National Institutes of Health

U.S. Public Health Service
Bethesda, Maryland 20892

Office of Biotechnology Activities
National Institutes of Health
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http://oba.od.nih.gov/

December 16, 2013

Daniel Uhlrich, Ph.D.
Associate Vice Chancellor for Research Policy
University of Wisconsin
327 Bascom Hall 3
500 Lincoln Drive
Madison, Wisconsin 53706

Dear Dr. Ulrich:

We are following up on our series of teleconferences regarding your November 15, 2013, report to the National Institutes of Health (NIH) Office of Biotechnology Activities (OBA) describing a November 9, 2013, incident in which a University of Wisconsin researcher spilled approximately 8 mL of H5N1-containing media onto the floor of the ABSL3+ laboratory. According to your report, the spill occurred shortly after the researcher collected H5N1 culture supernatant samples into three 6-well tissue culture plates. The researcher stacked the three plates on top of each other and transported the plates from the biosafety cabinet to the tissue culture incubator. After opening the door of the incubator, the researcher dropped one of the 6-well plates onto the laboratory floor.

Immediately following the spill, the researcher closed the door to the incubator and returned the well plates that were not dropped to the biosafety cabinet. The researcher then picked up the dropped plate and immersed it in a chemical disinfectant solution within the biosafety cabinet. [redacted] then saturated [redacted] outer gloves with 70-percent ethanol, disposed of them in the biohazrdous waste bin and donned a new pair of outer gloves. At this time, the researcher noticed some of the spilled material had landed on [redacted] Tyvek suit just below the knee. In response, [redacted] applied 70-percent ethanol to both the arms and legs of the suit, [redacted] shoe covers, and the uncovered skin between the bottom of the suit and [redacted] shoes. Next, the researcher cleaned the spill by covering the affected area with paper towels soaked in chemical disinfectant. After allowing 20 minutes for the towels to soak up the spilled material, the researcher mopped the floor using a viral disinfectant. The biosafety cabinet and the tissue culture incubator were then decontaminated using 70-percent ethanol. All cleanup materials were placed in a biohazardous waste bag for autoclaving. When the spill was fully cleaned up, the researcher phoned the on-call scientist to report the incident, removed [redacted] personal protective equipment, and reported to the building conference room to wait for further instructions.

When the on-call scientist received the notification of the spill, [redacted] phoned the Alternate Responsible Official (ARO) and left a message describing the situation. The ARO returned the call, and was briefed. The ARO then called the researcher involved in the incident to obtain additional information. She informed the researcher to remain in the conference room while she consulted with the University of Wisconsin infectious disease physician. After considering the facts of the incident, the infectious disease physician determined that treatment with antivirals would not be necessary. This determination was based on the fact that the appropriate disinfection procedures had been used, and the risk of infection from any skin exposure would be low. The ARO nonetheless insisted that the researcher be given a prescription for Tamiflu as a precautionary measure. The infectious disease physician agreed, and a prescription was written for the researcher. At that time, the ARO called the researcher and informed [redacted] that [redacted] was cleared to leave the building, and quarantine would not be necessary. The researcher was instructed to self-monitor for any change in body temperature and report any feelings of illness [redacted] experienced. The researcher began the Tamiflu course of treatment on the afternoon of November 9. To date, no symptoms of illness have been reported by the researcher.

While the actions taken by the University of Wisconsin in response to this incident appear appropriate, we do not consider it acceptable biosafety practice to have uncovered skin in an ABSL3+ laboratory. It was unclear from your original report whether any of the spilled media splashed onto the bare ankles of the researcher. In subsequent communications, the University of Wisconsin informed us that the researcher did not spill any of the material on [redacted] ankles; the spill was limited to the researcher's Tyvek suit and the laboratory floor. That said, to be compliant with Appendix G-II-C-5-a-(1) of the *NIH Guidelines*, researchers must be fully covered with no exposed skin when performing research with RG3 influenza strains, including HPAI H5N1. We have discussed the issue of bare skin in the ABSL3+ laboratory with the United States Department of Agriculture (USDA) Select Agent Program, and they are in agreement that bare skin is unacceptable at this level of containment. The University must take immediate action to ensure that, in the future, no workers in this or any other high containment laboratories have exposed skin. **Please provide us with a corrective action that details how the University of Wisconsin will address this deficiency no later than December 23, 2013.**

Please contact OBA staff by email at oba@od.nih.gov or by telephone at (301) 496-9838 if you have any questions.

