NIH POLICY MANUAL

3043-1 - Introduction of Rodents, Rodent Products and Rodent Pathogens
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1. **Explanation of Material Transmitted:** This chapter describes procedures to be followed when rodents, rodent products and rodent pathogens originating from sources other than those approved by the NIH Rodent Import Officer are introduced into NIH facilities. This chapter has been revised to broaden the definitions of approved source, Quarantine Facility, and Isolation Area; to clarify NIH excluded pathogens and other terms; and to include the handling of rodent pathogens in the laboratory. The objective is to facilitate intramural NIH research through the sharing of rodent resources from outside of the NIH campus while preventing the inadvertent introduction of infected rodents, rodent products and rodent pathogens. The NIH Rodent Import Coordinator and NIH Rodent Import Officer will have central e-mail and fax for communications. Web links have been added.

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A. Purpose

This manual chapter establishes procedures designed to prevent the inadvertent introduction of infected rodents, rodent products and rodent pathogens into the National Institutes of Health (NIH) and/or its holding facilities. Introduction of unwanted pathogens to a defined health status facility can adversely affect the health of the colony and directly or indirectly interfere with critical research programs and the mission of user ICs. In addition, the introduction of unwanted zoonotic agents can pose a health hazard to personnel.

B. Background

The conduct of a vigorous research program necessitates the movement of animals, their tissues and other rodent products from animal colony to animal colony, both within the NIH and from external sources. This movement creates opportunities for the introduction of unwanted pathogens into established colonies which can have an adverse affect on the animals, research and personnel, resulting in the loss of valuable government resources and/or pose a human health hazard. For example, hantaviruses present in some rats and wild rodents poses a risk to both established rodent colonies and to the humans who come into contact with infected animals. Current federal regulations pertaining to the movement of laboratory rodents or their products relate mainly to organisms causing disease in humans or domestic livestock. Therefore, it is important for the NIH to supplement these regulations with policies and procedures designed to protect our rodent colonies and research mission. It is the goal of this policy to establish a dynamic balance between the need for animal movement and the protection of both human health and research critical to the mission of the NIH.

C. Applicability

The policies and procedures in this chapter apply when rodents and rodent products for *in vivo* use are introduced into NIH facilities from sources other than those approved through the Division of Veterinary Resources (DVR), Office of Research Services (ORS). In addition to applying to all

facilities located on the NIH Bethesda campus, any off-campus facility covered under the Association for Assessment and Accreditation of Laboratory Animal Care International's (AAALAC International) accreditation file number 000777 is subject to this policy.

D. Policy

This policy is designed to reduce the risk of introducing unwanted pathogens, infectious and zoonotic, into animal facilities and protect the mission of the NIH. Rodents from non-approved sources shall not be introduced into NIH animal facilities without prior written approval of the applicable Institute or Center's (IC) Scientific Director or a delegate thereof (i.e., IC Rodent Import Officer (IC RIO); and the facility veterinarian of the facility where the animal(s) are to be housed. In addition, it is the IC's responsibility to ensure that, at a minimum, the Animal Program Director (APD) of the involved IC and the DVR Director or delegate thereof (i.e., the NIH Rodent Import Officer (NIH RIO) has knowledge of the introduction of rodents from non-approved sources prior to their introduction. Similarly, rodents from non-approved sources shall not be introduced into an NIH laboratory without the written approval of the applicable Scientific Director or the IC RIO. (See Appendix 1, Flow Chart).

Rodents or rodent products (to be used in rodents) inadvertently infected with lymphocytic choriomeningitis virus (LCMV), hantavirus or other assayable zoonotic agents of moderate potential hazard to people are excluded from NIH facilities. With adequate justification, exemptions for research purposes can be issued but must be approved in writing by the IC RIO, as well as the NIH Institutional Biosafety Committee through the Biosafety Officer in the Division of Occupational Health and Safety (DOHS), ORS. The IC RIO is responsible for maintaining copies of approvals. Intentionally infected rodents or rodent products used to intentionally infect rodents for *in vivo* studies of LCMV, hantavirus or other assayable zoonotic agents are exempt when their use has been approved on an animal study proposal.

The NIH Laboratory Safety course and Animal User and Principal Investigator Training courses shall contain material to heighten the awareness of the risk associated with rodents and rodent products from zoonotic and rodent specific pathogens both to humans and other animals in the NIH facilities.

The IC APD or their delegate (i.e., facility veterinarian, etc.) is responsible for the disposition of animals harboring infectious agents introduced into their areas of responsibility.

Laboratory Principal Investigator(s) and their Laboratory/Branch Chief(s) are responsible for the handling and disposition of rodent pathogens and products introduced for *in vitro* use into their laboratory. Rodent pathogens and products for *in vitro* use shall be handled in a manner which prevents the inadvertent introduction of the agent(s) or material into other NIH facilities.

E. References

1. Animal Welfare Act (7 U.S.C. 2131 et. seq.), as amended, and implementing regulations at 9 C.F.R., Part 1, et. seq. http://www.nal.usda.gov/awic/legislat/awa.htm and http://www.nal.usda.gov/awic/legislat/usdaleg1.htm
2. 9 C.F.R. Part 3 http://www.access.gpo.gov/nara/cfr/waisidx_03/9cfr3_03.html
3. Public Health Service Act, Sections 361-369 (42 U.S.C. 264-272), as amended and it's implementing regulations at 42 C.F.R. Parts 71 and 72 http://www.fda.gov/opacom/laws/phsvcact/phsvcact.htm
4. PHS Policy on Humane Care and Use of Laboratory Animals, 2002 http://grants.nih.gov/grants/olaw/references/phspol.htm
5. NIH Manual Chapter 3040-2, Animal Care and Use in the Intramural Program http://www1.od.nih.gov/oma/manualchapters/intramural/3040-2/
6. National Research Council Guide for the Care and Use of Laboratory Animals, 1996 http://oacu.od.nih.gov/regs/guide/guide.pdf
7. USDA, Live Laboratory Mammals and Their Material (for research purposes), 10/1998, Guidelines for Importation #1103 http://www.aphis.usda.gov/import_export/animals/animal_import/downloads/ilivemam.html

