June 12, 2024

Information on how to Complete the Health Canada "Application Form for an Exemption to Use a Controlled Substance for Scientific Purposes"

All researchers who need to use controlled substances in research animals must apply to Health Canada for an Exemption. The Exemption allows the individual to purchase and possess the specified quantity of the controlled substance listed on the Exemption as to administer the controlled substance to animals for the purpose of research.

The application form, and other important information, can be found here: https://www.canada.ca/en/health-canada/services/health-concerns/controlled-substances-precursor-chemicals/exemptions/application-form-exemption-use-controlled-substance-scientific-purposes.html

The Animal Care Protocol must be approved by the Animal Care Committee prior to application for an exemption.

The application form has different sections and each section must be completed.

1. Application type

There are 6 categories of application types:

New: this applies to all researchers who have never applied for an exemption previously from Health Canada.

Extension (no additional quantities): This is for researchers who have an approved exemption with enough drug in stock and have no other changes to their application (i.e. Animal Care Protocol certificate still current, supplier still current, etc.). Exemptions are only valid for 1 year and then need to be renewed annually.

Extension (additional quantities): This is for researchers who have an approved exemption and require additional quantities of the drugs listed and have no other changes to their application (i.e. Animal Care Protocol certificate still current, supplier still current, etc). Exemptions are only valid for 1 year and then need to be renewed annually.

Amendment of a valid exemption: This is what you would choose if you have to make any changes to the exemption while the exemption is still valid. This can be done at any time during the one year exemption but not after the exemption has expired. For example, adding or changing an Animal Care Protocol, changing the number of animals, adding additional drugs not previously on the exemption, changing supplier, etc.

Cancellation of a valid exemption: This is what you would choose if you no longer need the exemption. All drugs that still remain must be properly disposed of as stipulated in the Exemption documentation.

Transfer of controlled substances from one researcher to another within an institution: This is for researchers who will be taking over the project and will now be named on the exemption. Examples of this are if the Principal Investigator retires and

another PI is taking over the Animal Care Protocol and project. This can also be used if one researcher no longer needs the drugs and another researcher is willing to take on the responsibility for them.

2. Identification

This must be the Principal Investigator listed on the Animal Care Protocol. Complete all sections of this section.
The person applying for the exemption must have a minimum of a B.Sc. In an appropriate field of research.
2.3 Address where the substance will be used: This will be the location where the drugs will be administered. A room number is not critical if it is unknown or may change.
2.4 Mailing address: If this is different from the address above, provide this information. This must match the address that will be used to receive the controlled substances. If the room number may change, then this can be left off the application and only stipulated when ordering from the supplier.
2.5 Storage address: This may be the same as either above or a separate area where the drugs will be stored between uses.

3. Project or Study Description

Project title: The title provided here must match the title of the approved Animal Care Protocol.
You may list multiple Animal Care Protocols per application but ensure that the titles of each Animal Care Protocol matches what is placed on the application. In addition, all controlled drugs listed on the protocol(s) for all the species listed on the protocol(s) can be requested on one exemption application.
Required documents: attach a copy of the approved Animal Care Protocol(s) and the Animal Care Protocol certificates (which can be found on RISE. Go to the Animal Care tab, click your protocol, click the correspondence tab and look for “Approved” which will have a link to the Approval Letter).
Please Provide any further information: This section can be used to describe what amendments (if any) are being made to the application and why.
Brief description of the use of the substance: Provide one or two sentences of how these drugs will be used. For example: “Anesthetics, Analgesics and Euthanasia drugs for use in mice and rats.”
Reason for Requiring and extension, cancellation of transfer of responsibility: This is the section that you would complete if you wish to extend or cancel your exemption. The description can be that the project is continuing for another year so the exemption needs to be extended for another year, the original PI is retiring, the project is over, etc.

