



April 8, 2020

Animal and  
Plant Health  
Inspection  
Service

(b) (6), (b) (7)(C)

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(b) (6), (b) (7)(C)

Oregon Health & Science University (OHSU)

Animal Care  
4700 River  
Rd  
Riverdale,  
MD 20737

Dear (b) (6), (b) (7)(C):

I reviewed your request from February 20, 2020, for another exception to the regulatory requirement under 9 C.F.R. § 2.31(d)(1)(x) that limits an animal to one major operative procedure. Your previous exception expires June 11, 2020. In your request you indicate female nonhuman primates in the Time Mated Breeding colony under protocol # IP00000580 will be used on different studies that require a major operative procedure, with no animal undergoing more than four survival major operative procedures. You provided additional information about the study on February 27, 2020.

Your exception is **approved** from **June 11, 2020 to June 17, 2022**, provided OHSU ensures:

1. The work is performed in accordance with protocol # IP00000580.
2. No more than 160 nonhuman primates are used for research under this exception.
3. No more than 4-research related survival major operative procedures are performed per animal per lifetime.
4. No animal undergoes a major operative procedure under this exception after June 17, 2022 without written approval from this office.
5. Animals are appropriately identified to facilitate monitoring.
6. Adequate recordkeeping is maintained regarding the number of surgeries performed.
7. The IACUC evaluates animal well-being along with the effectiveness and soundness of methods and procedures, a minimum of every six months during the approval period.

Any failure to abide by the above provisions will result in the automatic withdraw of APHIS' approval of this exception. This approval is in accordance with 9 C.F.R. § 2.31(d)(1)(x)(C). If there are any questions, please contact your inspector, the Fort Collins office at (970) 494-7478, or send inquiries to [animalcare@usda.gov](mailto:animalcare@usda.gov). Thank you.

Sincerely,

(b) (6), (b) (7)(C)

Betty Goldentyer, DVM  
Deputy Administrator  
USDA, APHIS, Animal Care



Research & Innovation Office

February 20, 2020

Dr. Robert Gibbens  
USDA/APHIS/AC  
2150 Centre Ave  
Building B, Mailstop 3W11  
Fort Collins, CO 80526-81117

(b) (6), (b) (7)(C)

(b) (6), (b) (7)(C)

(b) (6), (b) (7)(C)hsu.edu  
www.ohsu.edu/research

Mail code: (b) (6), (b) (7)(C)  
3181 S.W. Sam Jackson Park  
Rd.  
Portland, OR 97239-3098

Dear Dr. Gibbens:

Oregon Health & Science University (OHSU) would like to request renewal of our existing exemption for multiple major survival surgical procedures in our Rhesus macaque Time Mated Breeding (TMB) colony (IACUC protocol #IP00000580 "Operation of Time Mated Breeding Colony"). Our current exemption is for a period of three years beginning June 2017 through May 2020, and we are requesting to renew this exemption for an additional three years. We request approval to perform up to four major survival surgical procedures on individual animals. We estimate 160 female macaques will be assigned to the TMB colony protocol over the three-year period. The OHSU West Campus IACUC has approved the request for this exemption.

Animals are selected for the TMB colony based upon normal menstrual cycles, pregnancy history, and ability to adapt to awake blood sampling and/or jacket and tether systems. This selection process involves screening multiple animals in order to identify those that will successfully adapt to the needs of the program. Because Rhesus macaques are a limited resource, especially those of breeding age, we request approval to perform up to four major survival surgical procedures per animal to support a variety of research protocols. The ability to reuse TMB females in multiple research protocols will decrease the number of animals enrolled in the TMB program, which in turn will decrease the number of animals removed from the overall breeding colony. This exemption will also decrease stress on colony females, as fewer will undergo screening for the TMB program. Additionally, the ability to have TMB females utilized in multiple protocols will eliminate the need to screen additional animals and adapt them for awake blood sampling, thereby avoiding delays in the various research protocols supported by the TMB colony.