8. 42 CFR 71.56 and 21 CFR 1240.63, and CDC, Monkey pox, Final Rule Prohibiting Importation of African Rodents and Prairie Dogs http://www.cdc.gov/ncidod/monkeypox/animals.htm
9. USDA Import/Export Manuals, Reference 3, Live Animals and Related Material http://www.aphis.usda.gov/import_export/plants/manuals/ports/apm.shtml
10. Federation of International Mouse Resources http://www.fimre.org
11. NIH Manual Chapter 1340-1, Permits for Import or Export of Biological Materials http://www1.od.nih.gov/oma/manualchapters/management/1340%2D1/
12. NIH Manual Chapter 1743, "Keeping and Destroying Records." Appendix 1, NIH Records Control Schedule: http://www1.od.nih.gov/oma/manualchapters/management/1743
13. Biosafety in Microbiological and Biomedical Laboratories. Centers for Disease Control and Prevention/National Institutes of Health, 5th Edition, Feb 2007 http://www.cdc.gov/od/ohs/biosfty/bmbl5/bmbl5toc.htm
14. NIH Manual Chapter 1130 "Delegations of Authority," DOA Number 31, NIH Intramural Animal Care Program: http://delegations.od.nih.gov/DOADetails.aspx?id=1673

F. Definitions

1. **Animal Program Director (APD):** A veterinarian who receives delegated program authority from the IC Director or IC Scientific Director for all activities involving animals in the IC.
2. **APDs' Committee:** An NIH committee that consists of the APD from each IC.
3. **Application:** Refers to the NIH Form 2369-1, "Application for Permit to Introduce Rodents" The issued permit is valid for a twelve (12) month period.
4. **Approved Source:** A source of rodents or rodent products to supply genetically-defined, specific pathogen-free animals to NIH investigators. These sources characteristically require barrier production practices, genetic management and monitoring, microbiologic standards and health surveillance equal to that outlined in the DVR-held NIH Animal Procurement Contract, and shipment in a manner to assure maintenance of health status. Contracts may be available for some sources which have defined relationships with NIH. Wild caught rodents or colonies founded with wild caught stock must provide evidence that colonies are free of LCMV and hantaviruses, or indirect testing may be done using sentinels during NIH Quarantine. The NIH Rodent Import Coordinator (NIH RIO Coordinator) maintains a list of sources that meet the Approved Source criteria (http://dvrnet.ors.od.nih.gov/). Sources must be approved by the APDs' Committee in order to be added to the Approved Sources list. For consideration for approval, documentation of the source's program to provide specific pathogen-free animals must first be reviewed and endorsed by the NIH RIO and Rodent Import Advisory Subcommittee (RIAS).
5. **Exemptions:** An exemption from Quarantine for a particular shipment of rodents that do not meet the NIH minimum health standard may be obtained with appropriate justification and approval (See Section D. Policy).
6. **Facility Veterinarian:** A veterinarian who has direct or delegated responsibility for the management of the animals in a facility.
7. **Isolation:** Refers to the receipt, housing, husbandry and health testing of animals at a DVR or IC operated Rodent Isolation Area for the purpose of this policy.
8. **Isolation, Rodent:** A containment facility for the holding and testing of rodents believed to be free of specific rodent pathogens and zoonotic agents. The design and operation of the area shall ensure the isolation and containment of rodent pathogens and zoonotic agents at the cage level. The physical and procedural attributes of an Isolation barrier are similar or identical to that of a Quarantine Facility. The APD of the Lead or sponsoring IC, or in the case of a centrally run Isolation Area the Director DVR, is accountable for the adequacy of isolation and containment. The establishment of an Isolation Area within a shared or central animal holding facility shall have the review and endorsement of the animal facility's user ICs.
9. **Laboratory Principal Investigator(s) and their Laboratory/Branch Chief(s):** The individuals within a laboratory or branch with responsibility and accountability for the

compliance of the laboratory or branch with all established NIH and PHS policies, procedures, and guidelines.

10. **Minimum Health Standard, NIH:** All rodents introduced into NIH facilities must be shown to be free of LCMV and hantaviruses, as applicable (for laboratory rats and wild rodents). The sending facility must provide assurance and/or evidence that annual testing for the specified agents is performed throughout their facility, or it must be demonstrated (serology or Polymerase Chain Reaction (PCR)) that the specific animals to be shipped are likely free of these agents. Unless approved for scientific study of ectromelia infection under an animal study protocol, rodent products for use in mice must also be shown to be free of ectromelia virus. (See Section K. Procedures for Introduction of Rodent Products).
11. **NIH Facility:** Any building, structure, laboratory or other facility, whether or not animals are housed or used there, associated with the NIH intramural research program. This includes any facility on the Bethesda, Maryland, campus, the NIH Animal Center (NIHAC) in Poolesville, Maryland, off-campus leased facilities, and other sites where intramural research is performed under AAALAC International accreditation file number 000777.
12. **Non-approved Source:** A source of rodents or rodent products that does not meet the definition of an Approved Source.
13. **Quarantine:** Refers to the receipt, housing, husbandry and health testing of animals at a DVR or IC operated Rodent Quarantine Facility for the purpose of this policy.
14. **Quarantine Facility, Rodent:** A containment facility for the holding and testing of animals with known, suspect or unknown health status. The design and operation of the facility shall ensure the isolation and containment of rodent pathogens and zoonotic agents at the cage level. The ideal barrier would:
    a. Physically separate the Quarantine Facility from other rodent holding facilities or areas;
    b. Use certified Class II Biological Safety Cabinets for cage changing and handling of animals;
    c. Have the ability to autoclave contaminated bedding and supplies out of the area;
    d. Have the ability to control and limit access to key personnel;
    e. Utilize appropriate disposable or dedicated personal protective equipment (PPE) (e.g. jumpsuits, shoe covers, hair covers, gloves, etc.);
    f. Have access to shower facilities; and,
    g. Have established standard operating procedures for the daily husbandry, testing and disposition of animals.

    Because a Quarantine Facility can accept animals with suspect or unknown health status, a break in the physical or procedural barrier poses a significantly higher risk to other nearby colonies, than the risk posed by an Isolation Facility which only accepts animals believed to be free of unwanted pathogens or zoonotic agents. Therefore, the establishment of a Quarantine Facility within a shared or central animal holding facility shall have the review and endorsement of the animal facility's user ICs. The APD of the Lead or sponsoring IC, or in the case of a centrally run Quarantine Facility the Director DVR, is accountable for verifying the adequacy of isolation and containment, as well as ensuring that the Quarantine Facility is on file with the NIH RIO.
15. **Quarantine Permit Service Office (QPSO):** An office in the Division of Occupational Health and Safety (DOHS) that assists investigators in obtaining permits that may be required when importing/exporting animals, animal products, etiologic agents, or vectors of human or animal disease. Permits must be obtained from the NIH Institutional Biosafety Committee through the Biosafety Officer in coordination with the IC RIO and the NIH RIO. http://dohs.ors.od.nih.gov/Import_Permits_Export_Declarations.htm and http://dohs.ors.od.nih.gov./ic_safety_committees.htm or telephone 301-496-2960.
16. **Rodent:** A mammal of the order Rodentia, including but not limited to mice, rats, guinea pigs, and hamsters.
17. **Rodent Import Coordinator, NIH (NIH RIO Coordinator):** An administrative assistant working with the NIH Rodent Import Officer to receive, process, and maintain files and lists associated with this policy. Fax: 301-480-8222, or e-mail Global Directory- OD DVR Rodent Import (oddvrrimport@mail.nih.gov).