Sincerely,

Jacqueline Corrigan-Curay, M.D., J.D.
Acting Director
Office of Biotechnology Activities

cc: Mark D. Markel, D.V.M., Dean, School of Veterinary Medicine, University of Wisconsin
Martin Cadwallader, Ph.D., Vice Chancellor for Research, University of Wisconsin
William Mellon, Ph.D., Associate Dean for Research, University of Wisconsin
Rebecca Moritz, Select Agent Program Manager, University of Wisconsin
Yoshihiro Kawaoka, D.V.M., Ph.D., Principal Investigator, University of Wisconsin
Jim Turk, M.S., Biological Safety Officer, University of Wisconsin
Capt. Robbin Weyant, Ph.D., Director, Division of Select Agents and Toxins, CDC
Freeda E. Isaac, D.V.M., Director, Agriculture Select Agent Program, USDA APHIS
Teresa Hauguel, Program Officer, NIAID, NIH
Amy P. Patterson, M.D., Associate Director for Science Policy, NIH
Allan C. Shipp, Director of Outreach, Office of Biotechnology Activities, NIH
Ryan Bayha, Senior Analyst for Science Policy Outreach, Office of Biotechnology Activities, NIH
Kathryn Harris, Ph.D., RBP, Senior Outreach and Education Specialist (contractor),
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December 16, 2013

Daniel Uhlrich, Ph.D.
Associate Vice Chancellor for Research Policy
University of Wisconsin
327 Bascom Hall 3
500 Lincoln Drive
Madison, Wisconsin 53706

Dear Dr. Ulrich:

We are following up on our series of teleconferences regarding your November 17, 2013, and November 19, 2013, report to the National Institutes of Health (NIH) Office of Biotechnology Activities (OBA) describing a November 16, 2013, incident in which a University of Wisconsin researcher stuck [redacted] with a syringe containing a recombinant form of H5N1. The virus contained the HA gene from H5N1 while the remaining genes came from H1N1 A/California (2009 H1N1) strain.

The needlestick occurred in the ABSL3+ laboratory while the researcher was attempting to collect tissue culture supernatant. Immediately following the incident, the researcher sprayed the wound site with disinfectant and washed the site of the wound for fifteen minutes. The researcher contacted the laboratory manager and reported the exposure. The laboratory manager then informed the Alternate Responsible Official (ARO) of the incident and requested that the University of Wisconsin infectious disease physician be contacted for a consultation. The laboratory manager called the researcher back and instructed [redacted] to put on a new pair of gloves, clean up [redacted] work area, follow the shower-out procedures, and report to the building conference room to await further instructions.

After the ARO briefed the infectious disease physician on the exposure, the University determined that the researcher should be placed under quarantine at [redacted] home. The laboratory manager phoned the researcher's family members and informed them of the situation. The researcher's family was subsequently escorted to a hotel room for the duration of the researcher's quarantine. The researcher was provided with a prescription of Tamiflu and was then driven home by the laboratory manager. During the transport from the laboratory to the researcher's house, the researcher wore a glove on the hand that had the puncture wound as well as an N-95 respirator. The following morning (November 17), nasal and throat swab testing began. To date, the researcher has not shown any signs or symptoms of illness.

