P B A C

presidential biosafety advisory committee

# IMPLEMENTATION DIRECTIVE

## IN VIVO DOWNGRADE CRITERIA

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## INTRODUCTION

*In vivo* models of infectious disease or gene transfer vectors have become a staple of current preclinical research methodologies. With respect to gene transfer vectors, safety features have been engineered into these constructs which confer defects in replication and tropism or include division of the minimally required genome into separate plasmids. Although these features do mitigate some risk with respect to infection and replication, oncogenic transformation is still possible depending on the genes being transferred. Recombination with wildtype vectors in those workers with pre-existing/latent infection is another risk that is still possible.

*In vivo* work with such pathogens poses safety risks which are primarily mitigated by using animal containment practices suitable for working with the wildtype pathogen itself. Increasing use of physiological testing equipment, imaging equipment and other instruments require the transport and use of animals in lower containment areas. In most cases, retro-fitting equipment or construction of custom HEPA filtered enclosures is cost-prohibitive.

Downgrade of *in vivo* work implies the following:

- The downgrade implies from BSL2 or BSL3 to BSL1/conventional/SPF.
- The downgrade implies data is provided to support lack of pathogen recovery from the animal at specific time-points post-exposure.
- The animal cages must be clearly marked per CAF SOP GEN1016.
- The animals remain housed in and returned to BSL2 unless other space has been approved and allocated by CAF administration per CAF SOPs.
- The animals may be transported at BSL1 per CAF SOPs.
- The animals may be removed from their cages and subjected to physical manipulations and physiological or behavioural measurements at BSL1 according to recovery data.
- Blood collection, sampling, surgery or sacrifice of the animals will depend on recovery data from tissues and body fluids. If no data exists, these procedures must be carried out at the original containment level.

## DOWNGRADE CRITERIA FOR PHYSICAL MANIPULATION AND PHYSIOLOGICAL OR BEHAVIOURAL MEASUREMENTS

The researcher must demonstrate an absence of viable pathogen in the following samples:

- Urine
- Feces
- Saliva (buccal swab)
- Nasal swab
- Any additional sample requested by the PBAC or the University Veterinarian

In order to demonstrate absence of viable pathogen, culturing dilutions of the above samples in an attempt to **amplify the pathogen** would be the most functional assay. **Detection of genomic or transgene sequences**, with both positive and negative controls should show a negative result to imply absence of pathogen, however positive results do not imply that the pathogen is viable although present.

## DOWNGRADE CRITERIA FOR BLOOD COLLECTION, SAMPLING, SURGERY AND SACRIFICE

The researcher must demonstrate an absence of viable pathogen in the **additional** following samples:

- Blood/serum
- Target tissue
- Any additional sample requested by the PBAC or the University Veterinarian

In order to demonstrate absence of viable pathogen, culturing dilutions of the above samples in an attempt to **amplify the pathogen** would be the most functional assay. **Detection of genomic or transgene sequences**, with both positive and negative controls should show a negative result to imply absence of pathogen, however positive results do not imply that the vector is pathogen.

## SUBMISSION OF SUPPORTING DOCUMENTATION

A researcher may submit their own data, an article or collection of articles to support *in vivo* downgrade. The documentation should be submitted to the McMaster Biosafety Office before the second to last Monday of the month. The documents will be distributed to the PBAC for discussion on the next Monday. At that time, an *ad hoc* subcommittee will be formed, including the University Veterinarian to review the submitted documents. The subcommittee will present their recommendations at the following PBAC meeting where a decision will be made.

If successful, the new criteria set will be added to the section entitled "Currently Acceptable Sets of Downgrade Criteria" and all supporting documentation shall be retained by the Biosafety Office. Notice will also be sent to the researcher, the Chair of AREB and the University Veterinarian to initiate amendment of the AUP to include the new criteria set required for downgrade.

If unsuccessful, the subcommittee will recommend changes to the parameters or additional verification requirements which will further support the literature presented.

If still unsuccessful, the committee will notify Chair of AREB and the University Veterinarian that the downgrade cannot be accomplished.

The minimum timeline is one month and one week from the time of submission to be notified of the results of the review.

## USE OF CAF SOPS

Once a downgrade has been reviewed and approved by the PBAC, its conditions will be amended to this PID. The researcher must describe their experimental protocols to include the following parameters in their AUP and those parameters must match one of the currently approved criteria to be eligible for downgrade. These parameters must include:

- Species and strain
- Route
- Vector or pathogen species

- Vector backbone if applicable
- Dose (can be less in the proposed project)
- Time point (can be more in the proposed project)

If the proposed experiment does not match the animal or pathogen strain, genotype or background, the downgrade must be reviewed on a case by case basis. In this case, the downgrade data should be submitted to the PBAC for assessment.

## Appeals Process

If a researcher has objection to any decision reached by the PBAC, they may option to invoke the Appeals Process as described in RMM#600.

http://www.workingatmcmaster.ca/med/document/RMM-600-Biosafety-Program-1-36.pdf

## Mechanism to Monitor PID Effectiveness

- User feedback directly related to the PID
- # of researchers referencing the SOP in their AUP
- Audit results

## CURRENTLY ACCEPTABLE SETS OF DOWNGRADE CRITERIA

1. Adenovirus, Mouse/Rat
    - Experimental protocol and results found in committee documentation pbac_doc005 (March 2013)
    - Adenovirus, serotype 5, E1 or E3 deleted
    - 5x10^8 pfu intranasally for mice
    - 5x10^8 pfu intratracheally for rats
    - For physical manipulation, physiological or behavioural procedures including transport, the animals may be at Level 1 containment at 3 days post inoculation.
    - For blood collection, surgery and sacrifice the animals must remain at level 2 containment since there is no target tissue data other than 3 days post inoculation, which was positive.
    - It is recommended that cages be changed 72 hours post inoculation and those cages be treated as Level 2 waste.