18. **Rodent Import Officer, NIH (NIH RIO):** A veterinarian appointed by the Director of the DVR, ORS, with delegated responsibility for activities defined in this policy and for overseeing activities at the DVR operated Rodent Quarantine Facilities.
19. **Rodent Import Officer, Institute/Center (IC RIO):** A veterinarian, the APD of an IC and/or their designee, with responsibility for import activities defined in this policy within their IC.
20. **Rodent Import Advisory Subcommittee (RIAS):** A committee appointed by the APDs to serve in an advisory capacity to the NIH RIO in periodic reviews of this policy. The NIH RIO may seek the counsel of the RIAS in reviewing applications for Approved Source status, and to settle disputes involving this policy.
21. **Rodent Products:** Any rodent tissue or derivative directly introduced into a rodent or combined with another product for rodent *in vivo* use. Products include but are not limited to antibodies (polyclonal or monoclonal), body fluids, proteins, embryos, sperm or cells.

G. Responsibilities

1. **Director, DVR, ORS** Implements those aspects of this policy relating to the DVR and the NIH RIO.
2. **The Facility Veterinarian** choices of action include:
    a. Approve the animals for entry into their animal facility (from approved source with known acceptable health history).
    b. Approve animals for entry into an Isolation Area (minimal risk based on health history).
    c. Approve animals for entry into areas where infectious studies will be performed, such as ABSL3 or Isolation Areas designated for studies of specific infectious agents.
    d. Require the animals to be quarantined with further testing.
    e. Reject the animals for entry into their facility.
    f. Require more information before making a decision.

    In the first four cases, (a-d), the facility veterinarian approves the import and forwards the application to the NIH RIO Coordinator. In the latter two cases, (e and f), the facility veterinarian returns the application to the submitting IC RIO. After animals have completed Quarantine including testing, their health status is documented on NIH Form 2369-4 "Rodent Quarantine Release" and they are offered for release. The facility veterinarian determines if and when isolated animals can enter their facility.
3. **IC RIO**
    a. Assists the principal investigator/applicant in securing approvals, permits, transportation, etc., related to the introduction of rodents or rodent products into an animal facility or laboratory. The above includes obtaining health monitoring and husbandry information for review by the facility veterinarian using NIH Form 2369-2 "Animal Health Data Request Template."
    b. Reviews and approves or disapproves applications for the introduction of rodents from non-approved sources into NIH IC animal facilities, under their purview (NIH Form 2369-1), based on the supportive evidence for absence of LCMV and hantaviruses (if applicable) and other murine pathogens excluded from their facility. Forwards applications for introduction of rodents from non-approved sources to the facility veterinarian.
    c. Reviews and approves or disapproves applications for the introduction of rodent products and pathogens (NIH Form 2369-3), into NIH IC animals, under their purview, based on the supportive evidence for the absence of LCMV, hantaviruses (if applicable) and ectromelia.
    d. Reviews and approves or disapproves applications for introduction of rodents from non-approved sources into laboratories of an IC.
    e. Provides oversight within their IC to ensure Quarantine of animals until such time that data can be generated to verify that the animals are, at a minimum, free of LCMV, and hantaviruses, as applicable. Forwards data to the NIH RIO.

4. **IC Scientific Director** ensures compliance with this policy by intramural staff within his/her IC.
5. **NIH RIO Coordinator**
    a. Assigns and applies a Rodent Import Permit number to each application received.
    b. Provides a copy of the numbered permit to the IC RIO, the requesting investigator, and the facility veterinarian after approval. A copy is also provided to the designated Quarantine or Isolation manager and that facility's veterinarian. Changes to the contact list may be requested by the IC RIO.
    c. Maintains a file (paper and/or electronic) of IC RIO approved Rodent Import Permits and the supportive health information.
    d. Maintains electronic lists on the DVR Website: http://dvrnet.ors.od.nih.gov/ of Approved Sources and all Rodent Quarantine Facilities.
6. **NIH RIO**
    a. May suspend an approved permit within 24 hours, pending further discussion with the IC RIO, if it is determined that a high risk decision was made. In general a 1-2 business day turn around time is expected.
    b. Coordinates use of the DVR Rodent Quarantine facilities.
    c. Sets testing requirements for and releases animals from DVR Quarantine sites once testing demonstrates the rodents meet the NIH minimum health standard. NIH Form 2369-4, "Rodent Quarantine Release."
    d. Provides guidance on this policy to IC RIOs and facility veterinarians.
    e. Evaluates and approves proposals for import permit exemptions. Approved exemptions will be reviewed annually
7. **Principal Investigator/Applicant**
    a. Initiates rodent import application(s) for approval of shipments from non-approved sources for:
        i. rodents into NIH laboratories or animal facilities
        ii. rodent products to be introduced into NIH rodents
    b. Initiates any additional permits/applications which may be required, such as United States Department of Agriculture permits, when necessary (See Section M. Additional Information).
8. **RIAS** is a committee appointed by the APDs, which:
    a. Reviews proposed approved sources with the NIH RIO for purposes of this policy.
    b. Provides mediation for disputes if necessary.
    c. Reviews revisions to this Policy (The RIAS should seek scientific representation by a member of the Animal Research Advisory Committee [ARAC] for major policy revisions).

H. Procedures for Introduction of Rodents

See Appendix 1, Flow chart of Procedures

Note: Section K covers Introduction of Rodent Products

1. The introduction of rodents from non-approved sources requires submission and approval of NIH Form 2369-1, "Application for Permit to Introduce Rodents" It is particularly important that the name, telephone number, and e-mail address of the veterinarian or other person responsible for animal health at the originating facility is provided. Since overseas telephone contact is often difficult and expensive, listing an e-mail address or fax number is recommended. In situations where Quarantine is likely, applications should be submitted at least 60 calendar days prior to the anticipated date of entry into an NIH animal facility to allow time for diagnostic testing. Procedures for submission and approval are as follows:
    a. The principal investigator must complete their sections of NIH Form 2369-1 "Application for Permit to Introduce Rodents" and submit the application to their IC RIO. The IC RIO reviews health information for compliance with the minimum

health standard, then approves the import or submits the application to the facility veterinarian for the facility in which the animals are to be housed.

b. A NIH Form 2369-2, "Animal Health Data Request Template" may be helpful to NIH veterinarians when contacting the originating facility, and later when evaluating documentation of their pathogen monitoring and control program. All information acquired should be submitted to the IC RIO Coordinator along with the application. The NIH RIO requires that testing for LCMV and hantavirus if applicable be conducted within the last 12 months. If an exemption to the Quarantine policy is desired, contact the NIH RIO.

c. The application and supporting documents are then routed to the facility veterinarian of the final location where animals or tissue will be housed and/or used. In addition to meeting the minimum health standard, animals destined for an NIH animal facility must also meet the health requirements of the receiving facility. The facility veterinarian reviews the health information submitted for compliance with their facility's requirements. The facility veterinarian then forwards the approved application, with supporting documents, to the NIH RIO Coordinator (Fax: 301-480-8222 or e-mail Global Directory- OD DVR Rodent Import(oddvrrimport@mail.nih.gov)

d. Note: The NIH RIO Coordinator will not assign a Rodent Import Permit number unless the facility veterinarian for the final housing location has signed it.