This event raises several questions regarding the University of Wisconsin's policies and procedures. First, we learned in subsequent conversations with the University that the use of a needle for the collection procedure in question is a violation of the University of Wisconsin's own policies, which only permit needles to be used in the ABSL3+ laboratory to anesthetize research animals, draw blood from research animals, or inoculate eggs. It is unclear from your report why the researcher was using a syringe to collect a supernatant sample, when the use of sharps for that activity was prohibited. Your report indicated that the researcher would be retrained and the standard operating procedure for sharps use in the ABSL3+ will be rewritten to articulate more clearly the allowed uses of sharps. **Please indicate when this training occurred and provide OBA copies of the training materials that were used, as well as your policy describing the use of needles in the ABSL3+ laboratory.**

In follow-up conversations with you and Rebecca Moritz regarding your occupational health plans, you state that all exposures, including high risk exposures, would follow the same protocol, i.e. home isolation after removing the family from the house. Your decision was based upon consultation with your infectious disease experts and the state health department. You had rejected using a hospital room for quarantine because of the stress on the laboratory worker. This policy is not what was communicated to us in Dr. Kawaoka's application to perform research with mammalian transmissible strains of H5N1 that was provided to the Department of Health and Human Services. In a May 6, 2013, plan provided to NIH, Dr. Kawaoka indicated that he had access to a "designated quarantine apartment" in which researchers could be placed for 10-14 days in the event of an accidental exposure. Since then, the University of Wisconsin's Associate Dean for Research and ARO have indicated to OBA that there was a miscommunication between the PI and the University administration regarding the availability and appropriateness of such a quarantine apartment.

The University must find a dedicated facility outside of the individual's permanent residence (1) in which an individual can be safely isolated for up to 10 days, and (2) that can be decontaminated easily after the individual's departure. An isolation room in a hospital would be appropriate. An individual's permanent residence is not appropriate due to the fact that many residences are in buildings with high occupancy that share air exchange and other infrastructure. **Please provide revised SOPs that reflect an appropriate quarantine arrangement. No research with mammalian transmissible H5N1 stains may be carried out until this plan is operationalized.**

Please provide all requested materials by **December 23, 2013.** You may contact OBA staff by email at oba@od.nih.gov or by telephone at (301) 496-9838 if you have any questions.

Sincerely,

Jacqueline Corrigan-Curay, M.D., J.D.
Acting Director
Office of Biotechnology Activities

cc: Mark D. Markel, D.V.M., Dean, School of Veterinary Medicine, University of Wisconsin
Martin Cadwallader, Ph.D., Vice Chancellor for Research, University of Wisconsin
William Mellon, Ph.D., Associate Dean for Research, University of Wisconsin
Rebecca Moritz, Select Agent Program Manager, University of Wisconsin
Yoshihiro Kawaoka, D.V.M., Ph.D., Principal Investigator, University of Wisconsin
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Capt. Robbin Weyant, Ph.D., Director, Division of Select Agents and Toxins, CDC
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December 17, 2013

Martin Cadwallader, Ph.D.
Vice Chancellor for Research and Dean of the Graduate School
University of Wisconsin
333 Bascom Hall
500 Lincoln Drive
Madison, WI 53706-1380

Dear Dr. Cadwallader:

We are writing in regard to two incidents involving recombinant research with highly pathogenic avian influenza (HPAI) H5N1 that have occurred recently in the ABSL3+ laboratory of Dr. Yoshihiro Kawaoka. After reviewing the details of these two incidents, NIH has significant concerns relating to the University of Wisconsin's apparent lack of a dedicated quarantine facility other than the researcher's home. We also have concerns relating to the biosafety practices associated with these incidents. Our concerns are detailed below.

Lack of a dedicated quarantine facility

In the needlestick incident that occurred on November 16, 2013, a decision was made to home quarantine the individual because the route of exposure (needlestick) was not expected to place the researcher at high risk for infection and this influenza strain, which contained the HA gene from H5N1, was determined not to be a mammalian-transmissible strain. However, in conversations with the University of Wisconsin Alternate Responsible Official, Ms. Rebecca Moritz, regarding this incident, Ms. Moritz informed us that all researchers exposed to H5N1 would be quarantined at home, regardless of the risk of infection or whether the strain was mammalian-transmissible or not.

In a subsequent phone conversation with the University of Wisconsin Senior Associate Dean for Research, Dr. William Mellon and Ms. Moritz, the policy for home isolation for all incidents was reiterated to us. We were told by Dr. Mellon and Ms. Moritz that the decision was based upon consultation with University of Wisconsin infectious disease experts and the state health department. We were also informed that the use of a hospital room for quarantine was rejected due to the stress it would place on the laboratory worker.