A unique number identifies each animal, and their participation in research protocols at the ONPRC is tracked. All animals entering the TMB colony undergo a full physical exam by a clinical veterinarian and continue to receive one or two exams per year while enrolled in the program. Records of all surgical procedures performed on animals at the ONPRC are maintained in an electronic health record system (PRIME). Additionally, veterinary approval is required prior to assignment to any study. During this veterinary approval process, the surgical history of the animal is reviewed to prevent animals from undergoing more than the number of procedures approved by the IACUC. All surgical procedures

associated with the TMB program are performed at the Oregon National Primate Research Center (ONPRC) by trained personnel under direct supervision of the veterinary staff in the Surgical Services Unit in the Division of Comparative Medicine. Rhesus macaques undergoing major surgical procedures are provided pre-, intra-, and post-operative multi-modal analgesics that includes opioids and local anesthetics. Other analgesics, such as nonsteroidal anti-inflammatory medications, may be prescribed as appropriate.

Pregnant females from this colony contribute significantly to the research mission at the ONPRC. The TMB colony provides principal investigators with pregnant females of known gestation by tracking menstrual cycles, serum hormones and specific timed mating to produce fetuses of known gestational age. We regularly collect blood samples to measure estrogen and progesterone levels, and create in collaboration with the Division of Reproductive & Developmental Sciences a hormonal profile for each animal. Knowing this hormonal profile increases pregnancy success, thus reducing the overall number of animals necessary for studies.

Research protocols that utilize TMB animals include studies in non-invasive imaging of fetal development, impacts of substance abuse on fetal development and placental function, premature lung development, cerebral palsy, Zika virus infection and, most recently, development of genetically modified NHP models. The major surgical procedures that TMB females will undergo are based on the specific IACUC-approved study to which they are assigned and may include cesarean section, hysterotomy for placental access, intra-amniotic catheter implantation, fetal catheter implantation, and embryo transfer. Under the current TMB exemption, approximately 40 females from the TMB colony have undergone multiple major survival surgeries. Once an animal is withdrawn from a research study, she is typically given a rest period of 4-10 months before being re-assigned to a new study. Complications for animals in the TMB colony are rare; if any are noted, the animals are withdrawn from the TMB program after consultation and evaluation by veterinary staff.

For these reasons, we request a renewal of our current exemption under 2.31(d)(1)(x)(c) allowing multiple major operative procedures on individual animals assigned to separate protocols. This exemption will allow us to continue to support critical research programs involving fetal and reproductive health while minimizing the number of Rhesus macaques used in research. OHSU complies with all requirements of the Animal Welfare Act and Regulations, and this request is consistent with the requirements of the Public Health Service and other funding agencies and accrediting bodies. Thank you for your consideration of this request.

Sincerely,

(b) (6), (b) (7)(C)

Oregon Health and Science University

**From:** [Clarke, Carol L - APHIS](#)  
**To:** (b) (6), (b) (7)(C)  
**Subject:** RE: Question from the USDA  
**Date:** Friday, February 28, 2020 7:47:00 AM

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Thank you so much!

Carol Clarke, DVM, DACLAM  
Research Program Manager  
USDA/APHIS-Animal Care  
4700 River Rd Unit 84  
Riverdale, MD 20737  
(O) 301 851 3724

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**From:** (b) (6), (b) (7)(C) @ohsu.edu]  
**Sent:** Thursday, February 27, 2020 5:14 PM  
**To:** Clarke, Carol L - APHIS <carol.l.clarke@usda.gov>  
**Subject:** RE: Question from the USDA

Dear Dr. Clarke,

Thank you for your email. Please see below for responses to your questions:

1. Approval date 6/18/2019; expiration date 6/17/2022
2. Following the 4th major operative procedure, the animal is either released from the time-mated breeding (TMB) protocol into the colony or identified for a study requiring a non-survival/terminal caesarean section (i.e. Zika virus infection) where the animal is not recovered from the C-section and is delivered directly to pathology for study endpoint under a deep surgical plane of anesthesia. If released from TMB, it is flagged as "pool 204 surgically restricted" in our Electronic Health Record and would not be assigned to a protocol where it would undergo any further major survival surgeries.