2. Applications to introduce rodents into a laboratory for acute studies (holding for less than 12 hours), where no contact with other animals is planned may be approved by the IC RIO.
3. The IC RIO must ensure that the imported animals represent a low risk to both personnel and animal colonies for LCMV and hantaviruses, as applicable. The approved application is forwarded to the NIH RIO Coordinator who assigns it a rodent import number, provides a copy to the IC RIO, and files the application.

I. Quarantine/Isolation Facilities and Procedures

1. The DVR operated and IC operated Rodent Quarantine facilities are used for rodents entering the NIH from facilities or colonies of unknown or high risk health status. An import permit is required.
2. DVR, IC, and Shared Facility Isolation Areas may be utilized for rodents entering the NIH from colonies with known, acceptable, low risk health status at the discretion of the IC RIO and facility veterinarian. An import permit is required.
3. Monitoring in Quarantine/Isolation Facilities for Potential Pathogens
    a. Direct testing of imported animals provides the best indicator of their health status. Test procedures for animals in Quarantine Facilities are designed to comply with this policy and are performed in accordance with the Quarantine Facility's standard operating procedures. The IC RIO and/or Facility Veterinarian may request direct testing of imported animals, use of direct/contact sentinels, or use of indirect sentinels to test for LCMV and hantavirus (for laboratory rats and wild rodents). All imported animals will be direct tested for endo- and ectoparasites. Animals will be considered for release from Quarantine upon receipt of negative results from tests performed after 3-4 weeks of quarantine, with direct serology for immunocompetent animals, or 3-4 weeks of cohabitation with direct sentinels. If indirect, non-contact sentinels are used, they must test negative after 4-6 weeks exposure to bedding from experimental animal cages.
    b. Testing procedures for animals in Isolation Areas are designed to comply with this policy and the requirements of the receiving facility. Testing imported animals for endo- and ectoparasites is highly encouraged. Additional testing by serology, PCR, or a combination thereof is decided after a thorough review of the health history of the imported animals, the health history of the sending facility, and the specific pathogen-free status of the receiving facility.
    c. Non-standard testing will be conducted as requested by the IC RIO and/or the facility veterinarian.

4. Release of Animals from Quarantine/ Isolation Facilities
    a. The NIH or IC RIO offers the quarantined animals for release when test results indicate that the animals are free of LCMV and hantaviruses if applicable. Release from Quarantine is documented using NIH Form 2369-2 "Rodent Quarantine Release." A summary of Quarantine test results is provided on this form to the receiving facility veterinarian, and the IC RIO. IC Quarantine Facilities will provide this report to the NIH RIO. IC Isolation sites will provide test results for LCMV and hantavirus if applicable to the NIH RIO. If confirmed test results indicate that the quarantined rodents have unanticipated LCMV, hantaviruses, or ectromelia virus positive animals will either be relocated to an off campus non-NIH holding facility or be immediately euthanized following discussions with the importing institute veterinarian.
    b. The facility veterinarian for the receiving facility must evaluate the health status of the animals in light of that facility's policy. If the rodents have pathogens that are not acceptable at the facility they are slated to enter, the owning IC may elect to find alternative housing and eradicate the pathogen(s). If the eradication process is conducted in DVR Rederivation/Special Studies facilities, it must be accomplished within a reasonable period of time; reasonable period of time is dependent upon other demands for the use of the Rederivation/ Special studies space. If rederivation is used, the procedures should meet the guidelines adopted by the International Embryo Transfer Society (IETS) http://www.iets.org/manual.htm, as modified for rodents. (See Appendix 2 "Requirements for Handling Imported Mouse and Rat Embryos, Oocytes, Ovaries or Sperm".)

J. Establishment of Quarantine Facilities

1. Rodent Quarantine may be conducted at facilities other than DVR Quarantine Facilities. IC Quarantine Facilities must meet the definition of Section F.14 "Quarantine Facility, Rodent." The NIH RIO must first review a written outline of the procedures to be used to protect both rodent colonies and personnel from LCMV, and hantaviruses if applicable, during the quarantine period and also, if applicable, upon subsequent entry into an NIH facility. Documents must include the location of the facility, standard operating procedures governing policies, procedures and practices of the Quarantine Facility, and individual accountable for the site. Unresolved issues between an IC and the NIH RIO shall be brought to the RIAS for resolution.
2. The NIH RIO Coordinator will inform the facility veterinarian of an impending import using NIH Form 2369-1 "Application for Permit to Introduce Rodents" (See Section H. "Procedures for Introduction of Rodents").

K. Procedures for Introduction of Rodent Products and Rodent Pathogens

1. Rodent products and rodent pathogens for *in vitro* use only (that will never be in contact with reagents, cells, etc., to be used in live rodents) require no testing or permit. However, the Laboratory Principal Investigator(s) and Laboratory/Branch Chief(s) must ensure that products for *in vitro* use are handled and disposed of in a manner that prevents accidental exposure of personnel or rodents to chance contamination and prevents the inadvertent introduction of the agent(s) or material into other NIH facilities. *in vitro* experiments utilizing a natural rodent pathogen (e.g. ectromelia virus, epizootic diarrhea of infant mice virus (EDIM), mouse hepatitis virus (MHV), mouse parvovirus (MPV), murine norovirus (MNV), Helicobacter, etc.) must be performed with appropriate caution using biosafety level 2 (BSL2) practices or greater, as required for zoonotic agents. The APD and/or the NIH Biosafety Officer can assist laboratory personnel in the development of policies and procedures for the safe handling of rodent products and rodent pathogens. In general, rodent pathogens must be handled in a certified biosafety cabinet and all contaminated materials disposed of as medical pathological waste or chemically inactivated.