The University of Wisconsin's policy on home quarantine communicated to us by Dr. Mellon and Ms. Moritz is not in keeping with what was communicated to us in Dr. Kawaoka's application to the Department of Health and Human Services to perform research with mammalian transmissible strains of HPAI H5N1. In a May 6, 2013, plan provided to NIH, Dr. Kawaoka indicated that he had access to a "designated quarantine apartment" in which researchers could be placed for 10-14 days in the event of an accidental exposure (Attachment A). Dr. Mellon and Ms. Moritz have indicated to OBA that there was a miscommunication between the PI and the University of Wisconsin administration regarding the availability and appropriateness of such a quarantine apartment.

The University of Wisconsin's policy on home quarantine is inconsistent with the requirements for this research under the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*), and under the terms agreed to by the University as a condition of funding this project. **The University of Wisconsin must find a dedicated facility outside of the individual's permanent residence (1) in which an individual exposed to mammalian-transmissible HPAI H5N1 can be safely isolated for up to 10 days, and (2) that can be decontaminated easily after the individual's departure.** An isolation room in a hospital would also be appropriate. An individual's permanent residence is not appropriate when the risk of infection is high. For high risk exposures, it is critical to isolate the individual in a structure that does not have shared air exchange and can be quickly and efficiently decontaminated in the case of infection. In addition, if this structure is outside of a health care facility, there needs to be a plan in place regarding how this researcher could be safely transported to an isolation room in a health care facility, should he or she develop clinical symptoms, without the risk of exposure to other individuals.

Concerns relating to biosafety practices

In addition to the quarantine issue, NIH has significant concerns regarding the biosafety practices associated with both of the recent incidents.

The November 16, 2013, needlestick incident occurred when the researcher used a needle to collect tissue culture supernatant in violation of the University of Wisconsin's own policies, which only permits needles to be used in the ABSL3+ laboratory to anesthetize research animals, draw blood from research animals, or inoculate eggs. It was unclear from the University's response why this individual was using a needle for this type of procedure.

The University of Wisconsin report regarding the November 9, 2013, HPAI H5N1 spill described the researcher as having two to three inches of exposed skin between where [redacted] tyvek suit ended and [redacted] shoe covers began. While it was reported that none of the spilled material landed on the researcher's bare skin, we made it clear in our letter (Attachment A) and in a phone conversation with Ms. Moritz and Dr. Mellon that having bare skin in the ABSL3+ laboratory was unacceptable under the containment requirements for this research specified in the *NIH Guidelines*. During that phone conversation, Ms. Moritz and Dr. Mellon stated that the ABSL3+ laboratory had recently undergone a Select Agent inspection and the report from that inspection did not specifically mention a prohibition against working in the ABSL3+ laboratory

with bare skin. We have discussed the issue of bare skin in the ABSL3+ laboratory with the United States Department of Agriculture (USDA) Select Agent Program, and they are in agreement that bare skin is unacceptable at this level of containment.

Attachments B and Attachment C to this letter contain the NIH response to both H5N1 incidents. These letters contain requests for action regarding the quarantine situation and our biosafety concerns. We would appreciate any assistance you can provide to ensure that these requests are answered by December 23, 2013.

Finally, if your response is not received by this date or if does not fully address the issues we have described regarding a dedicated quarantine facility and inappropriate biosafety practices, as required by the terms and conditions of grant award, NIH will institute enforcement action(s) for the NIH grant 2 R01 AI069274-06A1, Transmissibility of Avian Influenza Viruses in Mammals, Yoshihiro Kawaoka, DVM, Principal Investigator. Such actions could include disallowance of costs, suspension, or termination of the grant award.

If you have any questions, please feel free to contact us.