Please let me know if you have any further questions.

Best,

(b) (6), (b) (7)(C)

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**From:** Clarke, Carol L - APHIS <[carol.l.clarke@usda.gov](mailto:carol.l.clarke@usda.gov)>  
**Sent:** Thursday, February 27, 2020 1:41 PM  
**To:** (b) (6), (b) (7)(C) @ohsu.edu>  
**Subject:** Question from the USDA

Dear (b) (6), (b) (7)(C) :

My name is Dr. Carol Clarke. I will be processing your recently submitted request to Dr. Gibbens for an exemption to the regulatory requirement under 9 C.F.R. § 2.31 (d)(1)(x).

Below are some questions to address which will help expedite processing:

1. What are the approval and expiration dates of the TMB protocol?
2. What is the disposition of an animal after the 4<sup>th</sup> major operative procedure has been performed?

I can be reached at 301 851 3724 if you have any questions. Best regards.

Carol Clarke, DVM, DACLAM  
Research Program Manager  
USDA/APHIS-Animal Care  
4700 River Rd Unit 84  
Riverdale, MD 20737  
(O) 301 851 3724

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GENERAL INFORMATION	
<p><b>Oregon Health &amp; Science University (OHSU) 92-R-0001:</b> requests an extension of the 2017-2020 exemption to the regulatory requirement limiting an animal to one major operative procedure for protocol # IP00000580.</p> <p>Original exemption for protocol # IP00000580 was approved by Bernadette Juarez from June 11, 2017 to June 11, 2020. The estimate was that 160 animals would be involved.</p> <p><b>E-mail from the VMO [Dr. Hallberg] 2/27/2020:</b></p> <ul style="list-style-type: none"> <li>Recent guidance given to research facilities was that if an exception is specifically allowed in the regulations, it doesn't need to be reported. Given this exemption is allowed under 2.31(d)(1)(x)(A), they no longer report it on the Annual Report.</li> <li>All the macaque work occurs on the West Campus – the campuses are mostly run separately. There are programs in place to monitor all procedures on the monkeys and flag numbers of procedures as well as drug sensitivities or other health concerns on each animal.</li> <li>I don't have concerns with extending this exemption as has been done before.</li> </ul>	<p><b>Requestor:</b></p> <ul style="list-style-type: none"> <li>(b) (6), (b) (7)(C)</li> </ul> <p><b>Primary Point of Contact</b></p> <ul style="list-style-type: none"> <li>(b) (6), (b) (7)(C)</li> </ul> <p>Oregon Health &amp; Science University  (b) (6), (b) (7)(C)  (b) (6), (b) (7)(C)@ohsu.edu</p>
DETAILS	
Current study	Other Studies
<p><b>IP00000580-Operation of Time Mated Breeding Colony</b>  Approval date 6/18/2019; Expiration date 6/17/2022</p> <p>Animals will undergo up to 4 major operative procedures distributed amongst protocols. Animals have unique IDs and will be monitored for the number of surgeries it undergoes.</p> <p>There is a 4-10 wk. break before an animal is assigned to a new study.</p> <p>Following the 4th major operative procedure, the animal is either released from the time-mated breeding (TMB) protocol into the colony or identified for a study requiring a non-survival/terminal caesarean section (i.e. Zika virus infection) where the animal is not recovered from the C-section and is delivered directly to pathology for study endpoint under a deep surgical plane of anesthesia. If released from TMB, it is flagged as "pool 204 surgically restricted" in our Electronic Health Record and would not be assigned to a protocol where it would undergo any further major survival surgeries.</p>	<p>Approximately 40 animals have already undergone more than one major operative procedure under this exemption</p> <p>Veterinary approval is required before animals goes on the other study. Medical records are kept in their electronic database (PRIME). The number of surgeries are also kept in this database.</p>

**From:** [Hallberg, Gwynn M - APHIS](#)  
**To:** [Clarke, Carol L - APHIS](#)  
**Cc:** [McKinnie, Carolyn - APHIS](#)  
**Subject:** Re: OHSU  
**Date:** Thursday, February 27, 2020 12:19:29 PM

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Hi Carol:

Thanks for contacting me about this. That study was not the one cited for not being reported.