2. Rodent pathogens for *in vivo* use must be described in the Principal Investigator's approved Animal Study Proposal (ASP) and have the concurrence of the facility housing the animals prior to the commencement of work with the pathogen.
3. Rodent products for *in vivo* use must meet the NIH minimum health standard. Their introduction requires the submission and approval of NIH Form 2369-3 "Application for Rodent Products or Rodent Pathogens for Use *in vivo* Biological Assessment" to the IC RIO with some exceptions. Products contained in commercially available test kits, or reagents that have been produced (e.g. in bacteria) or processed (e.g. affinity purified antibodies) in a manner that shall exclude or inactivate all pathogenic agents do not require a permit. Rodent products containing a known pathogen used to intentionally infect rodents for *in vivo* studies of the pathogen are exempt when the use of the pathogen has been approved on an animal study proposal.
    a. **Rodent Products: Other than Frozen or Fresh Embryos, Sperm, Oocytes and Ovaries**
        i. The Principal Investigator should first ensure that the procedures and rodent products or treated materials to be used *in vivo* are listed on an approved Animal Study Protocol. If not, they must submit an amendment to add the product.
        ii. The Principal Investigator must complete and submit a NIH Form 2369-3, "Application for Rodent Products or Rodent Pathogens for Use *in vivo* Biological Assessment" to the IC RIO for approval.
        iii. Routinely the IC RIO will require material testing using PCR or Mouse Antibody Production (MAP)/Rat Antibody Production (RAP)/Hamster Antibody Production (HAP) prior to *in vivo* use to ensure the products are free from LCMV, ectromelia, hantaviruses and other agents as required by the designated animal facility.
        iv. Investigators may request and submit for use specific test data obtained by any other IC RIO for cells or materials obtained from another NIH Principal Investigator as long as both Principal Investigators certify that the materials had no further exposure to any rodent products.
        v. The IC RIO reviews the application and any testing data, and if approves, signs and sends it on to the Facility Veterinarian. The Facility Veterinarian, reviews for facility and room specific agents and provides final signature. It is then returned to the IC RIO's office for filing and to inform the Principal Investigator of final approval.
        vi. Rodent products for *in vivo* use that do not meet the minimum health standard and are not exempted from the standard due to their research use may not be imported or must be disposed of if already introduced into an NIH laboratory. The finding must then be reported to the NIH RIO who will alert the NIH community and keep a record of the finding on file for a period of 3 years.
    b. **Rodent Products: Frozen or Fresh Embryos, Sperm, Oocytes and Ovaries**
    The freezing of embryos, sperm, oocytes or ovaries provides no assurance that they are free of horizontally or vertically transmitted pathogens. Therefore, the following procedures are required for all imported frozen or fresh embryos, sperm, oocytes or ovaries brought into the NIH and recommended for all frozen or fresh embryos, sperm, oocytes or ovaries derived from colonies of unknown or suspect health status being brought into a specific pathogen free facility. The reconstitution of lines from frozen or fresh embryos, sperm, or oocytes derived from colonies of unknown or suspect health status, shall follow the same procedures used for embryo rederivation of lines contaminated with unwanted pathogens. Frozen or fresh imported embryos, or embryos derived from *in vitro* fertilization using imported frozen or fresh sperm or oocytes, must be carefully washed prior to implantation into recipient females, in accordance with the latest edition of the Manual of the International Embryo Transfer Society, http://www.iets.org/manual.htm, as modified for rodents (See Appendix 2

"Requirements for Handling Imported Mouse and Rat Embryos, Oocytes, Ovaries or Sperm"). The reconstitution of lines from frozen or fresh ovaries derived from colonies of unknown or suspect health status shall also be carefully washed prior to implantation. In all cases, recipient female(s) and their offspring shall be held in a Rodent Isolation Area or Quarantine Facility until their health status is confirmed by the testing (See Section I. Quarantine/Isolation Facilities and Procedures 3.a-c). In the case of transferred embryos, a minimum of one recipient mother from each group of transferred washed embryos shall be tested.

c. **Application Process**
The IC RIO or facility veterinarian approves and forwards a copy of the application to the NIH RIO Coordinator, who provides it to the NIH RIO for review of the application, assigns it an import number, provides a copy to the IC RIO and facility veterinarian, and files the application.

4. The Quarantine Permit Service Office, NIH Institutional Biosafety Committee should be consulted to determine if a USDA permit is required (for reasons stated below). Assistance in making this determination is available from the NIH Biosafety Officer, DOHS. http://dohs.ors.od.nih.gov/Import_Permits_Export_Declarations.htm or telephone 301-496-2960.

L. Quarantine Permit Service Office (NIH Institutional Biosafety Committee through the Biosafety Officer)

Several agencies of the United States Government regulate and require permits for the importation, transfer, shipment, or exportation of certain animals, animal products, or etiologic agents or vectors of human or animal diseases. Investigators must work with their IC RIO to determine whether an import permit other than a NIH Form 2369-1 "Application for Permit to Introduce Rodents" or NIH Form 2369-3 "Application for Rodent Products or Rodent Pathogens for Use *in vivo* Biological Assessment," covered by this policy, is required. The IC RIO will coordinate with the NIH RIO and the QPSO to come to a decision regarding the need for additional permits. The QPSO will provide investigators with assistance and appropriate application forms to import, export, or transport regulated materials or animals. Import and Export Permits are also available on-line. The website is:
http://dohs.ors.od.nih.gov/Import_Permits_Export_Declarations.htm.

1. The USDA Animal and Plant Health Inspection Service (APHIS) has statutory authority to regulate the importation of any animal-derived material or biological material that has been in contact with material of animal origin. Thus, USDA permits are required for the importation of monoclonal antibodies, hybridoma cell lines, cell cultures, and other biologic materials that have been in contact with material of animal origin, such as fetal bovine serum. USDA permit forms and information are available on-line. The website is: www.aphis.usda.gov/permits.
2. The Department of Health and Human Services (DHHS), Centers for Disease Control and Prevention (CDC) Etiological Agent Import Permit Program Atlanta, Georgia is responsible for regulations involving the importation into the United States or distribution after importation, of any etiologic agent or any arthropod or other animal host or vector of human disease (NIH Manual Chapter 1340-1, "Permits for Import or Export of Biological Materials," http://www1.od.nih.gov/oma/manualchapters/management/1340%2D1/, and 42 C.F.R. Part 71.54 http://www.fda.gov/opacom/laws/phsvcact/phsvcact.htm). A DHHS permit must be obtained for importation and/or distribution of these materials. The DOHS NIH Institutional Biosafety Committee through the Biosafety Officer has been authorized by the CDC to issue DHHS import permits.
3. Finally, the United States Fish and Wildlife Service (USFWS), United States Department of Interior, http://www.fws.gov/le/ImpExp/Info_Importers_Exporters.htm, has the authority under Federal regulations (50 C.F.R. 23) to control the import and export of all wildlife and specimens coming into or leaving the United States. Researchers must contact a biologist at the USFWS for clarification at (703) 358-2104.