Amy P. Patterson, M.D.
Associate Director for Science Policy
National Institutes of Health

Sally Rockey, Ph.D.
Deputy Director for Extramural Research
National Institutes of Health

cc: Mark D. Markel, D.V.M., Dean, School of Veterinary Medicine, University of Wisconsin
William Mellon, Ph.D., Associate Dean for Research, University of Wisconsin
Rebecca Moritz, Select Agent Program Manager, University of Wisconsin
James Turk, Biological Safety Officer, University of Wisconsin
Yoshihiro Kawaoka, D.V.M., Ph.D., Principal Investigator, University of Wisconsin
Jim Turk, M.S., Biological Safety Officer, University of Wisconsin
Capt. Robbin Weyant, Ph.D., Director, Division of Select Agents and Toxins, CDC
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Jacqueline Corrigan-Curay, J.D., M.D., Acting Director, Office of Biotechnology Activities, NIH

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December 20, 2013

Daniel Uhlrich, Ph.D.
Associate Vice Chancellor for Research Policy
Graduate School
University of Wisconsin-Madison

Dear Dr. Uhlrich,

In January 2012, the university started a long process to enhance pre-existing exposure control plans for various agents used on our campus. Our first task was revamping the plan for exotic influenza viruses by building upon previous meetings and bringing together the university's Select Agent program, University Health Services Occupational Medicine program, University Hospital's Infectious Disease consult team, the Wisconsin Department of Public Health and Madison/Dane County Public Health.

Many discussions and meetings later, we developed a comprehensive exposure control plan that accounts for potential exposures as well as if an individual comes develops influenza like symptoms. We determined home quarantine was appropriate for all exotic viruses even if an individual lives in an apartment complex unless treatment was required based on a medical reason. We have also made arrangements for individuals displaced by a quarantine of one of our researchers.

In March 2013, the National Institutes of Health Office of Biotechnology Activities (NIH OBA) revised its guidelines for work with specific exotic influenza viruses and no longer allowing home quarantine for specific situations and requiring a dedicated isolation facility outside of a personal residence that has the ability to be decontaminated easily. We have made plans to be in full compliance with these recommendations; however we do have concerns with this requirement which should be considered as we move forward.

- Most importantly, hospitals are not designed to be quarantine facilities for individuals who do not require medical intervention. The use of a hospital for this purpose puts undo strain on personnel and diverts resources from patients who need medical care.

- Based on available data, it is highly unlikely an individual exposed to influenza viruses sensitive to antivirals will become symptomatic if antiviral treatment is started shortly after a potential exposure.

- Isolation rooms in hospitals are not designed to be occupied by an able bodied individual. They rooms are uncomfortable and confining. We are concerned about the mental health and physical wellbeing of an individual quarantined in one of these types of facilities for an extended period of time as well as a potential impact on the willingness of researchers to come forward following exposures.

- There are a significant number of people who work in and visit hospitals on a daily basis. Due to sheer number of individuals it would be much harder to control the spread of information and as a result there would be a higher probability of incorrect information being told to general public and potentially members of the media.

- Influenza viruses are only stable in the environment for a few hours. Decontaminating a person's home can be accomplished with a few days and the appropriate disinfectant.

It is hoped that is the need for this isolation arises, that the duration of hospital facility quarantine can be limited. In these situations, we will work closely with our public health and federal partners to determine appropriate end points based on PCR testing for virus and prophylaxis treatment.

None the less, we understand the need for the university to have a facility dedicated for isolation under these specific circumstances for compliance with the guidelines and the terms and conditions of specific grants. With our options extremely limited, we feel an isolation room at UW Hospital is the only solution we can provide. We will work with our staff to inform them of the change and review the updated plans and procedures to accommodate these requirements.

Please contact us if you have any questions or concerns.

Sincerely,

Sarah Van Orman M.D., MMM

Executive Director
University Health Services

David Andes M.D.

Professor Department of Medicine and Microbiology
Chief Division of Infectious Diseases
University of Wisconsin

cc: Martin Cadwallader, Vice Chancellor for Research, University of Wisconsin
Tim Yoshino, Responsible Official, Select Agent Program, University of Wisconsin
Rebecca Moritz, Select Agent Program Manager, University of Wisconsin
Mark Markel, Dean, School of Veterinary Medicine, University of Wisconsin
Yoshihiro Kawaoka, Professor, School of Veterinary Medicine, University of Wisconsin

December 20, 2013

Jacqueline Corrigan-Curay, M.D., J.D.
Acting Director
Office of Biotechnology Activities
National Institutes of Health
6705 Rockledge Drive
Suite 750, MSC 7985
Bethesda, MD 20892

Dear Dr. Corrigan-Curay:

Thank you for the opportunity to respond to your letter dated December 16, 2013 regarding questions NIH OBA has about a small spill onto the floor of one our ABSL-3+ laboratories. Specifically, corrective action was requested in regards to exposed skin around the ankle of the researcher involved in the incident.