Recent guidance given to research facilities was that if an exception is specifically allowed in the regs, it doesn't need to be reported. Given this exemption is allowed under 2.31(d)(1)(x) (A), they no longer report it.

The protocol cited for not being reported was allowing surgery on non-rodent species in a non-dedicated surgical area (audiology study in ferrets and marmosets.) The cited study occurs on the Central and Waterfront campus.

All the macaque work occurs on the West Campus – the campuses are mostly run separately. There are programs in place to monitor all procedures on the monkeys and flag numbers of procedures as well as drug sensitivities or other health concerns on each animal.

I don't have concerns with extending this exemption as has been done before.

Gwynn Hallberg VMO  
USDA APHIS Animal Care  
240-461-9069

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**From:** Clarke, Carol L - APHIS <carol.l.clarke@usda.gov>  
**Sent:** Thursday, February 27, 2020 10:34:25 AM  
**To:** Hallberg, Gwynn M - APHIS <gwynn.m.hallberg@usda.gov>  
**Subject:** Re: OHSU

Hi! OHSU just submitted a request to extend the exemption to perform multiple major operative procedures on NHPs under # IP00000580 -TMB program for another 3-yrs. Enclosed is what we approved in 2017.

I am writing to get your opinion on (b) (5)

(b) (5)

(b) (5)

Looking forward to your thoughts. I realize you have many other concerns therefore a response by **March 6<sup>th</sup>** will be greatly appreciated.

P.S.

If there is anyone else that should be providing input, please forward. Best regards.

Carol Clarke, DVM, DACLAM  
Research Program Manager  
301 851 3724



Animal and Plant  
Health Inspection  
Service

Animal Care  
700 River Road  
Riverdale, MD 20737

March 15, 2017

(b) (6), (b) (7)(C)

Oregon Health & Science University (OHSU)

Dear (b) (6), (b) (7)(C)

I apologize for the delay in responding to your letter dated January 11, 2017, seeking an exemption allowing macaques to undergo four major operative procedures during their lifetime under protocols involving time mated breeding for research purposes. The Animal and Plant Health Inspection Service (APHIS) hereby approves your exemption, from June 11, 2017 through June 11, 2020, provided OHSU ensures:

1. All work is performed in accordance with protocol # IP00000580, and the letter dated January 11, 2017, seeking an exemption request.
2. No more than 160 macaques per year are used for research under this exemption.
3. No more than 4 research-related survival surgical procedures per animal per lifetime.
4. No macaque undergoes a major operative procedure under this exemption after June 11, 2020, without additional written approval from APHIS.
5. No macaque used under this exemption undergoes any other major operative procedure for research without written IACUC and APHIS approval.
6. Macaques are appropriately identified to facilitate monitoring.
7. Adequate recordkeeping is maintained involving the number of surgeries performed on each macaque used under this exemption.
8. The IACUC evaluates animal well-being along with the effectiveness and soundness of the methods and procedures not less than annually during the approval period.

Any failure to abide by the above provisions will result in the automatic withdraw of APHIS' approval of this exemption. This approval is in accordance with 9 C.F.R. § 2.31(d)(1)(x)(C), and must be reflected in OHSU's Annual Report each year as required under 9 C.F.R. § 2.36(b)(3). If you have any questions, please contact the Animal Care's office in Fort Collins, Colorado, at (970) 494-7478.

Sincerely,

(b) (6), (b) (7)(C)

Bernadette Juárez  
Deputy Administrator of APHIS-Animal Care

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