M. Additional Information

1. For further information on this policy, contact the NIH RIO at (301) 496-2527, e-mail Global Directory- OD DVR Rodent Import (oddvrrodentimport@mail.nih.gov) or the applicable IC RIO. For additional information on the importation or transportation of any etiologic agent or host or vector of human or animal diseases, or the importation of wildlife, contact DOHS at 301-496-2960, http://dohs.ors.od.nih.gov/about_dohs.htm.
2. All Federal requirements for the importation of rodents must be adhered to. Copies of the current requirements can be obtained from the NIH Institutional Biosafety Committee through the Biosafety Officer, the NIH RIO and the USDA requirements-website: http://www.aphis.usda.gov; CDC requirements-Permit Officer, Division of Quarantine, CDC; 404-639-8108 or by referencing 42 CFR, Section 71.54.
3. The NIH Institutional Biosafety Committee through the Biosafety Officer, DOHS, will provide assistance for the importation of rodents as outlined in Section L. Quarantine Permit Service Office (NIH Institutional Biosafety Committee through the Biosafety Officer), http://dohs.ors.od.nih.gov/Import_Permits_Export_Declarations.htm or telephone 301-496-2960.

N. Records Retention and Disposal

All records (e-mail and non-e-mail) pertaining to this chapter must be retained and disposed of under the authority of the NIH Manual Chapter 1743, "Keeping and Destroying Records," Appendix 1, NIH Records Control Schedule, Section 1100 - General Administration, Item 1100-B-1 - "Policy Files," Section 2600 Procurement, Property and Supply Management (all that apply), Section 3000 Intramural Activities, Items C. Veterinary Services Records of the Veterinary Resources Branch of the Office of Research Services (all that apply) and G. Biomedical Research Projects (all that apply), and Section 7000 - PART 4 PROTECTION FROM BIOHAZARDS CONTAMINANTS, POLLUTANTS AND RESEARCH RISKS, Items A. Protection of Research Subjects (all that apply) and B. Biohazards (all that apply).

NIH e-mail messages: NIH e-mail messages (messages, including attachments, that are created on the NIH computer systems or transmitted over the NIH networks) that are evidence of the activities of the agency or have informational value are considered Federal records. These records must be maintained in accordance with current NIH Records Management guidelines. Contact your IC Records Officer for additional information.

All e-mail messages are considered Government property, and if requested for a legitimate Government purpose, must be provided to the requester. Employees' supervisors, the NIH staff conducting official reviews or investigations, and the Office of Inspector General may request access to or copies of the e-mail messages.

E-mail messages must also be provided to the Congressional Oversight Committees, if requested, and are subject to the Freedom of Information Act requests. Since most e-mail systems have back-up files that are retained for significant periods of time, e-mail messages and attachments are likely to be retrievable from a back-up file after they have been deleted from an individual's computer. The back-up files are subject to the same requests as the original messages.

O. Management Controls

The purpose of this manual issuance is to establish procedures designed to prevent the introduction of infected rodents and rodent products into the NIH which could adversely affect the health of rodents used in research, directly or indirectly interfere with research, or pose a health hazard to personnel.

1. **Office Responsible for Reviewing Management Controls Relative to this Chapter:** Through this manual issuance, the Division of Veterinary Resources, Office of Research Services is responsible for ensuring that management controls are implemented and working.
2. **Frequency of Review** (in years): Ongoing; triennially.
3. **Method of Review:** Alternative Review; NIH RIO in consultation with the RIAS, and final approval by the NIH Animal Research Advisory Committee.

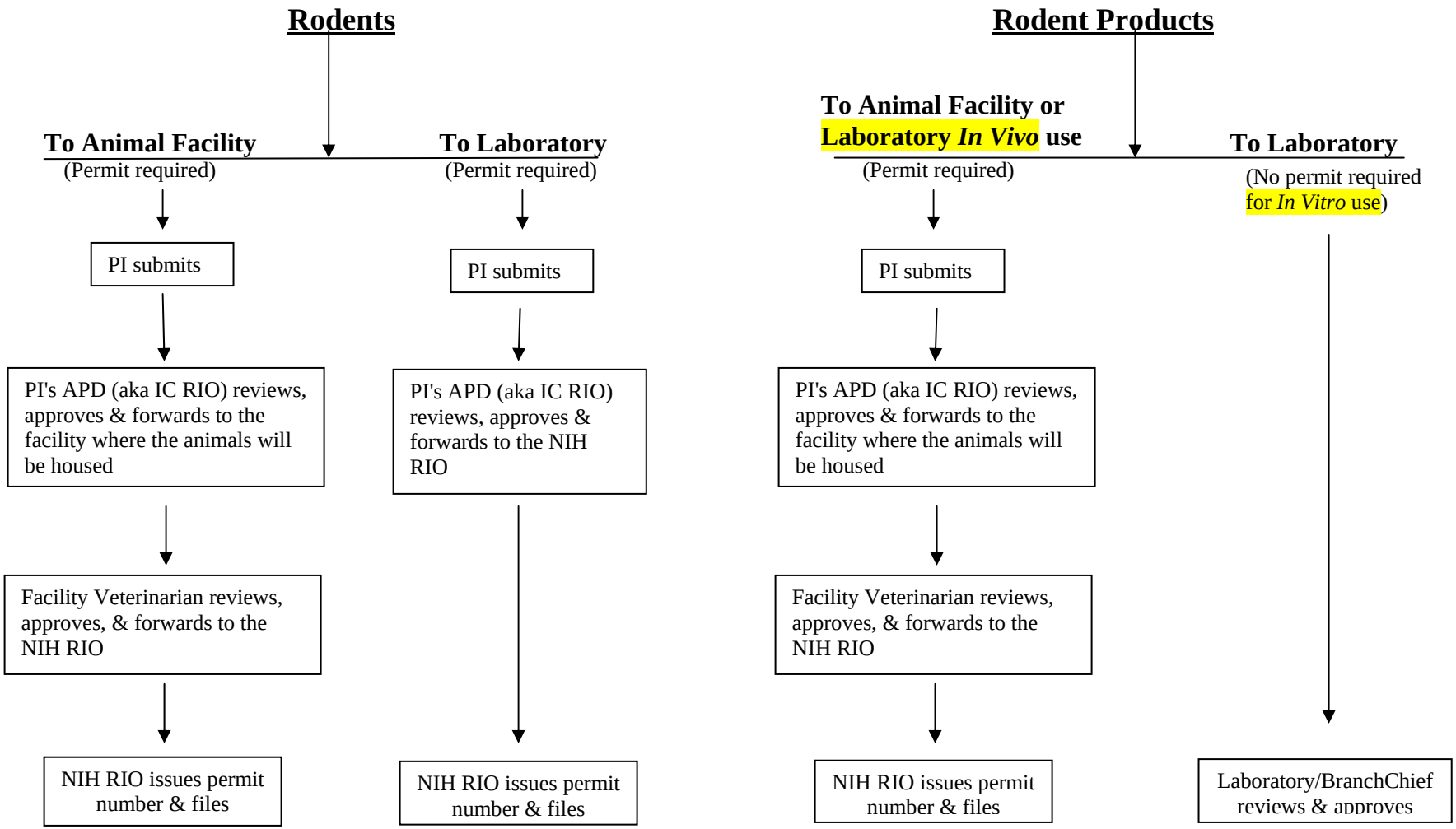
Each APD is responsible for monitoring the compliance of his/her IC through internal control review. At a minimum of every three years a risk assessment will be performed to ensure that internal controls are in place and are working properly. Results of these reviews should be submitted to the DVR RIO in order to maintain a record of compliance. DVR will ensure that new APDs receive information regarding this policy and will provide guidance to all users as needed. DVR will maintain records of IC internal compliance reviews and will conduct such review of the DVR managed facilities. If any compliance concerns are not resolved at the IC or DVR level they will be submitted to the RIAS. Any significant noncompliance will also be reported to the APD's Committee and the NIH Animal Research Advisory Committee (ARAC).

