WRRHC is a successful community health center that provides services to 10 counties within Arkansas and has over 22 years of experience in managing State and federally funded programs, including three previous Rural Health Services Outreach grants. The comprehensive services that WRRHC provides and their ability to expand their service area will enable WRRHC to maintain the current scope of service and activities as originally awarded under the grant to Siloam Springs Memorial Hospital. This replacement award will help ensure the continued improvement of health care systems in the targeted service area. WRRHC has a demonstrated record of sound stewardship of Federal funds and can effectively serve as the network lead for the remainder period of support in a manner which minimizes any disruption of services provided by the network. Consequently, White River Rural Health Center has been designated the replacement award recipient.

HRSA is unaware of any other entity that both meets the statutory eligibility requirements and has the ability to carry out these activities.

FOR FURTHER INFORMATION CONTACT: Tom Morris, Associate Administrator, Office of Rural Health Policy, Health Resources and Services Administration, 5600 Fishers Lane, Rockville, MD 20857; phone 301–443–0835; *tmorris@hrsa.hhs.gov*.

Dated: September 16, 2009.

Mary K. Wakefield,

Administrator.

[FR Doc. E9–22815 Filed 9–21–09; 8:45 am]

BILLING CODE 4165–15–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of Biotechnology Activities; Recombinant DNA Research: Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)

AGENCY: National Institutes of Health (NIH), Department of Health and Human Services (HHS).

ACTION: Notice of changes to the NIH Guidelines.

SUMMARY: Concerns about the emergence of a pandemic influenza virus have spurred research on influenza viruses that have either caused pandemics or are believed to have the potential to cause a pandemic. These viruses include human H2N2 virus, which circulated from 1957–1968, the 1918–1919 H1N1, which caused the deadliest pandemic in the past century, and the Highly Pathogenic Avian Influenza (HPAI) H5N1 virus that is thought to have pandemic potential. The public health benefits of this research include developing a better understanding of the pathogenicity of pandemic influenza viruses, their virulence mechanisms, mechanisms of host adaptation, and ultimately the development of vaccines and antiviral drugs. These benefits are balanced against the potential risks that might include the inadvertent release of a highly transmissible and potentially virulent influenza virus. Consequently, explicit and uniform biosafety containment practices are critical to the safe conduct of research with these agents. The *NIH Guidelines* provide a framework for assessing the risks of such research. However, after extensive consultation with the NIH Recombinant DNA Advisory Committee (RAC), experts in biosafety and influenza, the Centers for Disease Control and Prevention (CDC), and the U.S. Department of Agriculture (USDA), the NIH Office of Biotechnology Activities (OBA) concluded that more specific guidance in the *NIH Guidelines* is warranted to promote uniform biosafety practices for recombinant research with these viruses.

The resulting amendments are ''Minor Actions'' under Section IV–C–1–(b)–2 of the *NIH Guidelines* and, therefore, will be implemented immediately upon publication in the **Federal Register.** While a Minor Action only requires consultation with the RAC chair and one or more RAC members, as necessary, as noted above, these changes were developed after extensive consultation with the full RAC and other experts and were discussed at three public RAC meetings. The RAC voted on March 4, 2009 to recommend these changes. They are being published to inform the scientific and biosafety communities, as well as to solicit continued scientific input should further revisions be needed.

The *NIH Guidelines* are being changed to provide the following biosafety guidance for research with potentially pandemic influenza viruses:

- Designation of human H2N2 viruses that circulated from 1957–1968 (human H2N2 (1957–1968)), the fully reconstructed 1918–1919 H1N1 influenza virus (1918 H1N1), and Highly Pathogenic Avian Influenza (HPAI) H5N1 within the Goose/Guangdong/96-like H5 lineage (HPAI H5N1) as Risk Group 3 agents. Risk Group 3 agents have the potential to cause serious or lethal disease in humans for which preventative and therapeutic measures may be available. Up until this revision, all influenza viruses (Orthomyxoviruses) were Risk Group 2 agents, which are agents that are associated with human disease that is rarely serious and for which preventative and therapeutic agents are often available.
- Requirement for enhanced biosafety practices, including the use of powered air purifying respirators (PAPRs) and other personal protective equipment to prevent laboratory worker exposure and minimize the risk of spread outside of the laboratory.
- Guidance on the containment for research with influenza viruses generated by recombinant methods (*e.g.,* generation by reverse genetics of chimeric viruses with reassorted segments, introduction of specific mutations) containing one or more genes and/or segments from human H2N2 (1957–1968), 1918 H1N1 or HPAI H5N1. For 1918 H1N1, the *NIH Guidelines* will require Biosafety Level 3 enhanced containment for all influenza viruses that contain one of more genes and/or segments from 1918 H1N1 because of the uncertainty about the virulence factors for this agent.
- Guidance on occupational health practices, including policies regarding the use of prophylactic antiviral agents and isolation of laboratory workers who are exposed to one of these viruses.

