



4. The Production of Laboratory Animal Bio- Products

Project duration

5 years 0 months

Project purpose

- Basic research
- Translational or applied research with one of the following aims:
 - Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants
 - Assessment, detection, regulation or modification of physiological conditions in man, animals or plants
- Development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs and feedstuffs or any other substances or products, with one of the following aims mentioned in paragraph (b)

Key words

Vaccinations, Virology, Blood, Plasma

Animal types	Life stages
Mice	Adult
Guinea pigs	Adult
Ferrets	Adult
Rats	Adult
Beagles	Adult

Retrospective assessment

The Secretary of State has determined that a retrospective assessment of this licence is required, and should be submitted within 6 months of the licence's revocation date.

Reason for retrospective assessment

This may include reasons from previous versions of this licence.

- Uses cats, dogs or equidae

Objectives and benefits

Description of the projects objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?



To supply animal blood products, to generate data to support the development of effective and safe medicines to treat diseases in humans and animals where there is currently a clinical unmet need.

A retrospective assessment of these aims will be due by 27 April 2029

The PPL holder will be required to disclose:

- Is there a plan for this work to continue under another licence? Did the project achieve its aims and if not, why not?

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.

Why is it important to undertake this work?

Bio-products services providing animal blood products, will support the generation of scientific data to support the development, manufacture and testing the quality of new and approved medicines within the field of Human and Animal health.

The continuation of supply would further assist in scientific insight underpinned by this project license and will lead to a greater understanding of pathogens, contributing to research publications and advances in the prevention of human and animal diseases. The scientific data generated by using blood products taken from animals will also reduce the number of potential new medicines requiring further research in living animals by establishing ethically whether conducting experiments on living animals is necessary.

What outputs do you think you will see at the end of this project?

The supply of animal blood products will contribute to the development, manufacture and testing of the quality of new and approved medicines within the field of Human and Animal health.

The continuation of supply will further support the generation of data to enable understanding and predictions of drug concentrations to determine dose levels in pre-clinical phases allowing for more treatments to progress towards clinical trials and approval by the regulatory authorities.

Who or what will benefit from these outputs, and how?

Animal blood products supplied under this Project Licence will be used to validate methods to support GLP toxicity studies, by providing data to assess the stability of potential medicines in blood. This is to ensure the integrity of blood collection in GLP studies, and the scientific validity of data produced from the blood samples. This is in line with The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) validation guidelines and to comply with the expectations of the Medicines and Healthcare products Regulatory Agency (MHRA) in performing validations to support GLP toxicity studies.



How will you look to maximise the outputs of this work?

We carefully monitor and manage production levels of animals on a month-by-month basis looking at animals produced vs sales. Ex-breeding stock and animals not utilised for use in direct research will be considered to provide a pool biological material. As these products are required to allow for the continuation in contributing to the development, manufacture and testing of the quality of new and approved medicines within the field of Human and Animal health.

We will collaborate on a supplier level and gain insight into future demand and review ethical viability along with continued forecasting updates to allow for the continued supply at a minimal level.

Species and numbers of animals expected to be used

- Mice: 50
- Guinea pigs: 50
- Ferrets: 50
- Rats: 50
- Beagles: 250

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

Explain why you are using these types of animals and your choice of life stages.

The animals used under this project licence are currently being bred to support scientific research. Only ex-breeding stock and animals not required in direct use for research purposes will be considered for use to supply blood products to the research community.

Typically, what will be done to an animal used in your project?

Under Protocol 1, ex-breeding stock and animals not required to be used for direct research purposes from species such as Mice, Rats, Guinea Pigs, Ferrets and Beagles will be reviewed and considered as potential donors. If ethically, there is a requirement to supply the research community, then in line with the protocol, animals will be placed under general anaesthesia and the required volumes of blood will be withdrawn. Once sampling has been completed, they will be humanely killed via a suitable scheduled 1 method without regaining consciousness.

Donor Beagle dogs for protocol 2 will be selected from a small group of ex-breeding stock or animals not required for direct use in research. These will be reviewed for suitability to be considered for blood sampling without anaesthesia. This group of beagle dogs will be housed at the establishment and used to supplying small quantities of fresh blood products to the research community.



