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United States Government Accountability Office
Washington, DC 20548

February 22, 2007

The Honorable Bart Gordon
Chairman
Committee on Science and Technology
House of Representatives

Subject: *Biological Research Laboratories: Issues Associated with the Expansion of Laboratories Funded by the National Institute of Allergy and Infectious Diseases*

Dear Mr. Chairman:

The fall 2001 anthrax attacks revealed gaps in the nation's preparedness for public health emergencies resulting from bioterrorism. Among the tools needed for responding to such emergencies are vaccines to prevent the spread of disease; tests for rapid diagnosis; and therapeutics, including drugs, for treatment. Because the pathogens that could be used in bioterrorist attacks carry the risk of significant morbidity or are potentially lethal, biological research aimed at providing the tools needed to combat these agents is required to be conducted in facilities known as biocontainment laboratories. These facilities are to be designed, constructed, and operated in a manner to prevent accidental release of infectious or hazardous agents within the laboratory and to protect laboratory workers and the environment external to the laboratory, including the community, from exposure to these research materials.

The National Institute of Allergy and Infectious Diseases (NIAID) is the primary institute at the Department of Health and Human Services' (HHS) National Institutes of Health (NIH) that is responsible for research on pathogens that could be used in a bioterrorist attack and for research on emerging infectious disease pathogens.[1] The Centers for Disease Control and Prevention (CDC) is also responsible for research on such pathogens. Following the anthrax attacks, NIAID expanded its research program to emphasize biodefense research. In February 2002, it issued the *NIAID Strategic Plan for Biodefense Research*, which outlined a need for research aimed at the development of vaccines, diagnostics, and therapeutics and construction of additional biocontainment laboratories in which to conduct the research.[2] According to NIH, a shortage of high-level biocontainment laboratories exists.

[1]The U.S. Army Medical Research Institute of Infectious Diseases conducts research to develop vaccines and diagnostics to protect servicemembers from biological threats.

[2]Other biocontainment laboratories already exist in the United States. These laboratories are located at federal facilities and universities and in the private sector and are used to conduct biomedical research.

In response to the *Strategic Plan*, NIAID established the National Biocontainment Laboratory (NBL) and Regional Biocontainment Laboratory (RBL) construction programs. The overall objective of the NBL construction program is to provide funding to design and construct state-of-the-art biosafety level (BSL) 4, 3, and 2 laboratories, including associated research and administrative support space, and the objective of the RBL construction program is to provide similar facilities containing BSL-3 and -2 laboratories.[3] HHS's guidelines, entitled *Biosafety in Microbiological and Biomedical Laboratories* (BMBL),[4] specify four BSLs, which consist of combinations of laboratory practices and techniques, safety equipment, and facilities that are recommended for laboratories that conduct research on potentially dangerous pathogens and toxins, with BSL-4 being the highest level.[5] In fiscal year 2003, NIAID awarded funding to two universities to construct NBLs and to nine universities to construct RBLs, and in fiscal year 2005, NIAID awarded funding to four more universities to construct RBLs. As of January 2007, the NBLs and RBLs are at various stages of design and construction and are not yet operational.[6]

Because the deliberate or accidental release of biological pathogens from a biocontainment laboratory could have disastrous consequences, concerns exist about the oversight of these laboratories. This report responds to your November 30, 2005, request that we provide information associated with the construction of NBLs and RBLs funded by NIAID in fiscal years 2003 and 2005. Your questions covered requirements and guidance for these laboratories, funding award factors, communication with the public, and research agendas. Enclosure I provides background information for these questions and our answers to the questions, enclosure II provides lists of infectious agents with the potential to be used in bioterrorism, and enclosure III provides examples of regulations and guidelines applicable to NBL and RBL operations and security procedures.

To address these issues, we reviewed federal laws, regulations, and guidelines for these facilities. However, we could not examine laboratory operational activities, such as facility inspections, employee investigations, and research oversight because none of the NBLs and RBLs are operational. We also reviewed certain related state and local requirements. We interviewed NIH, NIAID, and CDC officials and local government representatives of some of the localities where the NBLs and RBLs are being built about the planned oversight of the new laboratories. We conducted site visits at the two universities where the NBLs are being built and at four universities where RBLs are being built and conducted a telephone conference with officials from a fifth university where an RBL is being built. We also interviewed NIAID officials regarding the NBL and RBL award process. We conducted our

[3]NIAID awarded funding for up to 75 percent of the cost of the project.

[4]Department of Health and Human Services, *Biosafety in Microbiological and Biomedical Laboratories*, 4th ed. (Washington, D.C.: May 1999).

[5]According to the BMBL guidelines, BSL-1 laboratories house pathogens and toxins that do not consistently cause disease in healthy adult humans. BSL-2 laboratories are capable of housing pathogens and toxins that are spread through puncture, absorption through mucous membranes, or ingestion of infectious materials. BSL-3 laboratories are capable of housing pathogens and toxins that have a potential for aerosol transmission and that may cause serious and potentially lethal infection. BSL-4 laboratories are capable of housing pathogens and toxins that pose a high individual risk of life-threatening disease, which may be aerosol transmitted and for which there is no available vaccine or therapy.

[6]Construction is complete on only one of the RBLs.

review from December 2005 through January 2007 in accordance with generally accepted government auditing standards. We provided a draft of this report to HHS for comment. The department provided technical comments, which we incorporated as appropriate.

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We are sending copies of this report to the Secretary of Health and Human Services and other interested parties. We will also make copies available to others on request. In addition, the report will be available at no charge on GAO's Web site at http://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7101 or bascettac@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. Other key contributors to this report were Michael T. Blair, Jr., Assistant Director; Lesia Mandzia; Roseanne Price; and Shannon Slawter.

