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Use of Non-Pharmaceutical Grade Compounds (Non-PGCs) and Discovery Compounds in Research Animals

Background

With the release of the NHMRC “*Best practice methodology in the use of animals for scientific purposes (2017)*” and ensuring the ANU is at the forefront of advancing animal welfare, the University’s Animal Experimentation Ethics Committee has reviewed the use of Non-Pharmaceutical Grade Compounds (Non-PGCs) in animal research. The review included consultation with a number of ANU research scientists currently using Non-PGCs.

Non-PGCs include two main subgroups of compounds including the use of some anaesthetics or euthanasia agents (e.g. avertin, urethane, clove oil) or the use of drugs that are currently under development and not yet available as medical grade. The cases for using Non-PGCs differs for these two subgroups and as such two separate policies have been developed.

The use of agents such as avertin, urethane and clove oil will, in many cases have suitable alternatives available. The proposed ANU policy for these substances is covered under the draft document “*Use of Non-Pharmaceutical Grade Compounds for Anaesthetising and Euthanasing Animals.*”

The use of drugs under development that are not yet available as Pharmaceutical Grade has been covered under the document “*Use of Discovery Compounds – Non Pharmaceutical Grade in Animals.*”

The use of Non-PGCs has been reviewed due to the increased risks of unwanted side effects when using these compounds. In many cases (such as avertin and urethane) the compounds have been found to cause cumulative organ damage, be less easily controlled during use, may have unexpected adverse effects and need to be compounded locally which increases the risk of dose miscalculations, contamination or degradation during storage.

Many researchers have used these compounds for a number of years without adverse events. However, this does not in itself justify the continued use of these compounds in the light of the NHMRC guidance. In many cases more modern and titratable compounds are available that have undergone specific testing for use in medical circumstances. This may include the use of inhalational anaesthetics, alternative injectable compounds or other methods.

International Status

Internationally the use of Non-PGCs (with the exception of discovery compounds) has actively been phased out by a number of institutions over recent years. The international perspective is important in ensuring the ANU remains compliant with the National Institute of Health (NIH) accreditation requirements. Without NIH accreditation, overseas funding opportunities and research collaborations available to the ANU could be negatively impacted.

The United States Department of Agriculture states:

“Non-pharmaceutical-grade substances should only be used in regulated animals after specific review and approval by the IACUC. The IACUC should develop a consistent evaluation process which includes but is not limited to the scientific justification and the availability of an acceptable veterinary or human pharmaceutical-grade product. Cost savings alone is not sufficient justification for using a non-pharmaceutical-grade substance in regulated species”

The National Institute of Health states:

“When compounds are used for the clinical treatment of animals or to prevent or reduce/eliminate animal pain or distress, PGCs must be used whenever possible. When compounds are used to accomplish the scientific aims of the study PGCs are preferred if available and suitable. The use of Non-PGCs in laboratory animals must be described and justified in the Animal Study Proposal and/or covered by an Institute/Centre Animal Care and Use Committee (ICACUC) policy developed for their use and approved by the ICACUC...”

“Where the use of Non-PGCs may be essential for the conduct of science, the goal of the IC ACUC should be to consider the health and well-being of the animals while aiding the researcher in minimizing potentially confounding experimental variables and maximizing reproducibility of the research. As stated by Office of Laboratory Animal Welfare, this Guideline suggests that the IC ACUC, in making its evaluation may consider factors including, for example grade, purity, sterility, acid-base balance, pyrogenicity, osmolality, stability, site and route of administration, compatibility of components, side effects and adverse reactions, storage, and pharmacokinetics.”

Australian Status

Section 2.4.18 of the NHMRC's *Australian Code for the care and use of animals for scientific purposes – 8th Edition* notes: *Investigators must take steps at all times to safeguard the wellbeing of animals by avoiding or minimising known or potential causes of harm, including pain and distress, to the animals. Steps include:*

- *ensuring the appropriate use of pharmacological and non-pharmacological means to minimise pain and distress (see Clauses 3.3.8–3.3.15). Use of pharmacological agents such as anaesthetics, analgesics and sedatives must be appropriate to the species, the individual animal (e.g. age, physiological status) and the scientific aims, and must be consistent with current veterinary or medical practice. Anaesthesia must be used for procedures that are likely to cause pain of a kind and degree for which anaesthesia would normally be used in veterinary or medical practice.*

The Australian National University

Given the research undertaken at ANU it is fair to make the following statements:

Given that these substances are no longer widely used, the reproducibility of experiments undertaken with non-PGCs would be compromised.

International funding bodies and welfare organisations are indicating that strong justification is required and that the routine use of these compounds is not acceptable.

The ANU Veterinarians and those representing the AEEC cannot approve the use of compounds that are not consistent with current veterinary practice without clear justification for their use

Given the above findings please see the attached proposed policy for the ANU. In summary it recommends that:

Use of Non Pharmaceutical Grade compounds must be clearly justified in the protocol and meet the requirements in line with the recommendations from the NIH.

In general, the use of Non-PGCs for anaesthesia will only be approved in terminal experiments unless the justification to do otherwise is exceptional.

For the use of avertin and urethane - Adverse Events relating to the use of NPGs must be reported at every incidence. This will allow the University to gather important information for future review of the use of these compounds.

For the use of novel compounds that are not yet available at pharmaceutical grade – the Primary Investigator must make it clear that any compound being used is not of pharmaceutical grade and demonstrate how they will provide additional monitoring and precautionary measures given the potential unknown effects on animals. An expected incidence of complication due to the fact that the compounds are discovery compounds must be included in protocols for consideration by the committee and any increase above the approved complication rate must be reported as an Unexpected Adverse Event.

Proposed Timeline

Current ANU AEEC Approved Protocols

Current protocols with approval to use non-PGCs that are anaesthetics (particularly urethane and avertin) will, working with the University Veterinarians be given 1 year to either:

- Provide justification via an amendment to the Animal Experimentation Ethics Committee (AEEC) for the ongoing use of these compounds based on a set list of questions under their current protocol.
- Request the use of alternative compounds that are of pharmaceutical grade via an amendment to the ethics committee.

To assist with any transition required the University provides free anaesthesia training through the Australian Phenomics Facility (APF) and with the assistance of the University Veterinarians. In the first instance to discuss alternative methods of anaesthesia that are suitable to your projects please contact the University Veterinarians via vetservices.rsd@anu.edu.au

Current protocols with approval to use Non-PGCs that are discovery or novel compounds and drugs will be asked to review their precautionary measures and additional monitoring to ensure it meets the expectations of the policy.

Future Protocols

As of March 2020 the Committee will place greater scrutiny on the request for use of non-PGCs in the review of all new ethics protocols.