What are the expected impacts and/or adverse effects for the animals during your project?

Blood sampling under general anaesthesia is a non-recovery procedure conducted with the animals under a species-specific general anaesthetic regime that has been developed in consultation with the NVS. We ensure the agent(s) and route(s) used are the ones which will cause minimal discomfort and distress to the animal during the induction of anaesthesia.

For blood sampling without anaesthesia, the techniques used have been refined with reference to:

The guidance information on the general principles of blood sampling of the NC3Rs website

The EFPIA/ECVAM good practice guide to the administration of substances and removal of blood, and Wolfensohn S and Lloyd M (2003). Handbook of Laboratory Animal Management and Welfare.

We may use local anaesthetic (LA) and reward incentive on dogs to reduce any stress. Due to the possibility of side effects e.g., dermatitis from prolonged numbing of the skin, it was felt the LA would and should only be applied to dogs that require it.

We also ensure that no more than 10% of the total blood volume (TBV) is removed in any 24-hour period and no more than 15% TBV in any 28-day period. All dogs will remain under NVS care during the duration of the project license. There are no further impacts and/or adverse effects expected during the project.

Expected severity categories and the proportion of animals in each category, per species.

What are the expected severities and the proportion of animals in each category (per animal type)?

Mice 100% general anaesthesia/non-recovery
Rats 100% general anaesthesia/non-recovery
Guinea Pigs 100% general anaesthesia/non-recovery
Ferrets 100% general anaesthesia/non-recovery
Beagles 86% general anaesthesia/non-recovery
Beagles 14% mild severity.

What will happen to animals at the end of this project?

- Killed
- Kept alive
- Rehomed

A retrospective assessment of these predicted harms will be due by 27 April 2029



The PPL holder will be required to disclose:

- What harms were caused to the animals, how severe were those harms and how many animals were affected?

Replacement

State what non-animal alternatives are available in this field, which alternatives you have considered and why they cannot be used for this purpose.

Why do you need to use animals to achieve the aim of your project?

Due to a lack of appropriate synthetic material from existing alternative sources or instances where it is not possible to use cell culture techniques. Researcher protocols still require blood products, obtained from animals that are not required for direct use in research.

The scientific data generated by using blood products taken from animals will also reduce the number of potential new medicines requiring further research in living animals by establishing whether conducting experiments on living animals is ethically valid.

Which non-animal alternatives did you consider for use in this project?

There are a number of early technologies in development which aim to utilise human cells to recreate the physiological functions without using animals, some of which have been made available on <https://nc3rs.org.uk/3rs-resources/improving-human-relevance-cell-culture-using-animal-free-culture-media#animal-products-in-culture-media>,

Why were they not suitable?

Although many technologies are moving quickly in the research sector favouring in-vitro approaches, it is not yet possible to fully offer synthetic material replacement for research animals and blood products, to support all protocols within research that contribute to the development of new medicines for humans and animals.

A retrospective assessment of replacement will be due by 27 April 2029

The PPL holder will be required to disclose:

- What, if any, non-animal alternatives were used or explored after the project started, and is there anything others can learn from your experience?

Reduction

Explain how the numbers of animals for this project were determined. Describe steps that have been taken to reduce animal numbers, and principles used to design studies. Describe practices that are used throughout the project to minimise numbers consistent with scientific objectives, if any. These may include e.g. pilot studies, computer modelling, sharing of tissue and reuse.



How have you estimated the numbers of animals you will use?

The experience of supplying blood products under previous Production of Laboratory Animal Bio- Products project licences, has given insight into current and future demand. This, along with continued updates of researcher forecasting of further demand will form part of an ethical review of the donor colony levels. Which will be deemed appropriate to optimise and maintain the required number of donors, in order to reduce total numbers of animals used in research.

What steps did you take during the experimental design phase to reduce the number of animals being used in this project?

Previous knowledge and experience in the Production and supply of Laboratory Animal Bio-Products has enabled us to establish the minimum number of donors required to re-use for blood sampling without anaesthesia. This means that from this pool multiple samples can be obtained from a smaller number of donors thereby reducing the need to euthanise animals for the purpose of taking each sample. This current level allows us to meet current research sector demand whilst also allowing suitable rest periods for each donor prior to re sampling.