DATES: The public is encouraged to submit written comments on this action. Comments may be submitted to OBA in paper or electronic form at the OBA mailing, fax, and e-mail addresses shown below under the heading **FOR FURTHER INFORMATION CONTACT**. All comments should be submitted by September 22, 2010. All written comments received in response to this notice will be available for public inspection in the NIH OBA office, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892–7985, weekdays between the hours of 8:30 a.m. and 5 p.m. and may be posted to OBA's Web site.

FOR FURTHER INFORMATION: If you have questions, or require additional information about these changes, please contact OBA by e-mail at *oba@od.nih.gov,* or telephone at 301–496–9838. Comments may be submitted to the same e-mail address or by fax at 301–496–9839 or by mail to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, Maryland 20892–7985. Background information may be obtained by

contacting NIH OBA by e-mail at *oba@od.nih.gov.*

SUPPLEMENTARY INFORMATION:

Background

Recently, NIH support for research with influenza viruses involving recombinant DNA technology has significantly increased. The development of new laboratory methods, such as reverse genetics, has allowed for easier and more rapid generation of infectious influenza viruses from DNA plasmids, *e.g.* reassortant viruses. An increasing proportion of such research has focused on pandemic or potentially pandemic viruses. These include previously pandemic viruses that are not currently circulating in the human population, such as the human H2N2 virus that caused a pandemic resulting in approximately 66,000 excess deaths in the U.S. in 1957 and the 1918 H1N1 virus, which caused 20–40 million excess deaths worldwide. Another focus of research is currently circulating highly pathogenic avian influenza viruses (HPAI) that may have potential to cause a human pandemic if efficient human-to-human transmission were to develop. Over 400 cases worldwide of human infection with the HPAI H5N1 virus have been reported to date with approximately 60% mortality rate; however, evidence of human-to-human transmission has been limited to small, familial clusters.

The public health benefits of research on potentially pandemic influenza viruses include identification of viral proteins that contribute to host adaptation and virulence to increase understanding of the pathogenicity of influenza viruses during pandemics, development of vaccine candidates, and identification of targets for antiviral drugs. While research into influenza viral virulence mechanisms and the development of vaccines and antiviral drugs are public health priorities, it is equally important that the research be performed under appropriate biocontainment to protect the health of laboratory researchers and the public.

There are currently other biosafety requirements for certain types of research with these viruses. The CDC/NIH *Biosafety in Microbiological and Biomedical Laboratories* (5th edition) (BMBL) recommends Biosafety Level 3 with additional personal protection equipment designed to minimize the risk of laboratory acquired infection for research with the reconstructed replication competent forms of 1918 H1N1 (i.e. Biosafety Level 3 enhanced). Reconstructed replication competent forms of 1918 pandemic influenza virus H1N1 were designated HHS/CDC Select Agents in 2005 (70 FR 61047). The BMBL also recommends Biosafety Level 3 containment level for research with the full human H2N2 virus (1957–1968) with enhancements designed to prevent laboratory acquired respiratory infection.

HPAI H5N1 influenza viruses are USDA Select Agents (9 CFR 121.3(b)). The USDA's Animal and Plant Health Inspection Service (APHIS) regulates as a Select Agent avian influenza viruses (and constructs thereof pursuant to 9 CFR 121.3(c)(3)) that demonstrate a high pathogenicity index in chickens, contain a specific poly-basic amino acid motif at the hemagglutinin (HA) gene cleavage site (or have an amino acid sequence at the cleavage site of the HA gene that is compatible with other highly pathogenic avian influenza viruses) and show growth characteristics of influenza virus in the presence and absence of trypsin. Avian influenza viruses that demonstrate evidence of attenuation in poultry can be excluded pursuant to 9 CFR 121.3(e). The biosafety containment level recommended for most Select Agent research with these viruses is a minimum of Biosafety Level 3 enhanced or Animal Biosafety Level 3 (ABSL3) enhanced. Influenza viruses containing genes from highly pathogenic avian influenza virus that are not classified as Select Agents by USDA are still regulated by that agency through ''permitting'' regulations (9 CFR 122), which govern imports and interstate movements of the viruses.