In an effort to comply with the spirit of the guidelines and in response to your memo, the principle investigator of the laboratory where the spill occurred has ordered high-top booties that will be worn underneath the tyvek suit and inside of the dedicated clogs which will be covered with normal shoe covers. Included with this memo are copies of the updated standard operating procedures for entry into the principle investigator's laboratories incorporating the change with the PPE.

A highest priority at UW-Madison is to assure that we are in complete compliance with federal regulations regarding select agent research. However, on occasion we have received mixed messages from agencies regarding aspects of our program, and this is a case in point. This was the first instance where we have been informed that our personal protective equipment (PPE) for RG3 influenza viruses was inadequate. Our researchers wear PAPRs, tyveks, shoe covers, dedicated garden clogs, shoe covers, and two pairs of gloves. Our university's select agent program has been inspected 10 separate times since the creation of the Federal Select Agent Program (FSAP) with 8 of those inspections involving RG3 influenza viruses. During these inspections, FSAP Inspectors from the Centers for Disease Control (CDC) and Animal and Plant Health Inspection Service (APHIS) enter into our laboratories wearing full PPE and exit in the same manner as our researchers do on daily basis. Our most recent FSAP inspection was in August 2013 and there was no mention of the PPE being inadequate. As required by the Federal Select Agent Program we notified the CDC and APHIS of the spill within a few hours of the incident and the report was reviewed by both agencies with APHIS handling the correspondence since the agent involved falls under their purview. We received a memo dated November 20, 2013 from an APHIS compliance manager, who reviewed our spill report that stated "At the time of incident the researcher was wearing appropriate personal protective equipment." Since our phone conference call with NIH on December 16,

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2013 we have received a more recent memo from APHIS dated December 17, 2013 stating after further review, they are concerned about the bare skin.

We are requesting clarification from NIH Office of Biotechnology Activities (OBA) in regards to this policy. Appendix G-II-C-5-a (1) does not specifically mention the requirement of no exposed skin nor does it discuss the type of PAPR a researcher working with RG3 influenza viruses should wear. As you know, many PAPRs lack shrouds and leave the researcher's neck exposed. Does the no-bare-skin requirement apply for all RG3 influenza viruses including wild type viruses or just mutant/reassortant viruses? The reason we ask is we would like to be consistent across all RG3 influenza virus laboratories at our institution. Further, we assume that many other institutions engaged in RG3 influenza research use safeguards similar to ours. They also would benefit from clarification of exposed skin and PAPR requirements.

Please contact me if you have any questions or concerns.

Sincerely,

Daniel Uhlrich
Associate Vice Chancellor for Research Policy

Attachments: Three SOPs for entry to facilities

December 20, 2013

Jacqueline Corrigan-Curay, M.D., J.D.
Acting Director
Office of Biotechnology Activities
National Institutes of Health
6705 Rockledge Drive
Suite 750, MSC 7985
Bethesda, MD 20892

Dear Dr. Corrigan-Curay:

Thank you for the opportunity to respond to your letter dated December 16, 2013 regarding questions NIH OBA has about an incident at our institution where a researcher used a needle inappropriately and in the process acquired a needle stick.

In response to this incident, there have been two training sessions so far to discuss this event. The first was a questions and answer session on November 19, 2013 involving all current and future biocontainment laboratory researchers. This was directed by a senior scientist and the University of Wisconsin Select Agent Program's trainer. They discussed the use the sharps in the containment labs. The second training session occurred on December 18, 2013 and was led by two senior scientists and the Select Agent Program trainer. The training materials are provided with this memo. In summary, the sharps standard operating procedure (SOP) has been revised to be more specific and modify current procedures to make them safer. Sharp needles will only be used for administering drugs to animals and drawing blood from animals. When either of these procedures are being done with reconstructed 1918 influenza virus or mammalians transmissible influenza viruses, two people will be required for the procedure. When inoculating eggs, only blunt or dispensing needles will be allowed. Lastly, the SOP was also updated to include the appropriate cleaning of necropsy tools.