4. **Review Reports are sent to:** The ORS Scientific Resources Manager, the Associate Director for Research Services (ADRS) and the Deputy Director for Intramural Research. Issues of concern will be brought to the immediate attention of the ADRS.

Appendices

1. Flowchart: Introduction of Rodents or Rodent Products from Non-approved Sources
2. Requirements for Handling Imported Mouse and Rat Embryos, Oocytes, Ovaries or Sperm
3. NIH Form 2369-1 "Application for Permit to Introduce Rodents"
4. NIH Form 2369-2 "Animal Health Data Request Template"
5. NIH Form 2369-3 "Application for Rodent Products or Rodent Pathogens for Use *in vivo* Biological Assessment"
6. NIH Form 2369-4 "Rodent Quarantine Release"

Introduction of Rodents or Rodent Products from Non-Approved Sources



Requirements for Handling Imported Mouse and Rat Embryos, Oocytes, Ovaries or Sperm

Oocytes are handled as outlined below for embryos. Ovaries or sperm received for introduction into rodents are handled in the same manner, except the washing steps are excluded.

Compile and submit information regarding the potential health status of the imported embryos as for a live rodent import.

Treat the shipping or transport vessel as contaminated on arrival at the facility; decontaminate the exterior with alcohol or Clidox. It is preferable to move the straws or tubes to a clean transport vessel (e.g. Dewar flask) on arrival, leaving the original shipper outside of the animal facility.

Consider the straw or tube that holds the embryos as contaminated and wipe down the exterior with Clidox or other approved disinfectant before use. Do not open straws or tubes where clean embryos are being transferred. If there is no dedicated area for working with potentially contaminated embryos, perform all embryo manipulations inside of a laminar flow hood that protects the environment. Discard straws and tubes as contaminated waste.

Only embryos free of gross adherent material should be washed; clean with hyaluronidase when necessary. Implant only zona pellucida-intact embryos. To confirm the zona pellucida is intact and free from adherent material, observe all surfaces of the embryos at a minimum magnification of 60X.

Regulate volumes so that each wash is approximately a 100-fold dilution of the previous wash. Wash a minimum of five to ten times in sterile medium (allow sufficient time for thorough, gentle mixing in each wash). Use a new sterile micropipette each time embryos are moved from one wash to the next.

House recipient dams and offspring separate from research colonies, preferably in a quarantine facility. Perform comprehensive serologic, bacteriologic, and parasitologic testing on the resulting pups and mother before release of the offspring into general housing.

Department of Health and Human Services
Public Health Service, National Institutes of Health

Application for Permit to Introduce Rodents

See NIH Manual 3043-1 for complete instructions.
Use additional sheets if more space is needed.

1. From *(Name, address, E-mail address, phone no. and fax no. of facility)*

2a. To *(Name of requestor)*

2b. Institute/Laboratory

2c. NIH Address *(Bldg./Rm.)*

2d. E-mail address

2e. Phone No.

2f. Fax No.

3. Genus and Species, Common Name(s), Correct Nomenclature, Color, Strain/Stock *(Provide all information needed for cage cards; use an addendum, if necessary.)*

4a. Have these animals been injected/manipulated?

4b. Location currently housed
Building: Room:

5. Number of Animals to be Received
Male: Female: Age range:

6. Approximate Date of Arrival

7. Approved Animal Study Proposal No.

8a. Medical History of the Originating Colony

8b. Current Location or Source of the Colony

8c. What diseases or parasites are known to be present in the originating colony?

9. Has colony been checked for Lymphocytic Choriomeningitis (LCM) virus and hantavirus *(if applicable)*?
☐ Yes ☐ No ☐ N/A

10. Can these animals mount an antibody response?
☐ Yes ☐ No ☐ Unknown

11. Name, title, E-mail address, phone no., and fax no. of sending institution's facility veterinarian or designee

12a. Final Location where animals will be housed

12b. Is this location listed in the approved ASP?
☐ Yes ☐ No

12c. Quarantine/Isolation location

13. Special requirements for handling animals during the quarantine period
☐ Rederivation by IETS Standards (modified)
☐ Exemption from Quarantine
☐ Quarantine at: _____
☐ DO NOT BLEED
☐ Breed during quarantine
☐ Other: _____

I certify that these animals will be used in accordance with all restrictions and precautions as may be specified in the permit.

14a. Requestor's Name	14b. Signature	14c. Date Signed
15a. IC Animal Program Director's Name	15b. Signature	15c. Date Signed
16a. Facility Veterinarian's Name	16b. Signature	16c. Date Signed

17. Quarantine Requirements

18. Testing method(s) requested
☐ Direct testing ☐ Direct/contact sentinels ☐ Indirect sentinels
☐ Extra colony mice ☐ Other: _____

Permit to Introduce Rodents or Rodent Products

1. Permit Number

2. Remarks

Fenbendazole feed in 127/128 & 14G106

3. Quarantine location

4. Date Issued

Animal Health Data Request Template

NIH policy requires rodents to be free of lymphocytic choriomeningitis virus.

Use prescribed by NIH Manual 3043-1

RETURN TO:
National Institutes of Health
Bethesda, Maryland, U.S.A.