Sincerely yours,

Cynthia A. Bascetta
Director, Health Care

Background and Response to the Request Letter Questions

Background

The administration and the Congress responded to the 2001 terrorist attacks by increasing funding for biodefense preparedness and research. The National Institute of Allergy and Infectious Diseases (NIAID) has allocated its increased biodefense research funding to developing vaccines, therapeutics, and diagnostics against a range of bioterrorist threats. NIAID identified certain pathogens, such as viruses and bacteria, that could be used in a bioterrorist attack and placed them into three categories—A, B, and C—depending on how easily they could be spread and the severity of illness or extent of death they could cause.[7] NIAID's categorization is used for setting research priorities. In February 2002, the National Institutes of Health (NIH) convened the Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research. Incorporating advice from the Blue Ribbon Panel, NIAID developed three key documents to guide its biodefense research program:

- *The NIAID Strategic Plan for Biodefense Research* outlines plans for addressing research needs in the broad area of bioterrorism and emerging and reemerging infectious diseases and for constructing appropriate biocontainment laboratories in which to do the research.

- *The NIAID Biodefense Research Agenda for CDC Category A Agents* provides priorities and goals for research on Category A agents, also known as Category A priority pathogens, which cause diseases that include anthrax, smallpox, plague, botulism, tularemia, and viral hemorrhagic fevers. Category A agents are easily transmitted and would cause high mortality and social disruption, require special public health preparedness, and present the greatest bioterrorism danger.

- *The NIAID Biodefense Research Agenda for Category B and C Priority Pathogens* provides priorities and goals for research on Category B and C priority pathogens, also known as Category B and C agents. Category B agents, such as hepatitis A virus and salmonella, are easily transmitted, but they would result in lower mortality than Category A agents, and present the second greatest danger to the public. Category C agents, such as Crimean-Congo hemorrhagic fever virus and multidrug-resistant tuberculosis, are emerging pathogens that in the future might present a danger of potentially high rates of morbidity if they become readily available and easy to produce.

According to NIH, although many U.S. institutions and companies with infectious disease research programs have the biosafety level (BSL) 3 laboratories needed to perform their research, most such laboratories are small, dedicated to particular uses, or in need of modernization. In addition, NIH reported that as of May 2006 there were only four operational BSL-4 laboratories in the United States. One component of NIAID's *Strategic Plan* is to provide increased capacity through the construction of biocontainment facilities in which to conduct research on potentially dangerous pathogens safely and securely. As table 1 shows, in fiscal year 2003, NIAID awarded funding to two universities to construct National Biocontainment Laboratories (NBL) that will provide additional capacity for research at BSL-4, -3, and -2, and nine universities to construct Regional Biocontainment Laboratories (RBL) that will provide additional capacity for research at BSL-3 and -2. In addition, in fiscal

[7]NIAID's Category A, B, and C Priority Pathogens list is based on the Centers for Disease Control and Prevention Biological Diseases/Agents List that identifies agents that could have a significant public health impact on the U.S. population.

year 2005, NIAID awarded funding to four more universities to construct RBLs that will include BSL-3 and -2 laboratories.

Table 1: Summary of NIAID's NBL and RBL Awards and Projected Completion Dates

		Number of awards by fiscal year		Projected construction completion dates[a]			
Type of award	Total number of awards	Fiscal year 2003	Fiscal year 2005	Calendar year 2007	Calendar year 2008	Calendar year 2009	Calendar year 2010
NBL	2	2	0	0	2	0	0
RBL	13	9	4	3	6	2	1
Total	**15**	**11**	**4**	**3**	**8**	**2**	**1**

Source: NIAID.

Note: NBL and RBL awards were not provided in fiscal years 2004 or 2006. NIAID does not intend to make any additional NBL or RBL awards.

[a]Construction was completed at one RBL in 2006.

The NBLs and RBLs were funded to support NIAID's biodefense research agendas for Category A, B, and C priority pathogens. A number of the Category A, B, and C priority pathogens have also been designated by the Department of Health and Human Services' (HHS) Centers for Disease Control and Prevention (CDC) and the Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS) as select agents. (Enc. II contains a list of NIAID's Category A, B, and C priority pathogens and indicates whether they have been designated as select agents.) Like Category A, B, and C priority pathogens, select agents are pathogens and toxins that are capable of causing substantial harm to public health and safety. While NIAID's list is for setting research priorities, the HHS and USDA list is for controlling and monitoring access to select agents. NBLs and RBLs that intend to possess, use, or transfer select agents are required to register with CDC or APHIS. CDC is responsible for the registration and oversight of laboratories that possess, use, or transfer select agents that could pose a threat to human health. APHIS is responsible for the registration and oversight of laboratories that possess, use, or transfer select agents that could pose a threat to animal or plant health or animal or plant products. Some select agents, such as anthrax, pose a threat to both human and animal health and are regulated by both agencies.

Response to Request Letter Questions

1. What federal requirements and guidelines apply to NBL and RBL laboratory operations and security procedures?

The NBLs and RBLs are subject to a number of federal requirements and guidelines for laboratory operations and security procedures. (See enc. III for a list of some of these requirements and guidelines.) As a condition of the award, each NBL and RBL must attest that it will comply with applicable federal, state, and local regulations. As of January 2007, the NBLs and RBLs are at various stages of design and construction and are not yet operational.[8] The NBLs and RBLs must be designed and constructed in compliance with federal regulations and guidelines—a process that is being monitored by NIAID—and once

[8]Construction is complete on only one of the RBLs.

operational, they will be subject to federal regulations intended to ensure a safe and secure environment in which to conduct research on dangerous biological pathogens and toxins.