In regards to the second matter described in your letter, we have determined that your suggestion of a hospital isolation room at the University of Wisconsin Hospital is the best option to comply with the requirement to have a dedicated facility outside of a personal residence to quarantine. The University spent a significant amount of time enhancing our influenza exposure control plan in 2012. At that time, the University, our health care providers, and the Department of Public Health debated the best place for quarantine and determined that complications could arise with hospital quarantine. Based on these complications, they felt a home quarantine was appropriate for all exotic influenza viruses. When consulted about NIH OBA's requirement, our health care providers reiterated concerns but they have agreed to provide this service for us so our program is in compliance with the terms and conditions of the grant. Attached are the revised exposure control plan and exposure SOP reflecting these changes. The changes are effective immediately.

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It should be noted no work has been performed with mammalian transmissible H5N1 viruses at the University of Wisconsin-Madison since the start of the moratorium in January 2012. Currently, there are no plans over the next several months to resume experiments with these viruses. University administration will be informed before the experiments with mammalian transmissible H5N1 viruses resume.

Please contact me if you have any questions or concerns.

Sincerely,

Daniel Uhlrich
Associate Vice Chancellor for Research Policy

Attachments: IRI Sharps SOP
Incident Follow-up Training Materials - November 19, 2013
Incident Follow-up Training Materials - December 18, 2013
IRI Exposure Plan (Overview)
IRI Exposure Plan (SOP)

National Institutes of Health

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December 24, 2013

Daniel Uhlrich, Ph.D.
Associate Vice Chancellor for Research Policy
University of Wisconsin
327 Bascom Hall 3
500 Lincoln Drive
Madison, WI 53706-1380

Dear Dr. Uhlrich:

We are writing in reply to your correspondence of December 20, 2013, that responded to two letters from the National Institutes of Health (NIH) Office of Biotechnology Activities (OBA), dated December 16, 2013. These two letters addressed two separate incidents involving recombinant DNA research with highly pathogenic avian influenza (HPAI) H5N1 that have occurred recently in the ABSL3+ laboratory of Dr. Yoshihiro Kawaoka.

In our December 16, 2013, letters we detailed our concerns regarding the University of Wisconsin's lack of a dedicated quarantine facility to house individuals who have experienced a high-risk exposure to mammalian-transmissible strains of HPAI H5N1. We also conveyed our concerns regarding specific biosafety practices associated with these incidents.

After reviewing the information you have submitted, NIH OBA has determined that the University of Wisconsin has adequately responded to our concerns. Detailed information regarding your response appears below.

Lack of a dedicated quarantine facility

In our December 16, 2013, letter regarding the needlestick incident, we stated that to be compliant with the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*), the University of Wisconsin must find a dedicated quarantine facility outside of the individual's permanent residence (1) in which an individual exposed to mammalian-transmissible HPAI H5N1 can be safely isolated for up to 10 days, and (2) that can be decontaminated easily after the individual's departure.

In your response, you stated that the University of Wisconsin will utilize the University of Wisconsin Hospital as a quarantine facility in the event of a high-risk exposure to mammalian-transmissible strains of H5N1. Your response also included an updated standard operating procedure (SOP) that reflects this change.

Concerns relating to biosafety practices

Both of our December 16, 2013, letters conveyed our concerns regarding the biosafety practices associated with each incident. Specifically, we were concerned that a researcher's personal protective equipment did not cover [redacted]ankles while in the ABSL3+ laboratory, creating an opportunity for dermal exposure to hazardous agents. We were also concerned that a researcher had used a needle to collect tissue culture supernatant in violation of the University of Wisconsin's own policies, which only permit needles to be used in the ABSL3+ laboratory to anesthetize research animals, draw blood from research animals, or inoculate eggs.