Institute Name:

Contact:

E-mail address:

Originating Facility:

Originating Institution:

Investigator's Last Name: First Name:

E-mail:

Vivarium: Vivarium Room:

Veterinarian's Last Name: First Name:

Vet Voice: Fax:

Vet E-Mail: Additional Contact(s)?:

Colony Description:

Approximate Colony: Size In Room? Immune Status: ☐ Normal ☐ Deficient ☐ Undetermined

Breeding In Room?: ☐ Yes ☐ No

Colony Status ☐ Closed ☐ Open w/ Quarantine Required ☐ Open

Do Incoming Animals Come from Multiple Sources? ☐ Yes ☐ No

Sentinel Program:

Please attach a letter explaining your sentinel program & known positives, or complete this section & provide a copy of the latest sentinel test results.

Sentinel Boxes In Room: Animals tested : ☐ Retired breeders ☐ Sentinels ☐ Experimental

Frequency of Monitoring? ☐ Quarterly ☐ Semi-Annually ☐ Annually ☐ Other

Sentinel on Dirty Bedding ☐ Yes ☐ No (☐ Other method of sentinel exposure:)

Any Pathogens or Other Health Problems In Room in Previous Year?

Please List Pathogens or Potential Pathogens Present in other Rodent Rooms in Same Vivaria:
☐ None Present *or* ☐

Husbandry:

Is Husbandry Shared With Any Rooms that Contain Potential Rodent Pathogens?: ☐ Yes ☐ No

If Yes, List Organisms

Caging System: ☐ Conventional ☐ Microisolator ☐ Flow through ☐ Other

Protective Equipment: ☐ Gloves ☐ Shoe covers ☐ Hair covers ☐ Masks
☐ Dedicated clothing ☐ Disposable clothing ☐ Change hoods ☐ Shower-in

Testing Biologicals:

Are biologicals for use in animals routinely tested before use in your facility?: ☐ No ☐ Yes ☐ Unknown

Veterinarian: _____
(Print name) *(Signature)* *(Date)*

Questions? Contact the Import Coordinator: E-mail: or phone: 301-

Appendix 5 Form NIH 2369-1 (Rev. 3/09)

Department of Health and Human Services
National Institutes of Health

Application for Rodent Products or Rodent Pathogens for Use *In Vivo* Biological Assessment

Use prescribed by NIH Manual 3043-1

Complete one form for each biological. This form is used to determine if testing of a biological is required prior to in vivo use.

Please e-mail the completed form to:

Name of Requestor –

Date of Request –

E-mail address –

Phone number –

IC QA Code:

ASP(s) *to be used on –*

Facility *to be used in –*

Species *to be used with –*

Name of APD/IC RIO –

Name of Facility Veterinarian –

Note: If a cell line, product of a cell line, or other biological for use in rodents has been exposed to rodents or rodent products, they must be tested prior to use.

1. Type of biological (please select one)
   - a) ◯ cell line
   - b) ◯ antibody
   - c) ◯ hybridoma
   - d) ◯ parasite
   - e) ◯ antigen (specify in description)
   - f) ◯ microbe (specify in description)
   - g) ◯ biochemical (specify type in description)
   - h) ◯ adjuvant (specify in description)
   - i) ◯ known rodent pathogen

   Other ◯ specify *(e.g. bone marrow, serum)*

2. Complete name of the biological –
   a) Description of Biological –

3. Where was the biological obtained from? *(If a commercial source please state company name; if from another NIH lab please give the lab name and the name of the PI; if from another outside source please state institute name and PI name.) –*

4. Is this biological of rodent origin Yes ◯ No ◯ Unknown ◯

5. Has the biological been exposed to any rodent products? *(e.g. serum)*
   Yes ◯ No ◯ Unknown ◯

6. Will this biological be maintained using products that contain or have been exposed to rodents or rodent products? Yes ◯ No ◯ *(if yes, explain)*

7. If you answered yes to any of questions 4-6, will the biological be purified before use in animals?
   Yes ◯ No ◯ *(If yes please elaborate on the method of purification to be used)*

8. Other comments *(provide information you feel would be helpful in determining the risk level of the biological to the recipient animals)*:

9. If the product has been PCR or MAP/RAP/HAP tested previously, include results with the application.

I certify that the biological will be used in accordance with all restrictions and precautions as specified in NIH Policy 3043-1.	Requester's Name ▶	Signature	Date Signed
	IC Animal Program Director's Name	Signature	Date Signed
	Facility Veterinarian's Name	Signature	Date Signed

NIH 2369-3 (Rev. 5/09)

Appendix 6 Form NIH 2369-1 (Rev. 3/09)

Department of Health and Human Services
National Institutes of Health

Rodent Quarantine Release

Use prescribed by NIH Manual 3043-1

Permit Number	Date

Name of NIH Investigator

These rodents have been examined for evidence of the following diseases or agents. The results are indicated.

Rodents *Species, strain:*

1.Murine Viruses/Bacteria

Pos.	*Neg.*	*Titer*	
☐	☐		MHV
☐	☐		EDIM
☐	☐		GDVII
☐	☐		MPV
☐	☐		MMV
☐	☐		MNV
☐	☐		Mouse Adenovirus
☐	☐		PVM
☐	☐		Polyoma
☐	☐		Sendai
☐	☐		REO-3
☐	☐		Helicobacter
☐	☐		Mycoplasma pulmonis
☐	☐		Ectromelia
☐	☐		LCM
☐	☐		Rat coronaviruses
☐	☐		Hanta
☐	☐		MCMV
☐	☐		Rat parvovirus
☐	☐		CAR Bacillus

2. Microbiology

☐ Fecal Culture

Respiratory System:

☐ Mycoplasma ☐ *Positive* ☐ *Negative*

☐ Bacteria

☐ Ear, middle

☐

3. Parasitology

Pos.	*Neg.*	
☐	☐	Endoparasites (pinworms)
☐	☐	Ectoparasites (fur mites)

4. ☐ Pathology, Gross

5. ☐ Pathology, Histology

6. ☐

Comments

Status of Rodents or Rodent Tissues

☐ A. These rodents or rodent tissues are released from quarantine. They may be used at NIH without further restriction. However, if unexpected illness or death occurs in these animals or animals with which they are associated, it is recommended that you contact your IC veterinarian and the DVR Rodent Import Officer.

☐ B. These rodents or rodent tissues were found to be infected with the agents cited above. The following restrictions apply to their holding at NIH.

☐ C. Due to evidence of infection noted above, these rodents or rodent tissues cannot be held or used at NIH in accordance with NIH Manual 3043-1.

Signature of DVR or IC Rodent Import Officer or designee	Date Signed