What measures, apart from good experimental design, will you use to optimise the number of animals you plan to use in your project?

The number of animals used will be minimised by using proven collection techniques including taking blood under non-recovery general anaesthesia, to ensure that large volumes of samples can be obtained. The use of blood products, that are obtained from animals not required for direct use in research, will also reduce the total number of live animals required for research. Individual research requests will be co-ordinated in order to supply multiple samples from one animal, aiding in further reduction of the total number of animals used.

A retrospective assessment of reduction will be due by 27 April 2029

The PPL holder will be required to disclose:

- How did you minimise the numbers of animals used on your project and is there anything others can learn from your experience?

Refinement

Give examples of the specific measures (e.g., increased monitoring, postoperative care, pain management, training of animals) to be taken, in relation to the procedures, to minimise welfare costs (harms) to the animals. Describe the mechanisms in place to take up emerging refinement techniques during the lifetime of the project.

Which animal models and methods will you use during this project? Explain why these models and methods cause the least pain, suffering, distress, or lasting



harm to the animals.

All Ferrets, Mice, Guinea Pigs, Rats and approximately 86% of Beagle dogs will be sampled under non recovery general anaesthesia, which is deemed the least invasive method in causing suffering, distress, or lasting harm to the animals.

Approximately 14% of Beagle dogs will be used for live blood sampling and a suitable pool of donor individuals will be trained and assessed for suitability of this mild procedure.

Why can't you use animals that are less sentient?

Where possible, sampling will be performed under non recovery general anaesthesia.

However, some research protocols require low volumes of dog blood as fresh as possible to perform their regulated assays and currently no surrogate matrix is available. In cases like this, sampling via non-recovery anaesthesia is not deemed a viable option to fully utilize the donor dogs to the wider research community.

Therefore, blood sampling without anaesthesia is deemed the most appropriate method to supply these smaller volume demands. Donor beagle dogs used for the protocol will have been assessed for suitability. These beagle dogs are of an age to be able to receive suitable training allowing for an easy process and reducing associated stress.

How will you refine the procedures you're using to minimise the welfare costs (harms) for the animals?

Staff will be trained in suitable techniques for handling and restraint of donor beagle dogs during sampling. Staff required to perform sampling will have been trained and assessed for competency by a qualified PIL/NAWCO overseen by the NTCO for the techniques required to perform live sampling.

Donor dogs will also be assessed prior to being submitted and approved for sampling suitability. They will receive training to sit calmly on an examination table and acclimatized to manual restraint and the sound of the clippers beforehand. After blood sampling they will receive food treat reward making the process easier and reducing stress associated with the techniques when future live sampling is required.

Prior to each sampling request, a NACWO will check and ensure the blood volume to be collected is within the daily/ 28-day limits set in the project license and the donor has not been sampled in the last 7 days. Before each re-use, the NVS will perform a health check of the dog, to assess its suitability for re-use.

Additionally, once a month each blood donor dog is health checked by a NACWO (nails clipped, check for any visible abnormalities, check weight), followed by a monthly general health check by the NVS. Twice a year, a haematology and biochemistry review is carried out for each donor dog, to ensure these parameters remain within the required limitation.

What published best practice guidance will you follow to ensure experiments are



conducted in the most refined way?

Recommendations provided by the recent reports on the NC3Rs website such as Blood sampling will be sought. Any advances will be discussed with the Animal Welfare and Ethical Review Body (AWERB) for implementation and reviewed at recorded AWERB committee meetings to determine effectiveness.

How will you stay informed about advances in the 3Rs, and implement these advances effectively, during the project?

Regular review of guidelines and recommendations provided by the recent reports on the NC3Rs website such as Blood sampling will be conducted and brought to the AWERB committee for discussion and actioned implementation.

A retrospective assessment of refinement will be due by 27 April 2029

The PPL holder will be required to disclose:

- With the knowledge you have now, could the choice of animals or model(s) used be improved for future work of this kind? During the project, how did you minimise harm to the animals?