With regard to the issue of bare skin, your response states that the principal investigator will require that high-top booties be worn underneath the researcher's tyvek suit and inside of the dedicated clogs. The clogs will then be covered with regular shoe covers. This change has been incorporated into the SOPs for the laboratory, and you have provided OBA a copy of that SOP. We also understand from your letter that you are requesting clarification regarding the issue of exposed skin in relation to Purified Air Powered Respirators, which we will respond to in a separate communication.

With respect to the needlestick incident, your response states that the University has conducted two training sessions since this event. The first session was aimed at all current and future biocontainment laboratory researchers and was led by a senior scientist at the University of Wisconsin. The second session was led by two senior scientists, and the slides from that training event have been included in your response. Additionally, the SOPs for sharps use in the ABSL3+ laboratory have been revised to be more specific. The new SOP articulates that sharps will only be used when administering drugs to an animal or drawing blood from an animal. When either of these procedures are being performed with mammalian-transmissible influenza viruses, two individuals will be required to be present for the procedure.

With respect to the issues above, the University of Wisconsin response is now consistent with the requirements of the *NIH Guidelines,* which are a term and condition of the funding of this project. As such, the resumption of research involving mammalian-transmissible strains of H5N1 is appropriate as our biosafety concerns have been addressed. In the meantime, if you have any questions about this letter, please feel free to contact us.

Sincerely,

Jacqueline Corrigan-Curay, J.D., M.D.
Acting Director
Office of Biotechnology Activities

cc: Martin Cadwallader, Ph.D., Vice Chancellor for Research, University of Wisconsin
Mark D. Markel, D.V.M., Dean, School of Veterinary Medicine, University of Wisconsin
William Mellon, Ph.D., Associate Dean for Research, University of Wisconsin
Rebecca Moritz, Select Agent Program Manager, University of Wisconsin
James Turk, Biological Safety Officer, University of Wisconsin
Yoshihiro Kawaoka, D.V.M., Ph.D., Principal Investigator, University of Wisconsin
Capt. Robbin Weyant, Ph.D., Director, Division of Select Agents and Toxins, CDC
Freeda E. Isaac, D.V.M., Director, Agriculture Select Agent Program, USDA APHIS
Amy P. Patterson, M.D., Associate Director for Science Policy, NIH
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Matthew Fenton, Ph.D., Director, Division of Extramural Activities, NIAID, NIH
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February 7, 2014

Daniel Uhlrich, Ph.D.
Associate Vice Chancellor for Research Policy
University of Wisconsin
327 Bascom Hall 3
500 Lincoln Drive
Madison, WI 53706-1380

Dear Dr. Uhlrich:

We are writing in reply to your correspondence of December 20, 2013, regarding research with highly pathogenic avian influenza (HPAI) H5N1. In your letter, you requested clarification regarding the issue of exposed skin in relation to the type of Purified Air Powered Respirators (PAPRs) used during research with risk group (RG) 3 influenza viruses.

Appendix G-II-C-5-a-(l) of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*) details the personal protective equipment researchers must use when working with RG3 influenza viruses. We recognize that Appendix G does not provide specific recommendations regarding the type of PAPR that should be used and specifically whether it is acceptable to have any exposed skin between the PAPR and the protective suit. This letter is to clarify that for recombinant research with RG3 influenza viruses, especially gain of function research, researchers should not have any exposed skin between their face and the beginning of the protective suit, i.e., the front of their body should be completely protected against any spills or splashes. Ideally, PPE should cover all skin, but we understand that some hood coverings do leave exposed areas on the back of the head. Given the low risk of exposure to the back of the head and the shower-out requirements for this research, we do not mandate a full shroud that covers the entire head.

As for other agencies' requirements for non-recombinant work, the Centers for Disease Control and Prevention (CDC) published Biosafety Recommendations for Work with Influenza Viruses Containing a Hemagglutinin from A/goose/Guangdong/1/96 Lineage (Morbidity and Mortality Weekly Report, June 28, 2013, http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6206a1.htm). The CDC recommends a disposable hood or head cover, in addition to respiratory protection.

I hope that this has answered your question. Please feel free to contact us by email at oba@od.nih.gov or by telephone at (301) 496-9838.

Sincerely,

Jacqueline Corrigan-Curay, J.D., M.D.
Acting Director
Office of Biotechnology Activities

cc:

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