The current (April 2002) *NIH Guidelines* classify influenza viruses A, B, and C as Risk Group 2 agents in Appendix B. No distinction is made between potentially pandemic strains of influenza and other lower risk influenza viruses. According to the *NIH Guidelines,* an initial risk assessment is based on the Risk Group (RG) of the parent agent; however, appropriate containment is set following consideration of the specific agent and how it is to be manipulated. The *NIH Guidelines* emphasize that containment levels for recombinant research may be raised or lowered relative to the RG classification of the parent agent after a comprehensive risk assessment.

Up until today, the *NIH Guidelines* had not been amended to address specifically recombinant influenza viruses that contain genes and/or segments from human H2N2 (1957–1968), 1918 H1N1 and HPAI H5N1 viruses. Therefore, to clarify and augment the current biosafety guidance in the *NIH Guidelines* for research with potentially pandemic influenza viruses, and to harmonize with the BMBL and other regulatory policies, NIH/OBA in consultation with the RAC and outside experts, including the CDC and USDA, reviewed and revised the Risk Group designations for potentially pandemic influenza viruses human H2N2 (1957–1968), 1918 H1N1, and HPAI H5N1 and developed additional containment and occupational health guidance for research involving recombinant influenza viruses containing genes from these influenza viruses.

In determining the Risk Group (RG) classification for human H2N2 (1957–1968), 1918 H1N1 and HPAI H5N1, the RAC considered the definition of risk groups in Appendix B. Risk Group 3 agents are those ''that are associated with serious or lethal disease for which preventative or therapeutic interventions may be available (high individual risk but low community risk).'' Each strain was considered to be a risk for serious or lethal disease, although it was recognized that the case fatality rate for HPAI H5N1 is very high, over 50 percent, whereas the case fatality rate for 1918 H1N1 is considerably lower in the range of 1–2 percent. Human H2N2 caused a much milder pandemic compared to 1918 H1N1, but because it has not circulated for over forty years, a large population will likely not have immunity to the virus and therefore is at risk of serious disease. ''Preventative or therapeutic interventions may be available'' for infection with each of these viruses as there is evidence that the antiviral agents used against seasonal influenza are effective for prophylactic and therapeutic use for each virus and antibiotics are available for secondary bacterial pneumonias should they develop. Virus specific vaccines are not currently available to prevent infection. However, they are being developed and stockpiled for HPAI H5N1, and sources exist for the possible development of 1918 H1N1 or human H2N2 (1957–1968) vaccines for laboratory workers who might be exposed or in the unlikely event of a release of the virus into the general population. In the case of human H2N2 (1957–1968), some pre-existing immunity is likely in the population that was exposed to human H2N2 while these viruses circulated from 1957–1968 or from cross-reactivity with N2 in the currently circulating H3N2 strain. For 1918 H1N1, partial immunoprotection may exist from previous exposure or vaccination with recently circulating H1N1 strains, but definitive data are lacking. An important additional consideration for

HPAI H5N1 RG classification was that, while the individual risk of serious or lethal disease is quite high, the community risk is currently considered low, as there is only limited evidence for human-to-human transmission. Based on these considerations, influenza viruses 1918 H1N1, human H2N2 (1957–1968), and highly pathogenic avian influenza H5N1 viruses within the Goose/Guangdong/96-like H5 lineage will be classified as Risk Group 3 agents in Appendix B–III–D. All viruses within HPAI H5N1 lineages that have been associated with human disease, whether it is mild or severe and fatal, will be classified as RG3 agents. Thus BL3 enhanced containment will apply to a virus evolving from the current lineages that causes milder disease in humans, which could indicate adaptation to the human host.

Because the generation of influenza viruses by reassorting RNA segments by recombinant techniques (*i.e.,* reverse genetics) does not take place in a single host-vector system, OBA has received questions about which sections of the *NIH Guidelines* apply to such research with influenza viruses. Sections III–D–1 or III–D–2 (research that falls under Section III–D requires Institutional Biosafety Committee approval before initiation) refer to specific host-vector systems and, therefore, do not specifically address this research. To clarify this, an additional section has been added: Section III–D–7–Experiments Involving Influenza Viruses. This section will apply to recombinant research with influenza viruses (*e.g.,* chimeric viruses with reassorted segments generated by reverse genetics, viruses in which specific mutations are introduced).