4. In Vivo administration

If using the controlled drugs in living animals, click the “In vivo administration” check box, otherwise click the “In vitro utilization” check box

If any of the drugs will be given to the animals by a licenced veterinarian only and for professional treatment for a condition that the animals are being treated for, then those drugs can be listed and do not require an exemption. The vast majority of controlled drugs, however, if administered by research staff or facility staff, must have an exemption.

Animal species: List each species separately. Additional pages can be added if more than one species is listed on the Animal Care Protocol(s) and is getting controlled substances.
Number of animals (to be used under this exemption): This is the number of animals that will get the controlled substances over a year (the approval period of the exemption). This must match the numbers in the approved Animal Care Protocol(s). If only some of the animals receive the controlled substances on the Animal Care Protocol(s), that is fine but you cannot list more than what is approved on the Animal Care Protocol(s).
Average Weight per animal: If in doubt, give the highest weight possible for the animals that will be used. You will be approved for a set amount of controlled substance based on this application. Losses can occur through expiry of diluted controlled substances (30 days from dilution), loss of volume in needle hubs (approximately 0.07 ml), unexpected requirement for redosing (animal is in pain for longer than expected or animal needs a top up of anesthetic drugs) so estimate higher rather than lower weights for the animals to ensure you have enough drug for unexpected situations.
Animal carcasses will be disposed of by: Check with your facility manager on how the carcasses will be disposed of. Most frequently it is by incineration but some facilities have access to other means such as Alkaline hydrolysis.

4.1. Controlled substances
Name of controlled substance: You do not need to list a specific brand name (i.e. Temgesic) unless you specifically want a certain brand. Some suppliers have the same drug under different brand names but the same concentration. If one is unavailable, the other can be substituted unless you listed a specific brand name.
Initial dose: This would be the first dose in mg/kg followed by total mg based on the weight provided that the animals would receive. If you have given a range in the Animal Care Protocol, provide the highest end of the range here.
Maintenance dose: This is for any additional doses the animals would receive in mg/kg. For example, the animal may get 0.05 mg/kg buprenorphine as its initial dose but then get 0.05 mg/kg afterwards. Again, if you provided a range in the Animal Care Protocol, provide the highest end of the range here. If the animal gets only one dose, you leave this blank.
Frequency of Maintenance dose: This is the number of doses the animal would receive (i.e. three times a day for 3 days).
Total dose per animal: This is the total of all doses each animal would receive in mg (based on weight, initial dose, maintenance dose, and frequency of dosing).

If you have more than 2 controlled substances listed on the protocol, you can add additional copies of this page for this section.

5. Supplier of the Controlled Substance:

For each controlled substance, provide the supplier you will purchase from. This may be the same supplier for all controlled substances or different suppliers if needed. If the supplier is foreign (i.e. not in Canada), the Office of Controlled substances may help you import but you must have a purchase order and Purolator account number. This is not necessary if the drugs are available from a Canadian supplier.

Brand Name: You do not need to list a Brand name unless you want a certain brand but if that brand is not available from the supplier, you will not be able to purchase a different brand.

Concentration: It is important to know what concentrations and volumes are available from the supplier before submitting the Exemption application since this is important for the amounts that will be approved for purchase on the Exemption.

Quantity required for all submitted protocols: This is the total quantity (in mg and ml) you have calculated for total number of animals (for all listed Animal Care Protocols), doses, and for all species listed on the exemption.

Quantity in inventory: This is for applications in which you already have remaining volumes of the drug from a previous exemption. Provide all remaining volumes here (if applicable).

Quantity to be purchased: This is the total volume you will be purchasing in one year based on the volumes of the bottles available at the supplier. The quantity to be purchased should be quantity required for all submitted protocols minus any remaining volume from the previous year if applicable).

****See end of document for an example of how to work out the amounts needed.**

For more than 2 controlled drugs, you can attach additional copies of this page in this section.

You will be approved for the smallest volume bottle you have justified on the Exemption (i.e: if you have listed that you need a total of 9 ml of ketamine, you will be approved to purchase the 10 ml bottle and not the 50 ml bottle. If you have listed 19 ml, you will be approved to purchase two 10 ml bottles and not one 50 ml bottle).