According to NIAID officials, during design and construction, the NBL and RBL awardees work with NIAID staff and NIAID's Construction Quality Management contractor to ensure that their facility design is in compliance with NIH policy, which reflects federal standards. In addition, NIAID staff must review and approve the design and cost estimates before bids and proposals can be solicited by the awardees for construction activities. NIAID officials also told us that NIAID monitors the awardees through monthly meetings, frequent site visits, and teleconferences. During the design and construction phase, the NBLs and RBLs must comply with the following:

- *The NIH Design Policy & Guidelines*, which establishes policy, design standards, and technical criteria for use in designing and constructing biomedical research laboratories and animal research facilities. This document includes a section on research laboratories and addresses biological safety of BSL-3 and -4 laboratories, including the restricted access of laboratories; heating, ventilation, and air conditioning systems; and the use of biological safety cabinets.

- *Physical Security Design Guidelines for Projects Using NIH Construction Grants*, which provides grantees, institute-designated officials, and grantees' architects and engineers with assistance in meeting the desired levels of protection of NIH-funded facilities and outlines requirements pertaining to perimeter barriers, controlled entrance access points, the storage of select agents, and additional security requirements for BSL-3 and -4 laboratories, such as closed-circuit television coverage of internal laboratory spaces.

- *The NIH Model Commissioning Guide*, which describes the means to ensure that (1) all building systems are installed and perform interactively according to the design intent, (2) the systems are efficient and cost effective and meet the user's operational needs, (3) the installation is adequately documented, and (4) the operators are adequately trained.

- *The National Environmental Policy Act of 1969*[9] (NEPA), which, according to the Environmental Protection Agency, requires the preparation of detailed statements involving an assessment of the impact of major federal actions significantly affecting the environment. The statements include a description of the purpose and need for the project, the alternatives to the proposed project, and a description of the affected environment and environmental consequences of the project.[10]

[9]Pub. L. No. 91-190, 83 Stat. 852 (1970) (codified at 42 U.S.C. ch. 55, as amended).

[10]After the award and prior to authorizing the use of any construction funding, NIH required the NBL awardees to prepare an Environmental Impact Statement (EIS) and the RBL awardees to prepare an Environmental Assessment (EA). Two public meetings are required for an EIS. The first meeting provides the public with an opportunity to comment on what they would like to see in the EIS, and the second provides an opportunity to comment on the draft report and suggest changes. Public meetings are not required for an EA; however, anyone can comment on an EA once it is complete. NIH's Office of Research Facilities oversees this process, and each EIS and EA becomes an NIH document once complete.

Once operational, the NBLs and RBLs will be subject to additional guidelines and regulations. For example, the *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) describes the combinations of standards, special practices, and safety equipment for BSL-1 through -4 facilities.[11] BMBL states that biosafety procedures must be incorporated into the laboratory's standard operating procedures or biosafety manual, personnel must be advised of special hazards and are required to read and follow instructions on practices and procedures, and personnel must receive training on the potential hazards associated with the work involved and the necessary precautions to prevent exposures. In addition, BMBL contains guidelines for laboratory security and emergency response, such as controlling access to areas where select agents are used or stored. It also states that a plan must be in place for informing police, fire, and other emergency responders as to the type of biological materials in use in the laboratory areas.

Furthermore, each NBL and RBL will be required to submit to NIAID an annual progress report that describes its activities and accomplishments during the prior funding period. The research activities of the NBLs and RBLs, once operational, will dictate which other regulations and guidelines apply to the NBLs and RBLs. For example:

- *NIH Guidelines for Research Involving Recombinant DNA Molecules*[12] (NIH rDNA Guidelines) applies to research involving recombinant DNA (rDNA).[13] These guidelines set the standards and procedures for research involving rDNA that institutions must follow when they receive NIH funding for this type of research. This includes the requirement to establish an institutional biosafety committee (IBC). The IBC is responsible for reviewing rDNA research conducted at or sponsored by the institution for compliance with the NIH rDNA Guidelines and for approving those research projects that are found to conform with the NIH rDNA Guidelines. IBCs also periodically review ongoing rDNA research to ensure continued compliance with the NIH rDNA Guidelines.

- For facilities registered with CDC and APHIS that possess, use, or transfer select agents, the Select Agent Regulations[14] require

  - a Federal Bureau of Investigation security risk assessment for a number of individuals, including each person who is authorized to have access to select agents and toxins,

  - written biosafety and incident response plans,

  - training of individuals with access to select agents and of individuals who will work in or visit areas where select agents or toxins are handled and stored,

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[11]The awardees were also required by the Notice of Grant Award to design and construct the NBLs and RBLs to be fully compliant with the design and construction guidance established in BMBL.

[12]66 *Fed. Reg.* 57970 (Nov. 19, 2001).

[13]DNA is the molecule that encodes genetic information in the nucleus of cells. It determines the structure, function, and behavior of the cell. In the context of the NIH rDNA Guidelines, rDNA molecules are defined as molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell. The definition also includes those molecules that result from the replication of those described above.

[14]42 C.F.R. pt. 73 (2006), 7 C.F.R. pt. 331 (2006), and 9 C.F.R. pt. 121 (2006).

- a security plan sufficient to safeguard the select agent or toxin against unauthorized access, theft, loss, or release, designed according to a site-specific risk assessment, and that provides protection in accordance with the risk of the agent or toxin,
- possible inspection by CDC or APHIS of the facility and its records prior to issuance of the certificate of registration,[15]
- records relating to the activities covered by the Select Agent Regulations, and
- facility registration with CDC or APHIS that indicates
  - each select agent the entity intends to possess, use, or transfer;
  - the building where it will be used and stored and the laboratory safety level;
  - a list of people authorized to have access to the select agents;
  - the objectives of the work for each select agent, including a description of the methodologies or laboratory procedures to be used;
  - a description of the physical security and biosafety plans; and
  - assurance of security and biosafety training for individuals who have access to areas where select agents are handled and stored.