Additional biosafety guidance for research with 1918 H1N1, HPAI H5N1 within the Goose/Guangdong/96-like H5 lineage and human H2N2 (1957–1968) has been included in Appendix G–II–C–5. Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses. In addition to the standard BL3 containment and practices, the RAC recommended specific enhancements for research with these viruses including personal protective equipment (*e.g.,* powered air-purifying respirators, protective suits), practices and procedures (*e.g.,* clothing changes, showers when appropriate). In addition, the RAC made specific recommendations on training for these enhanced practices. Guidance is also provided for avoidance of inadvertent cross-contamination during research. To address the potential public health risks of a laboratory exposure, this section also includes recommendations for development of a detailed occupational health plan for research with each virus, including how to respond to known laboratory exposures or development of an influenza-like illness in laboratory workers. The community risk from an inadvertent laboratory release of a virus with human H2N2 (1957–1968) or 1918 H1N1 is expected to be higher than for HPAI H5N1. Consequently, the occupational health recommendations for the response to a known laboratory exposure differ depending on whether the exposure was to HPAI H5N1, a virus that currently does not efficiently transmit human-to-human, or to either human H2N2 (1957–1968) or 1918 H1N1, both of which have previously caused pandemics, therefore demonstrating efficient human-to-human transmission. These recommendations regarding occupational health are also included in Appendix G–II–C–5.

During development of the occupational health recommendations, the RAC discussed the use of pre-exposure prophylaxis with antiviral agents (*e.g.,* oseltamivir) for research with 1918 H1N1. Initially, the RAC had proposed recommending a practice that is in place at the CDC (the first lab to work with 1918 H1N1), namely that researchers working with 1918 H1N1 take pre-exposure prophylaxis with the antiviral oseltamivir for their protection, and to further limit the risk to the public. In addition, the Intragovernmental Select Agents and Toxins Technical Advisory Committee (ISATTAC), an advisory body to the USDA and CDC Select Agent Programs, recommended that the CDC Select Agent Program require pre-exposure prophylaxis for research with 1918 H1N1 at BL3 enhanced but not at BL4 containment. This recommendation was adopted by the CDC Select Agent Program. However, as research on 1918 H1N1 progressed and more was learned about the virus, other influenza researchers expressed concerns that the risks of long-term use of antiviral drugs would not be balanced by potential benefit to the investigator or the public.

To address this issue, the RAC and ISATTAC convened a Safety Symposium on Public Health and Biosafety Practices for Research with 1918 H1N1 Influenza Virus on December 2, 2008 (a Webcast of the meeting is available at *http://oba.od.nih.gov/rdna_rac/rac_past_meetings_2000.html*). The discussion at the safety symposium focused on the scientific data regarding the efficacy of prophylactic administration and use of oseltamivir for extended periods of time, as well as public health and ethical issues. The RAC concluded that while prophylaxis can reduce the likelihood of an individual laboratory worker developing symptoms or complications should they become infected, it will not eliminate the risk of transmission to the community. Further, although the medications are generally safe, there are risks, and data on long-term use (beyond 6 weeks) are limited. Therefore, the RAC concluded that the data do not support mandating pre-exposure prophylaxis. Instead, the RAC recommended that the use of antiviral agents as pre-exposure prophylaxis be discussed with laboratory workers and used on a case-by-case basis, after a risk assessment and appropriate counseling of the laboratory worker about the risks and potential benefits. Antiviral agents are recommended for post-exposure prophylaxis after medical evaluation.

While most research with these viruses will be conducted at BL3 with specific enhanced practices, the RAC also considered whether certain research could be safely conducted at lower containment. After consulting with experts in influenza virology, the RAC concluded that due to the multigenic determinants of virulence observed in influenza viruses, it is difficult to predict the phenotype of recombinant influenza viruses created by reassorting segments from multiple strains of influenza viruses. As the current data are insufficient to generate a predictive framework upon which to base the risk assessment, a case-by-case evaluation is more appropriate.

Section III–D–7 will specify when an IBC may determine containment for certain research (*e.g.,* research with H2 HA in cold-adapted, live attenuated vaccine strains, or research with chimeric influenza viruses containing a minority of genes and/or segments from HPAI H5N1) and when requests to lower containment must be considered by the NIH (*e.g.,* research with recombinant viruses containing any gene and/or segment from 1918 H1N1).

Because the revisions outlined herein are considered Minor Actions as defined in Section IV–C–1–b–(2) of the *NIH Guidelines,* public and Federal Agency comment is not required and the changes are to be implemented immediately. However, in order to promote transparency and to gather ongoing input from scientific community, OBA is publishing these changes in the **Federal Register** with opportunity for public comment. The *NIH Guidelines* are intended to be an evolving document that may be modified to address new developments

in research. As the influenza virology field advances, new data will emerge to inform risk assessments for research with these viruses. The public is encouraged to submit written comments, in particular on the following question regarding containment for 1918 H1N1:

• What data can be used to confidently predict an influenza virus containing one or more genes from the 1918 H1N1 virus can be worked with safely at biosafety containment level lower than Biosafety level 3 enhanced? Are there animal models of infection that are consistent and predictive of attenuation or loss of virulence in humans? What data should be used to assess attenuation in animal model(s)? What criteria should be used to evaluate a request for reduction of containment?