For drugs such as Midazolam, Diazepam, Sodium Pentobarbital for euthanasia, Ketamine, Buprenorphine, the supplier can be:

CDMV
3400 Cartier Street
Saint-Hyacinthe, QC J2S 1L5
Telephone: 800-668-2368
Fax: 800-363-3134

THE UNIVERSITY OF BRITISH COLUMBIA
Animal Care Services
VP Research & Innovation

June 12, 2024

Contact: Hassan Malekeddine
Email: hassan.malekeddine@cdmv.com

CDMV has the following:

Drug name	Brand name	Concentration	Bottle size
Ketamine			
	Narketan Injectable	100 mg/ml	10 ml
	Narketan Injectable	100 mg/ml	50 ml
Sodium Pentobarbital			
	Euthanyl Regular	240 mg/ml	250 ml
	Euthanyl Forte	540 mg/ml	250 ml **not recommended for small animals. It is very thick and hard to inject.
Buprenorphine			
	Vetergesic Injectable	0.3 mg/ml	10 ml
Midazolam			
	Midazolam Injectable	1 mg/ml	2 ml
	Midazolam Injectable	1 mg/ml	10
	Midazolam Injectable	5 mg/ml	1 ml
	Midazolam Injectable	5 mg/ml	2 ml
	Midazolam Injectable	5 mg/ml	10 ml

There are other controlled substances available if listed on the approved Exemption. For any questions, please contact CDMV at:

1-800-668-2368
or email: controlled.substances@cdmv.com

For any other questions regarding exemptions or ordering, please contact your facility's clinical veterinarian.

6. Physical security

You will need to describe where the drugs will be secured so that unauthorized people do not have access. The following document has information of the physical security required based on the volumes present: https://www.hc-sc.gc.ca/hc-ps/alt_formats/hecs-sesc/pdf/pubs/precurs/dealers-distrib/phys_securit_directive/psreqs-eng.pdf

In general, the following requirements must be met for drug volumes less than $2500 street value (equivalent to: 500 ml of Ketamine (100 mg/ml), 500 ml of Sodium Pentobarbital (240 mg/ml) or 45 mls of Buprenorphine (0.3 mg/ml)):
Drugs can be stored in a cupboard, refrigerator, drawer in a steel cabinet or equivalent provided that:

-It prevents visualization of the controlled substance

-It is fastened to the room's floor or wall and cannot be removed or is of sufficient weight that it cannot be manually removed

-it must be double locked – pad lock, keyed lock, or combination lock (i.e.: in a locked cupboard within a locked room)

-it is located in a locked room that the public does not have access to (i.e.: not the staff lunch room)

7. **Declaration:** The Principal Investigator listed on the Animal Care Protocol must complete and sign this section

Record Keeping: The requirement for recording all doses of the controlled substances is stringent and these requirements will be stipulated in the documentation that accompanies the approved Exemption.
The following is required:

- Date purchased, the name and address of supplier, volume and concentration of the drug
- For each dosage administered
  -date used
  -Volume used (or removed from bottle)
  -volume remaining
  -Protocol #
  -species
  -animal ID or number of animals if rodents
  -Signature of person removing volume
- The record must be completed in pen and ["] marks are not acceptable. Authorities must be able to trace each dose back to a specific animal.
- If the drug is mixed or diluted the amount taken from the vial must be recorded and separate record sheet prepared for the dilution or mixture.
- The book containing the records must not have easily removable pages (i.e. a binder with removable pages will not be acceptable)

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Destruction of Controlled Substances:

For controlled drugs that have expired (including all diluted preparations), the drugs must be destroyed as they cannot be returned to the vendor. The disposal of controlled substances is governed by law and falls within the jurisdiction of the Compliance Division of Health Canada. The procedure for destruction of controlled drugs as per Health Canada is provided with the documentation accompanying the approved exemption and is outlined below.