- *Public Health Service Policy on Humane Care and Use of Laboratory Animals* applies if research involves animals and is supported by the Public Health Service. This policy requires the creation of an institutional animal care and use committee to oversee and evaluate all aspects of the institution's animal care and use program.

2. What are the requirements for the IBCs, including their role and responsibilities in reviewing research projects at the NBLs and RBLs?

The IBC is responsible for reviewing rDNA research conducted at the institution to ensure that it is in compliance with the NIH rDNA Guidelines. If an institution receives any NIH funding for rDNA research, it must observe the NIH rDNA Guidelines for all research involving rDNA molecules.[16] Thus, even if an institution has only one NIH-funded project subject to the NIH rDNA Guidelines, all rDNA research projects conducted at that institution must also adhere to the NIH rDNA Guidelines. The guidelines describe the institutional review, biosafety and containment, and oversight practices that must be observed by an

[15]According to CDC officials, prior to possessing select agents, an entity must be issued a certificate of registration from either the CDC or the APHIS Select Agent Program. Additionally, the CDC Select Agent Program currently inspects all entities prior to the initial issuance of the certificate of registration to ensure that these entities are compliant with the Select Agent Regulations. As part of an entity's renewal process that occurs every 3 years, the CDC Select Agent Program reinspects the entity.

[16]Research not involving rDNA is not subject to the NIH rDNA Guidelines. Also, the NIH rDNA Guidelines describe particular experiments involving rDNA that are exempt, generally because experience with these experiments has shown that they pose negligible risk to health or the environment.

institution receiving NIH funding for rDNA research and should be implemented by the institution to ensure that proper biosafety and containment practices are employed. NIH's Office of Biotechnology Activities (OBA) oversees rDNA research and develops and implements the NIH rDNA Guidelines.

To comply with the NIH rDNA Guidelines an institution must

- establish an IBC having a minimum of five members, at least two of whom are not affiliated with the institution and "represent the interest of the surrounding community with respect to health and protection of the environment";
- register the IBC with NIH's OBA;
- submit an annual report to OBA that includes a roster and description of each of the IBC committee members;
- upon request, provide to the public the IBC meeting minutes, committee rosters, and biographical sketches of members; and
- appoint a biological safety officer (BSO) if the institution conducts rDNA research at BSL-3 or -4 or engages in large-scale research.[17] The BSO's duties include conducting periodic inspections to ensure that standards are followed, developing emergency plans, investigating accidents, and reporting any violations to the IBC.

The principal investigator[18] is responsible for submitting the initial research protocol and any subsequent changes to the IBC for review. The IBC's review should include the following: an assessment of the BSL required for the research; an assessment of the facilities, procedures, practices, and training and expertise of personnel involved in the research; and a review of the emergency plans for handling accidental spills and personnel contamination. IBCs should capture the proceedings of their reviews in minutes. OBA guidance states that minutes should "offer sufficient detail to serve as a record of major points of discussion and the committee's rationale for particular decisions."[19]

All of the NBL and RBL awardees have an IBC currently registered with OBA. Because the NIH rDNA Guidelines apply only to research involving rDNA, the NBLs and RBLs are not required by the NIH rDNA Guidelines to submit all research projects to an IBC for review; however, officials at each of the seven universities we interviewed use an IBC or another institutional body to review all research involving pathogens and toxins. Five of the seven universities use an IBC to review all research involving biological pathogens and toxins. The

[17]The NIH rDNA Guidelines describe large-scale research as involving more than 10 liters of culture.

[18]The principal investigator is the person who is designated by an applicant institution to direct a research project, oversee the scientific and technical aspects of the award, and oversee the day-to-day management of the research.

[19]NIH does not prescribe the level of detail for the IBC meeting minutes but provides expectations with respect to the preparation of minutes. OBA suggests that the minutes should include the date and place of the meeting, names of attendees, indication of whether the meeting was open or closed, and all motions and points of order. There is no requirement that IBCs routinely submit their meeting minutes to OBA.

remaining two universities review all research involving biological pathogens and toxins but use different organizational bodies to conduct the research review. The first university uses the IBC to review research with rDNA or select agents and uses the university's occupational and environmental safety office to review all other research involving hazardous biological pathogens and toxins. The second uses the IBC to review all research involving biological pathogens and uses a chemical safety committee to review all research involving biological toxins.

3. What guidance and oversight was provided by NIH to the NBLs and RBLs regarding adherence to our treaty obligations under the 1972 Biological and Toxin Weapons Convention (BWC)?

NIH did not provide specific guidance to the NBL or RBL awardees regarding adherence to the 1972 BWC.[20] Article 1 of the 1972 BWC prohibits the development, production, stockpiling, acquisition, or retention of biological pathogens and toxins that are not used to develop or produce a protective medicine or for other peaceful purposes, and weapons or other equipment that could be used to deliver biological pathogens and toxins for hostile purposes or in armed conflict. The BWC was implemented in federal law through the Biological Weapons Anti-Terrorism Act of 1989.[21]

According to NIH officials, NIH has programs and policies governing compliance with all pertinent federal, state, and local laws, including provisions of the BWC. The NIH Grants Policy Statement mandates that applicants for and recipients of NIH awards adhere to all applicable federal, state, and local laws, statutes, regulations, ordinances, and policies. All recipients of NIH awards agree, as a term of award, that they will comply with all relevant federal, state, and local laws and regulations. While the BWC is not specifically highlighted, NIH officials stated that it falls within the scope of federal laws that must be followed. In the case of the NBLs and RBLs, NIH is funding the construction of the laboratories; should NIH fund research at these laboratories once they are operational, the same term of award will be applied. Additionally, the Notice of Grant Award for the NBLs and RBLs requires the awardees to use the space in support of the NIAID Biodefense Agenda or other NIAID-approved biomedical research activities. NIAID has clearly stated that bioweapons research is not part of that agenda.