When data are available to answer these questions, or new data emerges regarding other aspects of these changes, the framework will be reevaluated.

Amendments to the *NIH Guidelines*

In order to ensure that biosafety considerations for research with human H2N2 (1957–1968), 1918 H1N1 and HPAI H5N1 are addressed appropriately, the NIH/OBA has made the following changes to the *NIH Guidelines:*

Section III–D–7. Experiments Involving Influenza Viruses

This section will apply to recombinant experiments with influenza viruses that contain genes and/or segments from human H2N2 (1957–1968), HPAI H5N1, and 1918 H1N1 (*e.g.,* chimeric viruses with reassorted segments generated by reverse genetics, viruses in which specific mutations are introduced). Because the generation of viruses by reassortment of RNA segments does not involve a single host-vector system, such experiments do not fit neatly into Sections III–D–1 or III–D–2. The new Section III–D–7 states: ''Experiments with influenza viruses generated by recombinant methods (*e.g.,* generation by reverse genetics of chimeric viruses with reassorted segments, introduction of specific mutations) shall be conducted at the biosafety level containment corresponding to the risk group of the virus that was the source of the majority of segments in the recombinant virus (*e.g.,* experiments with viruses containing a majority of segments from a RG3 virus shall be conducted at BL3). Experiments with influenza viruses containing genes or segments from 1918–1919 H1N1 (1918 H1N1), human H2N2 (1957–1968) and highly pathogenic avian influenza H5N1 strains within the Goose/Guangdong/96-like H5 lineage (HPAI H5N1) shall be conducted at BL3 enhanced containment (see Appendix G–II–C–5, Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses) unless indicated below.''

Section III–D–7–a. Human H2N2 (1957–1968). Experiments with influenza viruses containing the H2 hemagglutinin (HA) segment shall be conducted at BL3 enhanced (see Appendix G–II–C–5, Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses). Experiments with the H2 HA gene in cold-adapted, live attenuated vaccine strains (*e.g.,* A/Ann Arbor/6/60 H2N2) may be conducted at BL2 containment provided segments with mutations conferring temperature sensitivity and attenuation are not altered in the recombinant virus. Experiments with Risk Group 2 influenza viruses containing genes from human H2N2 (1957–1968) other than the HA gene can be worked on at BL2.

Section III–D–7–b. Highly Pathogenic Avian Influenza H5N1 strains within the Goose/Guangdong/96-like H5 lineage (HPAI H5N1). Experiments involving influenza viruses containing a majority of genes and/or segments from a HPAI H5N1 influenza virus shall be conducted at BL3 enhanced containment, (see Appendix G–II–C–5, Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses). Experiments involving influenza viruses containing a minority of genes and/or segments from a HPAI H5N1 influenza virus shall be conducted at BL3 enhanced unless a risk assessment performed by the IBC determines that they can be conducted safely at biosafety level 2 and after they have been excluded pursuant to 9 CFR 121.3(e). OBA is available to IBCs to provide consultation with the RAC and influenza virus experts when risk assessments are being made to determine the appropriate biocontainment for experiments with influenza viruses containing a minority of gene/segments from HPAI H5N1. Such experiments may be performed at BL3 enhanced containment or containment may be lowered to biosafety level 2, the level of containment for most research with other influenza viruses. (USDA/APHIS regulations and decisions on lowering containment also apply.) In deciding to lower containment, the IBC should consider whether, in at least two animal models (*e.g.,* ferret, mouse, Syrian golden hamster, cotton rat, non-human primates), there is evidence that the resulting influenza virus shows reduced replication and virulence compared to the parental RG3 virus at relevant doses. This should be determined by measuring biological indices appropriate for the specific animal model (*e.g.,* severe weight loss, elevated temperature, mortality or neurological symptoms).

Section III–D–7–c. 1918 H1N1. Experiments involving influenza viruses containing any gene or segment from 1918 H1N1 shall be conducted at BL3 enhanced containment (see Appendix G–II–C–5, Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses).