- You are responsible for the destruction of any unused or expired narcotic.
- The destruction must be witnessed by a member of your research staff who is working on the same research project as specified in this exemption, and who works under your direction and control.
- The method of destruction used must alter or denature the narcotic in such a way as to make it non-recoverable and thus make their consumption improbable or impossible.
    - Do not flushing it down the sink since it can contaminate waterways and pose a risk for aquatic species
    - To denature the drug, create a slurry of the drug with soap and water and add to enough “Kitty Litter” so that it absorbs all liquid fully.
- You are required to keep and retain for a period of two years from the date of the making of the record, the following information:
    - The name, concentration, and quantity of the controlled substance to be destroyed
    - The date of destruction
    - The reason for destruction (i.e. contaminated, expired, etc.).
- Immediately following the destruction, you and the witness are required to sign and print your names on a joint statement indicating that you witnessed the destruction. and that the narcotic destroyed has been altered or denatured to such an extent that its consumption has been rendered impossible or improbable.
- Follow your facility’s directions for how to dispose of the denatured drug.
    - For UBC:
        - You MUST provide UBC’s Environmental Services Facility (ESF) with a copy of the Destruction Record (witnessed statement).
        - Place the destructed controlled drugs in a proper leak-proof container. Pharmaceutical waste containers (5-gallon white pails) are available from ESF
        - Add a Biological Waste Disposal Tag (Red) shown below.
        - Affix your waste generator barcode sticker on the container.
        - Check the “Controlled drugs (destructed)” box and place in your waste area for pickup. This waste will be shipped out by ESF as pharmaceutical waste.

    ESF: https://riskmanagement.sites.olt.ubc.ca/files/2020/02/Pharma-Controlled-Drugs-Disposal.pdf

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Example of calculations for determining quantity of drugs needed.

Two Animal Care Protocols will be listed on this exemption and they each have both mice and rats listed.
Weight of mice: 35 gm (0.035 kg)
Weight of rats: 450 gm (0.45 kg)
Number of mice: 140 total across both protocols
Number of rats: 25 total across both protocols
These animals will have buprenorphine (concentration 0.3 mg/ml) administered at the time of surgery as well as twice the day of surgery after recovery from anesthetic and three times a day for the following 2 days.
Initial dose for mice: 0.1 mg/kg
Initial dose for rats: 0.05 mg/kg
Maintenance dose for mice: 0.05 mg/kg for a total of 8 doses
Maintenance dose for rats: 0.02 mg/kg for a total of 8 doses.

→each mouse will receive a total of:
Initial dose: 0.035 kg x 0.1 mg/kg = 0.0035 mg
Maintenance dose: 0.035 kg x 0.05 mg/kg = 0.002 mg for each dose and the mouse would get 8 total doses for maintenance for a total of 0.016 mg.

→**Therefore, the total dose per mouse would be:**

Initial dose 0.0035 mg + 0.016 mg = 0.0195 mg

→Each rat would receive a total of:
Initial dose: 0.45 kg x 0.05 mg/kg = 0.0225 mg
Maintenance dose: 0.45 kg x 0.02 mg/kg = 0.009 mg for each dose and the rat would get 8 total doses for maintenance for a total of 0.072 mg.

→**Therefore, the total dose per rat would be:**

Initial dose 0.0225 mg + 0.072 mg = 0.0975 mg

Quantity required for all submitted protocols:
Total dose per mouse X number of mice

0.0195 mg x 140 mice = 2.73 mg or
divided by concentration of drug (0.3 mg/ml) = 9.1 mls

Total dose per rat x number of rats

0.0975 x 25 rats = 2.44 mg
divided by concentration of drug (0.3 mg/ml) = 8.1 mls

Total for both mice and rats = 5.17 mg or 17.2 ml

Quantity to be purchased: There is no remaining stock from a previous year and the supplier has buprenorphine in 10 ml vials so I will put 2 x 10 ml (20 ml total) for quantity to be purchased.