Furthermore, NIH uses the peer review process to ensure that research funded by the agency facilitates the exchange of equipment, materials, and scientific and technological information for the use of biological agents and toxins for peaceful purposes, which is a requirement under the BWC. The NIH peer review process provides assurances to NIH and HHS that agency funds are being used to support research for "prophylactic, protective or other peaceful purposes" in compliance with the BWC. NIH officials stated that ultimately, it is the awardee's responsibility to ensure proper use of NIH-awarded funds and ensure their compliance with the terms and conditions of the award. It is the responsibility of the awardee to ensure that its employees are not conducting illegal activities on its property or in its buildings, whether the facilities are federally or nonfederally supported.

[20]Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction, April 10, 1972, 1015 U. N. T. S. 163.

[21]Pub. L. No. 101-298, 104 Stat. 201 (codified at 18 U.S.C. §§ 175 et seq.).

4. Are the NBLs and RBLs barred from doing classified research, or can individual researchers obtain funding from other sources to do classified research at the facility? If classified work is permitted, who would oversee that work? What obligations, if any, would the facility have to inform local authorities or the local community that classified work was being done at the facility?

NIAID officials stated that the NBLs and RBLs would not be barred from conducting classified research with non-NIAID monies. They further stated that NIAID would not require each of the NBLs and RBLs to develop a policy for conducting such research. However, the officials said that NIAID did not fund classified research and that it had no plans to do so.[22] Representatives of the two NBLs stated that while neither institution had policies prohibiting classified research, it would not be conducted at their laboratories. Of the five RBLs whose officials we interviewed, three have institutional policies prohibiting classified research. Representatives at the two remaining RBLs stated that their institutions did not prohibit classified research and that they would consider it.

According to NIAID, if the NBLs and RBLs were to conduct classified research, they would have to comply with all federal, state, and local regulations regarding the oversight of classified research. Pursuant to executive order,[23] an agency head or senior agency official must establish controls to prevent access by unauthorized persons to classified information. There are no federal requirements that local authorities or the local community must be informed that classified work is being done at the facility.

5. What factors did NIAID consider when awarding funding for construction of the NBLs and RBLs? Did the award factors include consideration of the capability of the local public health authority to respond in the event of an accident, the relationship between the laboratory and the surrounding community, and the demographic and geographic environment of the laboratory that might affect risks to the laboratory or the community?

The following factors, which were required as part of the application, were considered by NIAID during the review and selection process for NBL and RBL awardees:

- association with the Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCE);[24]
- ability to support the desired scope of work;
- pertinent experience of the principal investigator and team;

[22]NIAID-funded research will not include research on bioweapons.

[23]Exec. Order No. 13292—Further Amendment to Executive Order 12958, as amended 68 *Fed. Reg.* 15315 (Mar. 28, 2003).

[24]There are 10 RCEs. The purpose of the RCE program is to create a network of institutions with staff and facilities dedicated to developing therapeutics, vaccines, and diagnostics for NIAID's Category A, B, and C priority pathogens.

- community relations plan, which describes how they propose to establish and maintain a strong community relations effort throughout the planning, design, construction, and operation of the facility;
- the ability to serve the purposes of the NIAID biodefense research agendas and to conduct research identified by NIAID as important to program goals;
- the ability to document the availability of matching funds; and
- geographic distribution of the facilities.

In addition, to comply with NEPA, prior to submitting the application for consideration, applicants were required to make a public disclosure to announce the construction project[25] and to analyze the probable environmental impact of proposed projects. Each of the awardees conducted this assessment using a checklist provided by NIH called the Environmental Analysis Form.[26] This form asked applicants to answer yes or no to a series of specific questions regarding the potential impact of the NBL or RBL construction projects. The analysis was intended to convey available environmental information with the initial award application. For example, see the following questions:

- Will the project
  - include the use of wetlands (swamps, marshes, etc.)?
  - decrease the volume of water in a lake, river table, reservoir, etc.?
  - not comply with the local and state land use planning?
  - increase identifiable ambient air pollution levels from a new emission source or from existing sources?
  - generate solid wastes that cannot be properly disposed of by existing facilities?
- Could the proposed project disrupt
  - food supplies, water supplies, or electrical power for 48 hours?
  - existing health services' response in case of a disaster?

[25]NEPA, § 102, as implemented by Exec. Order No. 11514, 35 *Fed. Reg*. 4247 (Mar. 5, 1970).

[26]A group of plaintiffs has filed a motion in Federal District Court, seeking an injunction on federal funding for one of the awardees. The Court has deferred ruling on the motion for preliminary injunction in this case until after conclusion of the supplemental environmental analysis, to be completed in 2007. This analysis will include an assessment of the public health consequences of the accidental release of communicable Category A pathogens and an analysis to determine whether siting of the facility in a less populated area would result in different public health consequences in the event of a release. The university has also committed to developing a community relations plan to improve community input and involvement, and to discussing DNA research protocols and limitations.

- Will the proposed project encroach upon any historical, architectural, or archeological cultural property?

Applicants were required to provide a brief description of the impact if the answer to any question was yes.

The NBL and RBL Request for Proposals and Applications did not require applicants to address the following factors in their applications: the capability of the local public health authority to respond in the event of an accident, the relationship between the laboratory and the surrounding community, and the demographic and geographic environment of the laboratory that might affect the risks to the laboratory or the community. Therefore, if applicants did not address these factors, they were not penalized. However, if the information was submitted as part of the application, it may have been considered by peer reviewers because peer reviewers are instructed to evaluate the application as a whole.