Section III–D–7-d. Antiviral Susceptibility and Containment. The availability of antiviral drugs as preventive and therapeutic measures is an important safeguard for experiments with 1918 H1N1, HPAI H5N1, and human H2N2 (1957–1968). If an influenza virus containing genes from one of these viruses is resistant to both classes of current antiviral agents, adamantanes and neuraminidase inhibitors, higher containment may be required based on the risk assessment considering transmissibility to humans, virulence, pandemic potential, alternative antiviral agents if available, etc. Experiments with 1918 H1N1, human H2N2 (1957–1968) or HPAI H5N1 that are designed to create resistance to neuraminidase inhibitors or other effective antiviral agents (including investigational antiviral agents being developed for influenza) would be subject to Section III–A–1 (Major Actions) and require RAC review and NIH Director approval. As per Section I–A–1 of the *NIH Guidelines,* if the agent is a Select Agent, the NIH will defer to the appropriate Federal agency (HHS or USDA Select Agent Divisions) on such experiments.

Appendix B. Classification of Human Etiologic Agents on the Basis of Hazard

Currently all influenza viruses types A, B, and C are classified as Risk Group 2 agents. Appendix B–II–D currently states:

Appendix B–II–D. Risk Group 2 (RG2)—Viruses

Orthomyxoviruses

—Influenza viruses types A, B, and C.

—Other, tick-borne orthomyxoviruses as listed in the reference source (*see Section V–C, Footnotes and Reference of Sections I through IV*).

The revised Appendix B–II–D states:

Orthomyxoviruses

—Influenza viruses types A, B, and C (except those listed in Appendix B–III–D (RG3)).
—Tick-borne orthomyxoviruses.

The phrase ''as listed in the reference source (see Section V–C, *Footnotes and References of Sections I through IV*)'' will be deleted from the revised Appendix B–II–D due to the fact that tick-borne orthomyxoviruses are not listed in the current version of the reference source.

The following is added to Appendix B–III–D. Risk Group 3 (RG3)—Viruses and Prions

Orthomyxoviruses

—Influenza viruses 1918–1919 H1N1 (1918 H1N1), human H2N2 (1957–1968), and highly pathogenic avian influenza H5N1 strains within the Goose/Guangdong/96-like H5 lineage (HPAI H5N1).

Appendix G–II–C–5. Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses

Appendix G–II–C–5 provides additional and specific biosafety guidance for research with 1918 H1N1, human H2N2 (1957–1968), and HPAI H5N1 viruses and is intended to supplement the guidance provided in Appendix G. Physical Containment and Appendix Q. Physical and Biological Containment for Recombinant DNA Research Involving Animals, which applies to large research animals. Any enhancements to standard BL3 facilities, practices, and procedures that are described in Appendix G–II–C–5–a shall be considered specific for research with the Risk Group 3 influenza viruses. Risk assessments for research with other agents may also determine that enhancements to standard containment are necessary, but such enhancements must be determined for the specific agents and experiments being proposed.

Influenza viruses that contain the hemagglutinin gene from a HPAI avian influenza are Select Agents and research with such viruses is regulated by the USDA. The fully reconstructed 1918 H1N1 virus is a Select Agent regulated by the HHS/CDC and certain experiments with genes and/or segments from 1918 may be regulated by HHS/CDC. Therefore, additional containment practices may apply and OBA will defer to the regulatory decisions of these agencies. Research with reassortant influenza viruses containing segments or genes from HPAI H5N1 will also require a permit from USDA/APHIS specifying containment and may require additional practices beyond those described in the *NIH Guidelines.*

Appendix G–II–C–5–a. Containment, Practices, and Training for Research with Risk Group 3 Influenza Viruses (BL3 Enhanced)

Appendix G–II–C–5–a–(1). In addition to standard BL3 practices, the following additional personal protective equipment and practices shall be used:

(1) Powered Air-purifying Respirators (PAPR) are worn.

(2) Street clothes are changed to protective suit (*e.g.,* wrap-back disposable gown, olefin protective suit).

(3) Double gloves are worn.

(4) Appropriate shoe coverings are worn (*e.g.,* double disposable shoe coverings, single disposable shoe coverings if worn with footwear dedicated to BL3 enhanced laboratory use, or impervious boots or shoes of rubber or other suitable material that can be decontaminated).

(5) Showers prior to exiting the laboratory should be considered depending on risk assessment of research activities.

Appendix G–II–C–5–a–(2). As proper training of laboratory workers is an essential component of biosafety, retraining and periodic reassessments (at least annually) in BL3 enhanced practices, especially the proper use of respiratory equipment, such as PAPRs, and clothing changes is required.

