERS-CoV, and influenza gain-of-function research projects pending further review. This moratorium followed biosafety lapses at the CDC in regards to anthrax exposure to 70 employees and the unexpected discovery of 16 vials of forgotten variola virus in a storage closet at the FDA’s Bethesda campus during a routine inventory. It is evident by the actions of the Federal Government that regulations and oversight guidance for life science research will continue to evolve and be further expanded as science and technology advance in the future (and, as will doubtless be the case, when new mishaps occur, even without injury or risk to humans, animals, or the environment).

IBCs – voluntarily staffed by researchers and community-based experts, and already tasked with extensive responsibilities – will face additional demands as regulations and guidelines continue to evolve, and it may be the case that these professionals will be reluctant to take additional time from already hectic schedules to address an expanding IBC agenda. Perhaps the solution is a paid committee with the appropriate expertise being responsible for the oversight of the myriad regulations at research institutions.
References

[1] Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology. Biotechnology research in an age of terrorism. Washington, DC: The National Academies Press; 2004.

[2] The Paul Berg papers recombinant DNA technologies and researchers’ responsibilities. Available from: <http://profiles.nlm.nih.gov/ps/retrieve/Narrative/CD/p-nid/260> [accessed 10.10.14].

[3] Berg P, Boyer HW, Cohen SN. Available from: <http://www.chemheritage.org/discover/online-resources/chemistry-in-history/themes/pharmaceuticals/preserving-health-with-biotechnology/berg-boyer-cohen.aspx> [accessed 10.10.14].

[4] NIH Office of Science Policy Biotechnology Assessment. Available from: <http://osp.od.nih.gov/office-biotechnology-activities/biomedical-technology-assessment/hgt/rac> [accessed 11.09.14].

[5] Office of Biotechnology Activities. Available from: <http://osp.od.nih.gov/office-biotechnology-activities> [accessed 11.09.14].

[6] Petsko G. An asilomar moment. Genome Biol 2002;3(10):1014.1–1014.3.

[7] Notice pertinent to the November 2013 revisions of the NIH Guidelines for research involving recombinant of synthetic nucleic acid molecules. Available from: <http://osp.od.nih.gov/sites/default/files/NIH_Guidelines_0.pdf>; November 2013 [accessed 12.09.14].

[8] NIH Office of Science Policy Institutional Biosafety Committees Requirements for IBC’s. Available from: <http://osp.od.nih.gov/office-biotechnology-activities/biosafety/institutional-biosafety-committees> [accessed 12.09.14].

[9] What is a serious adverse event? Available from: <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm> [accessed 12.09.14].

[10] Jackson RJ, Ramsay AJ, Christensen CD, Beaton S, Hall DF, Ramshaw IA. Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. J Virol 2001;75:1205–10.

[11] Cello J, Paul AV, Wimmer E. Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. Science 2002;297(5583):1016–8. Available from: <http://dx.doi.org/10.1126/science.1072266>.

[12] Rosengard AM, Liu Y, Nie YZ, Jimenez R. Variola virus immune evasion design: expression of a highly efficient inhibitor of human complement. Proc Natl Acad Sci USA 2002;99:8808–13.

[13] CDC reports potential Ebola exposure in Atlanta Lab. The Washington Post. Available from: <http://www.washingtonpost.com/national/health-science/cdc-reports-potential-ebola-exposure-in-atlanta-lab/2014/12/24/f1a9f26c-8b8e-11e4-8ff4-fb93129c9c8b_story.html> [accessed March 2015].

[14] Bureau of Industry and Security. Deemed exports and fundamental research for biological items. Available from: <http://osp.od.nih.gov/sites/default/files/resources/B_Dual_Use_Educational_Module_FINAL.pdf> [accessed 13.09.14].

[15] Federal Select Agent Program. Available from: <http://www.selectagents.gov/index.html> [accessed 26.09.14].

[16] Besser R. Oversight of select agents by the Centers for Disease Control and Prevention, U.S. Department of Health and Human Services Testimony. Available from: <http://www.hhs.gov/asl/testify/2007/10/t20071004c.html> [accessed 13.09.14].

[17] Backgrounder the select agent rule. CDC media relations. Available from: <http://www.cdc.gov/media/pressrel/b021210.htm> [accessed 13.09.14].
Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism (USA PATRIOT ACT) Act of 2001. (Public Law 107-56, October 26, 2001).

U.S. Congress. Public Health Security and Bioterrorism Preparedness and Response Act of 2002. P.L. 107-188. 42 U.S.C. 243, June 12. Available from: <http://tis.eh doe.gov/biosafety/library/PL107-188.pdf>.

National select agent registry history of the select agent program. Available from: <http://www.selectagents.gov/resources/42_cfr_73_final_rule.pdf> [accessed 25.09.14].

National Research Council. Available from: <http://www.nationalacademies.org/nrc/> [accessed 25.09.14].

Biotechnology Research in an Age of Terrorism Report in brief. Available from: <http://sites.nationalacademies.org/cs/groups/pgasite/documents/webpage/pga_054638.pdf/> [accessed 25.09.14].

National Science Advisory Board for Biosecurity (NSABB). Proposed framework for the oversight of dual use life sciences research. National Science Advisory Board for Biosecurity; 2007. Report number. Available from: <http://osp.od.nih.gov/sites/default/files/resources/Framework%20for%20transmittal%20duplex%209-10-07.pdf> [accessed 26.09.14].

National Institutes of Health, Office of Science Policy Dual Use Research of Concern. Office of Science Policy. Available from: <http://www.phe.gov/s3/dualuse/Documents/us-policy-durc-032812.pdf> [accessed 25.09.14].

Avian influenza and the dual-use research debate. Lancet Infect Dis 2012;12(3):167. http://dx.doi.org/10.1016/S1473-3099(12)70035-X.

Enserink, M. Free to speak, Kawaoka reveals flu details while Fouchier stays mum. Sci Insid 2012. Available from: <http://news.sciencemag.org/scienceinsider/2012/04/free-to-speak-kawaoka-reveals-flu.html?ref=hp> [accessed 26.09.14].

Cohen J. WHO group: H5N1 papers should be published in full. Science 2012;335(6071): 899–900. Available from: <http://dx.doi.org/10.1126/science.335.6071.899>.

Cohen J, Enserink M. Science now one of two hotly debated h5n1 papers finally published. 2012. Available from: <http://news.sciencemag.org/scienconow/2012/05/one-of-two-hotly-debated-h5n1-papers.html> [accessed 26.09.14].

Vaccines and global health: ethics and policy NSABB Policy update: manuscripts on transmissibility of A/H5N1 influenza virus. Available from: <http://centerforvaccineethicsandpolicy.net/2012/04/07/nsabb-policy-update-manuscripts-on-transmissibility-ofah5n1-influenza-virus> [accessed 26.09.14].

Frankel M. Regulating the boundaries of dual-use research. Science 2012;336(6088): 1523–5. Available from: <http://dx.doi.org/10.1126/science.1221285>.

United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern. United States Government, 2014. Available from: <http://www.phe.gov/s3/dualuse/Pages/default.aspx>.

Akst J. Moratorium on gain-of-function research. Scientist 2014 Available from: <http://www.the-scientist.com/?articles.view/articleNo/41263/title/Moratorium-on-Gain-of-Function-Research/> [accessed 26.09.14].

Greenfieldboyce, Nell NPR 2014 Scientists fight for superbug research as U.S. pauses funding. Available from: <http://www.npr.org/blogs/health/2014/10/23/358122198/scientists-fight-for-superbug-research-as-u-s-pauses-funding> [accessed 27.04.15].