6. In the event that containment of an NBL or RBL has been breached in some manner, what are the obligations of the facility to inform NIH, CDC, and the local public health authorities?

The containment of pathogens, including select agents, can be breached through theft, loss, or release.[27] According to NIAID, it does not have requirements that pertain to instances of the theft, loss, or release of Category A, B, and C priority pathogens.[28] However, laboratories must report such instances as required by the NIH rDNA Guidelines and the Select Agent Regulations and may be required to report such instances under state or local laws.

The NIH rDNA Guidelines specify reporting requirements for significant problems, violations of the NIH rDNA Guidelines, or any significant research-related accidents and illnesses. In general, all such events should be reported to NIH's OBA within 30 days of their occurrence, unless they fit the description of events that must be reported on a more expedited basis. Spills or accidents in the BSL-2 laboratories resulting in an overt exposure must be immediately reported to the IBC and NIH's OBA.[29] Spills or accidents occurring in BSL-3 or BSL-4 laboratories resulting in an overt or potential exposure must be immediately reported to the IBC, BSO, and NIH's OBA.

The Select Agent Regulations require that upon discovery of the theft or loss of a select agent, an individual or entity must immediately notify CDC or APHIS and appropriate federal,

[27]HHS and USDA define theft as the unauthorized removal of a select agent, loss as the failure to account for a select agent, and release as occupational exposure or release of a select agent outside of the primary barriers of the biocontainment area. (See APHIS/CDC Form 3.)

[28]A number of NIAID's pathogens are select agents. Enc. II contains a list of NIAID's Category A, B, and C priority pathogens and indicates whether they are select agents.

[29]Institutions working at a maximum containment level of BSL-2 are not required to have BSOs, and thus the NIH rDNA Guidelines are silent on reporting these events to the BSO, though OBA highly recommends reporting to the BSO as well, when one is on staff.

state, or local law enforcement agencies.[30] While NIAID does not have requirements for reporting theft or loss, CDC and APHIS regulations require that theft or loss of a select agent must be reported even if the select agent is subsequently recovered or the responsible parties are identified.

Upon discovery of a release of a select agent causing occupational exposure or release of a select agent outside the primary barriers of the biocontainment area, an entity or individual must immediately notify CDC or APHIS. After the initial reporting of a theft, loss, or release the entity must submit within 7 calendar days a completed Report of Theft, Loss, or Release of Select Agents and Toxins form.[31] The guidance document for completing this form also states that in the event of theft, loss, or release of select agents or toxins, entities should notify the appropriate local, state, and federal health agencies. Additionally, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002[32] states that if the Secretary of HHS determines, in the case of a release of a select agent, that the release poses a threat to public health or safety, the Secretary must take appropriate action to notify relevant state and local public health authorities, other federal authorities, and if necessary, the public.

State and local health departments in some of the NBL and RBL locations at which we conducted interviews have certain reporting requirements related to select agents. For example, one state requires that every laboratory possessing HHS select agents and conducting business in the state submit an annual report to the state's department of health. In the event of a suspected theft, loss, or release of any select agent, the laboratory's responsible official is required to report to the state's department of health within 24 hours. A local public health authority in a different state requires that an entity immediately report to the local public health department any of the following circumstances that involve specified biological agents, including select agents:

- any spill or accident that results in an exposure and
- any illness among persons caused or potentially caused by the specified biological agents or an attenuated strain[33] of the specified biological agents.

A 2004 incident involving the release of a select agent at a university resulted in that awardee's deciding to develop procedures to prevent this situation in the future. The awardee experienced an inadvertent release of the select agent *Francisella tularensis* in one of its existing laboratories. While CDC and the local public health department had concerns that gaps may have existed in the university's biosafety program that led to the exposure, after reviewing the events, CDC concluded that the university complied with the Select Agent Regulations notification requirements and took adequate actions after the exposure to

[30]42 C.F.R. § 73.19 (2006), 7 C.F.R. § 331.19 (2006), and 9 C.F.R. § 121.19 (2006).

[31]APHIS/CDC Form 3.

[32]Pub. L. No. 107-188, § 201, 116 Stat. 594, 637, 645.

[33]An attenuated strain is a strain of a microorganism that has been altered to diminish its virulence.

prevent similar events from occurring.[34] As a result of this incident, the university developed a policy for strain verification prior to a researcher's beginning any work.[35]

7. What degree of transparency and communication with the community is required of NBLs or RBLs with respect to their individual research projects?

NIAID does not have regulations that address transparency and communication with the community regarding individual research projects at NBLs and RBLs, but it supports a policy of encouraging publication and dissemination of research findings. Public information on federally funded biomedical research projects can be accessed through an Internet-based database called the Computer Retrieval of Information on Scientific Projects (CRISP). CRISP is maintained by NIH and contains information on biomedical research projects funded by a number of HHS agencies, including NIH and CDC. As part of the application for the award, NIAID asked the awardees to develop plans that describe their approach to developing community relations. Further, NIAID employs a community relations consultant, who is available to assist and advise the awardees on their ongoing community relations plans and practices. NIAID also holds annual community relations workshops for the NBLs and RBLs, where they can learn from each other and from NIAID how best to maintain positive relations with their communities and the general public. For example, one university representative at the community relations workshop held in April 2006 described the membership application process and guidelines for a community liaison committee the university was in the process of establishing.

A recent example of a local requirement that promotes transparency and communication with the community is a new regulation promulgated by a local health department in one location where an NBL is being constructed. This regulation applies to BSL-3 and -4 laboratories that operate within the health department's jurisdiction and will apply to any NBLs or RBLs that will operate in the jurisdiction. One of the regulation's requirements is that each entity hold an IBC meeting that is open to the public at least once per calendar year.[36] The regulation stipulates that during this meeting the IBC should review the type and nature of the biological research at BSL-3 and -4 that is conducted by the entity.