Appendix G–II–C–5–a–(3). Reporting of all spills and accidents, even if relatively minor, is required as described in Appendix G–II–C–2–q.

Appendix G–II–C–5–a–(4). To avoid inadvertent cross contamination of 1918 H1N1, HPAI H5N1 or human H2N2 (1957–1968):

(1) Containment facilities and practices appropriate for highest risk group virus shall be used at all times with lower risk group viruses, when studied in the same laboratory room.

(2) Tissue cultures with these viruses shall be conducted at separate times (temporal spacing) in the same room.

(3) Separate reagents shall be used to minimize risk of cross contamination.

(4) A laboratory worker shall not perform concurrent influenza virus experiments that carry the risk of unintended reassortment among 1918 H1N1, human H2N2 (1957–1968), HPAI H5N1 and other human influenza viruses.

(5) Two or more laboratory workers shall not perform within the same work area simultaneous influenza virus experiments that carry the risk of unintended segment reassortment between 1918 H1N1, or HPAI H5N1, or human H2N2 (1957–1968) and other human influenza viruses.

(6) Between experiments good biosafety decontamination practices (e.g., surface and biosafety cabinet surface decontamination according to standard BL3 procedures) shall be used and there shall be a thirty minute wait period after decontamination before equipment is used for experiments with any other influenza A viruses.

(7) Between experiments, in addition to decontamination of the work area, clothing changes and PAPR disinfection shall be performed prior to handling a different influenza virus in the same work area. (Shower-out capability may be required by USDA/APHIS for certain experiments with HPAI H5N1.)

Appendix G–II–C–5–a–(5). Continued susceptibility of the reassortant influenza viruses containing genes and/or segments from 1918 H1N1, HPAI H5N1, and human H2N2 (1957–1968) to antiviral agents shall be established by sequence analysis or suitable biological assays. After manipulation of genes that influence sensitivity to antiviral agents, susceptibility to these agents shall be reconfirmed.

Appendix G–II–C–5–b. Containment for Animal Research

Guidance provided in Appendix G–II–C and Appendix Q–II–C is applicable with the following emphasis on standard BL3 or BL3–N containment or additional enhancements.

Appendix G–II–C–5–b–(1). Research with small animals shall be conducted in a class II biosafety cabinet. Small animals such as rodents (e.g. mice, hamsters, rats, guinea pigs) can be housed within a negative pressure BL3 animal suite using high-density individually vented caging (IVC) systems that independently supply HEPA-filtered and directional air circulation. Other animals (e.g. rabbits, ferrets) that are of a size or have growth or caging requirements that preclude the use of high-density IVC systems are to be housed in negative pressure bioisolators.

Appendix G–II–C–5–b–(2). Large animals such as non-human primates shall be housed in primary barrier environments according to BL3–N containment requirements (see Section Q–II–c).

Appendix G–II–C–5–b–(3). Specialized training and proven competency in all assigned practices and procedures shall be required for laboratory staff, including staff involved in animal care.

Appendix G–II–C–5–b–(4). For HPAI H5N1 research, the *NIH Guidelines* defer to USDA/APHIS recommendations

for biocontainment practices for loose housed animals.

Appendix G–II–C–5–c. Occupational Health

A detailed occupational health plan shall be developed in advance of working with these agents in consultation, as needed, with individuals with the appropriate clinical expertise. In addition, the appropriate public health authority shall be consulted (*e.g.* local public health officials) on the plan and a mock drill of this plan shall be undertaken periodically. The plan should include an incident reporting system and laboratory workers shall report all incidents.

Appendix G–II–C–5–c–(1). Laboratory workers shall be provided with medical cards which include, at a minimum, the following information: characterization of the influenza virus to which they have been potentially exposed, and 24-hour contact numbers for the principal investigator and institution's occupational health care provider(s).

Appendix G–II–C–5–c–(2). A detailed occupational health plan shall include:

(1) Unless there is a medical contraindication to vaccination (*e.g.* severe egg allergy) annual seasonal influenza vaccination as prerequisite for research to reduce risk of influenza like illness requiring isolation and tests to rule out infection with experimental virus and possible co-infection with circulating influenza strains.

(2) Virus specific vaccination, if available, should be offered;

(3) Reporting of all respiratory symptoms and/or fever (*i.e.* influenza like illnesses); and

(4) 24-hour access to a medical facility that is prepared to implement appropriate respiratory isolation to prevent transmission and is able to provide appropriate antiviral agents. Real-time reverse transcription-polymerase chain reaction (RT–PCR) procedures should be used to discriminate these viruses from currently circulating human influenza viruses. For exposures to viruses containing genes from 1918 H1N1 or the HA gene from human H2N2 (1957–1968), specimens shall be sent to the CDC for testing (RT–PCR and confirmatory sequencing).