In another community, one awardee is working to promote transparency by forming a committee that consists entirely of individuals from the community who are not affiliated with the university. This university would like this committee to help the university better understand the interests and concerns of the community, enhance the dissemination of

[34]Researchers at the laboratory where this release occurred believed they had been working with a nonvirulent form of tularemia that was not a select agent and not subject to the Select Agent Regulations. The researchers became ill, and testing conducted by CDC revealed that the researchers had actually been working with a virulent form of the organism that was known to cause severe illness in humans. According to the local public health department, laboratory practices and safety measures used in the BSL-2 laboratory were inadequate to prevent exposure.

[35]The Occupational Safety and Health Administration conducted an inspection of the facility, but it did not issue a citation for the exposure.

[36]The NIH rDNA Guidelines, which apply to any institution that receives any NIH funding for rDNA research, states the following: "when possible and consistent with protection of privacy and proprietary interests, the institution is encouraged to open its Institutional Biosafety Committee meetings to the public."

information to the community about both the risks and the safety measures undertaken, and help the university develop an incident communication plan.

8. Who is responsible for setting the research agenda and establishing the research protocols for NBLs and RBLs—individual scientists or the manager of the facility?

While the NBLs and RBLs that NIAID funded are intended to conduct research on NIAID's Category A, B, and C priority pathogens in support of the NIAID biodefense agendas or other NIAID-approved biomedical research activities for 20 years, NIAID left it to the discretion of each awardee to establish the research agenda and the research protocols. The NBLs, RBLs, and RCEs are partners in the NIAID Biodefense Network, which helps define the direction and scope of biodefense and emerging infectious disease research activities within the NBLs, RBLs, and RCEs and ensures that the programs are meeting the goals of the NIAID *Biodefense Strategic Plan* and *Research Agendas*. The NIAID Biodefense Network meets at least annually, or as needed in the event of a biodefense emergency or an emerging infectious disease emergency. The purpose of these meetings is to share scientific information, assess scientific progress, identify new research and development and collaboration opportunities, and establish research priorities. Additionally, the facilities must be available and prepared to assist national, state, and local public health efforts in the event of a bioterrorist emergency. In addition, NIAID staff will be able to monitor the research conducted at each NBL and RBL by conducting periodic site visits to the facilities and reviewing the annual progress report that awardees are required to submit, which is supposed to describe the activities and accomplishments during the prior year.

NIAID Category A, B, and C Priority Pathogens and Those Designated as Select Agents

NIAID Category A, B, or C priority pathogen[a]	NIAID category			Select agent	Notes
	A	B	C		
Antimicrobial resistance, excluding research on sexually transmitted organisms			■		While not a specific pathogen, antimicrobial resistance is on the NIAID list. Antimicrobial resistance is the result of microbes changing in ways that reduce or eliminate the effectiveness of drugs, chemicals, or other agents to cure or prevent infections.
Bacillus anthracis (anthrax)	■			■	
Brucella species (brucellosis)		■			Three *Brucella* species—*Brucella abortus*, *Brucella melitensis*, and *Brucella suis*—are select agents.
Burkholderia mallei (glanders)		■		■	
Burkholderia pseudomallei		■		■	
Caliciviruses		■			
California encephalitis		■			
Campylobacter jejuni		■			
Clostridium botulinum [Botulinum neurotoxin producing species of *Clostridium*]	■			■	
Coxiella burnetii (Q fever)		■		■	
Crimean-Congo hemorrhagic fever virus			■	■	
Cryptosporidium parvum		■			
Cyclospora cayatanensis		■			
Dengue	■				
Diarrheagenic *E. coli*		■			
Ebola	■			■	
EEE [eastern equine encephalitis virus]		■		■	
Entamoeba histolytica		■			
Epsilon toxin of *Clostridium perfringens*		■		■	
Francisella tularensis (tularemia)	■			■	
Giardia lamblia		■			
Guanarito virus [South American hemorrhagic fever: Guanarito[b]]	■			■	
Hantaviruses	■				
Hepatitis A		■			

NIAID Category A, B, or C priority pathogen[a]	NIAID category A	B	C	Select agent	Notes
Influenza			■		Two influenza strains—Avian influenza virus (highly pathogenic) and reconstructed 1918 influenza virus—are select agents.
Japanese encephalitis virus		■		■	
Junin virus [South American hemorrhagic fever: Junin]	■			■	
Kyasanur Forest virus [Tick-borne encephalitis complex (flavi) virus: Kyasanur Forest disease]		■		■	
LaCrosse		■			
Lassa fever	■			■	
LCM (Lymphocytic choriomeningitis virus)	■				
Listeria monocytogenes		■			
Machupo virus [South American hemorrhagic fever: Machupo]	■			■	
Marburg	■			■	
Microsporidia		■			
Multidrug-resistant TB			■		
Nipah virus			■	■	
Other Rickettsias			■		One *Rickettsia* species, *Rickettsia rickettsii*, is a select agent and is a NIAID Category B pathogen.
Pathogenic vibrios		■			
Rabies			■		
Ricin toxin (from *Ricinus communis*)		■		■	
Rift Valley fever virus	■			■	
Salmonella		■			
Severe acute respiratory syndrome-associated coronavirus (SARS-CoV)			■		
Shigella species		■			The bacterial *Shigella* species are not select agents. Some bacterial *Shigella* species express a potent toxin called shiga toxins (shigatoxin) or shiga-like ribosome-inactivating proteins. Above a certain threshold amount listed at 43 C.F.R. § 73.3, shigatoxin and shiga-like ribosome inactivating proteins are select agents.
Staphylococcus enterotoxin B [staphylococcal enterotoxins]		■		■	Only staphylococcus enterotoxin B is a NIAID Category B pathogen; however, all staphylococcal enterotoxins are select agents.
Tick-borne encephalitis viruses			■		Five species of tick-borne encephalitis viruses are also select agents: central European tick-borne encephalitis, Far Eastern tick-borne encephalitis, Omsk hemorrhagic fever, and Russian spring and summer encephalitis.