Appendix G–II–C–5–c–(3). In preparing to perform research with 1918 H1N1, human H2N2 (1957–1968), or HPAI H5N1, principal investigators should develop a clear plan specifying who will be contacted in the event of a potential exposure (during and after work hours) to conduct a risk assessment and make decisions as to the required response, including the need for and extent of isolation of the exposed worker. After any kind of potential exposure, a rapid risk assessment shall be performed by the principal investigator, health and biosafety officials and subsequent actions should depend on the appraised level of risk of respiratory infection for the individual and potential for transmission to others. A laboratory worker performing research with either an influenza virus containing the HA gene from human H2N2 or an influenza virus containing genes and/or segments from 1918 H1N1, shall be informed in advance that, in the case of a *known* laboratory exposure with a high risk for infection, *e.g.,* involving the upper or lower respiratory tract or mucous membranes, the laboratory worker will need to be isolated in a predetermined facility, rather than home isolation, until infection can be ruled out by testing (*e.g.,* negative RT–PCR for 1918 H1N1 or human H2N2 (1957–1968)) of appropriately timed specimens. Laboratory workers shall be informed in advance that in the case of a known laboratory exposure to highly pathogenic avian influenza H5N1 strains within the Goose/Guangdong/96-like H5 lineage with high risk for infection, they should be prepared to self isolate (for example at home) until infection can be ruled out by testing (*e.g.,* negative RT–PCR for HPAI H5N1) of appropriately timed specimens. The action taken for other types of exposures should be based on the risk assessment. In addition, based on the risk assessment: (1) Treatment with appropriate antiviral agents shall be initiated, and (2) the appropriate public health authorities shall be notified.

Appendix G–II–C–5–c–(4). Influenza-like illness. If a laboratory worker, who had recent exposure (within ten days) to influenza viruses containing the human H2N2 HA gene or any gene from the 1918 H1N1 or HPAI H5N1 viruses, or to animals exposed to such viruses, demonstrates symptoms and/or signs of influenza infection (*e.g.,* fever/chills, cough, myalgias, headache), then the lab worker shall report by phone to the supervisor/principal investigator and other individuals identified in the occupational health plan. The laboratory worker shall be transported to a healthcare facility that can provide adequate respiratory isolation, appropriate medical therapy, and testing to determine whether the infection is due to a recombinant influenza virus. The appropriate public health authorities shall be informed whenever a suspected case is isolated.

Appendix G–II–C–5–c–(5). For 1918 H1N1 research, the use of antiviral agents (*e.g.,* oseltamivir) for pre-exposure prophylaxis shall be discussed with laboratory workers in advance including a discussion of the data on the safety of long term exposure to these agents and their ability to reduce the risk of clinical disease and the limits of the data regarding protection of close contacts and the community.

Appendix G–II–C–5–c–(6). Antiviral agents for post-exposure prophylaxis shall be provided only after medical evaluation. Home supplies shall not be provided in advance for research with 1918 H1N1 or influenza viruses containing the HA gene from human H2N2.

Dated: September 15, 2009.

Jacqueline Corrigan-Curay,

Acting Director, Office of Biotechnology Activities, National Institutes of Health.

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DEPARTMENT OF HOMELAND SECURITY

U.S. Customs and Border Protection

Agency Information Collection Activities: Application To Establish a Centralized Examination Station

AGENCY: U.S. Customs and Border Protection (CBP), Department of Homeland Security.

ACTION: 60-Day notice and request for comments; Extension of an existing collection of information: 1651–0061.

SUMMARY: As part of its continuing effort to reduce paperwork and respondent burden, CBP invites the general public and other Federal agencies to comment on an information collection requirement concerning the Application to Establish a Centralized Examination Station (CES). This request for comment is being made pursuant to the Paperwork Reduction Act of 1995 (Pub. L. 104–13; 44 U.S.C. 3505(c)(2)).

DATES: Written comments should be received on or before November 23, 2009, to be assured of consideration.

ADDRESSES: Direct all written comments to U.S. Customs and Border Protection, Attn: Tracey Denning, Office of Regulations and Rulings, 799 9th Street, NW., 7th Floor, Washington, DC 20229–1177.

FOR FURTHER INFORMATION CONTACT: Requests for additional information should be directed to Tracey Denning, U.S. Customs and Border Protection, Office of Regulations and Rulings, 799