NIAID Category A, B, or C priority pathogen[a]	NIAID category A	B	C	Select agent	Notes
Toxoplasma		■			
Typhus fever (*Rickettsia prowazekii*)		■		■	
Variola major (smallpox) and other pox viruses	■			■	In addition to *Variola major*, camel pox virus, goat pox virus, sheep pox virus, monkey pox virus, and *Variola minor* virus (Alastrim) are select agents and NIAID Category A pathogens.
VEE [Venezuelan equine encephalitis virus]		■		■	
WEE (Western equine encephalitis virus)		■			
West Nile virus		■			
Yellow fever			■		
Yersinia enterocolitica		■			
Yersinia pestis	■			■	

Source: GAO.

[a]Taxonomic names of pathogens are given in italics. If the name of the pathogen as designated by HHS or USDA differs from the NIAID designation, the select agent designation is given in brackets.

[b]There are six South American hemorrhagic fevers that are NIAID Category A pathogens and also select agents; however, only four are listed above—Guanarito, Junin, Lassa fever, and Machupo. The other two are Flexal and Sabia.

Examples of Regulations and Guidelines Applicable to the NBLs and RBLs

All NBLs and RBLs are required to comply with all federal, state, and local regulations and to sign assurances that they will comply with all regulations. In addition to the regulations and guidelines described in enclosure I, listed below are other federal regulations and guidelines that could affect NBL and RBL operations and security procedures.

Regulations

- 15 C.F.R. pts. 738, 742, 745, and 774 (2006)—Implementation of Unilateral Chemical/Biological Controls on Certain Biological Agents and Toxins—expands export and reexport controls on certain biological agents and toxins (referred to as select agents and toxins) that have been determined by CDC (HHS) and APHIS (USDA) to have the potential to pose a severe threat to human, animal, and plant life, as well as certain sectors of the U.S. economy (e.g., agriculture).

- 29 C.F.R. pt. 1910.1200 (2006)—Hazard Communication—requires that the hazards of all chemicals produced or imported are evaluated and that information concerning the hazards is transmitted to employers and employees. This transmittal of information is to be accomplished by means of comprehensive hazard communication programs, which are to include container labeling and other forms of warning, material safety data sheets, and employee training.

- 29 C.F.R. pt. 1910.1201 (2006)—Retention of DOT Markings, Placards and Labels—requires that an employer that receives a package of hazardous material which is required to be marked or labeled in accordance with the Department of Transportation's (DOT) Hazardous Materials Regulations shall retain the markings, placards, and labels on the package until the packaging is sufficiently cleaned of residue and purged of vapors to remove any potential hazards.

- 29 C.F.R. § 1910.1030 (2006)—Occupational Exposure to Bloodborne Pathogens—provides a standard on working safely with human blood and body fluids. This standard outlines the requirements for employers, including research laboratories, that are working with human body fluids, tissues, and potential bloodborne pathogens. The standard provides information concerning facility requirements, safe work practices, medical surveillance, personal protection, first-aid procedures, and worker training.

- 29 C.F.R. § 1910.1450 (2006)—Occupational Exposure to Hazardous Chemicals in Laboratories—requires that employers develop and carry out the provisions of a written chemical hygiene plan (CHP). The purpose of a CHP is to provide the necessary work practices, procedures, and policies to ensure that laboratory employees are protected from exposure to potentially hazardous chemicals in use in their work areas and that employees are trained in the plan.

- 42 C.F.R. pt. 72 (2006)—Interstate Shipment of Etiologic Agents—specifies packaging and labeling requirements and procedures for notification of successful delivery or failure of delivery of etiologic agents. CDC has proposed rescinding this regulation to alleviate confusion with existing regulations.[37]

[37]72 *Fed. Reg.* 92 (Jan. 3, 2007).

- 45 C.F.R. pt. 46 (2006)—Protection of Human Subjects—stipulates substantive and procedural requirements for investigators and institutions engaged in federally supported or federally conducted research with humans.

- 49 C.F.R. pts. 171-178 (2006)—Transportation of Hazardous Materials—provides regulations for the safe transportation of both biological and clinical specimens.

Guidelines

- *Guide for the Care and Use of Laboratory Animals* assists institutions in caring for and using animals in ways judged to be scientifically, technically, and humanely appropriate, and is also intended to assist investigators in fulfilling their obligation to plan and conduct animal experiments in accord with the highest scientific, humane, and ethical principles.

- "Laboratory Security and Emergency Response Guidance for Laboratories Working with Select Agents," *MMWR*, December 6, 2002, is intended for laboratories working with select agents under BSL-2, -3, or -4 conditions as described in sections II and III of BMBL, and includes recommendations for conducting facility risk assessments and developing comprehensive security plans to minimize the probability of misuse of select agents.

- *NIH Grants Policy Statement* is intended to make available to NIH awardees, in a single document, the policy requirements that serve as the general terms and conditions of NIH awards. This document also is designed to provide information about NIH—its organization, its staff, and its grant process.

- *Good Laboratory Practice for Nonclinical Laboratory Studies* applies if a laboratory conducts studies that support or are intended to support applications for research or marketing permits for products regulated by HHS's Food and Drug Administration (FDA).[38] Under these regulations, the facility and its records are subject to inspection by FDA.

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[38]The awardees are also required in the Notice of Grant Award to design the NBLs and RBLs in accordance with the Good Laboratory Practice guidelines.

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