

The Production of Laboratory Animal BioProducts

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.
 - Improvement of the welfare of animals or of the production conditions for animals reared for agricultural purposes.
- 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 aims mentioned in purpose (b)

Key words

Dog, Mouse, Guinea pig, Blood products

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.

- Required at inspector's discretion

Objectives and benefits

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

What's the aim of this project?

To use animals to provide blood and tissues to generate data to support the development of effective and safe medicines to treat diseases where there is currently a clinical unmet need e.g. cancer & heart disease.

Retrospective assessment

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Is there a plan for this work to continue under another licence?

Yes

Did the project achieve its aims and if not, why not?

The purpose of the work was to provide animal blood products to various UK users within the research community, by supplying fresh low volumes of blood products from the UK donor colony or larger volumes/multiple requests from animals placed under general anaesthesia.

During each request and prior to the supply of animal blood products under these protocols, the completion of a justification form was required. This form required researchers to provide information such as the type of study type the products will be used for and why another species or non-animal alternative methods cannot be used as a replacement for their research.

Each submission was then reviewed in prior consensus by the AWERB community to guarantee that requests received ethical approval, considering the scientific rationale, the availability of non-animal alternative methods or blood from another species could be used, and the accessibility of these methods to the researcher. If concerns were raised during its review the permission to supply would have been denied and the request would have been rejected.

This continuation of supply enabled researchers to adhere to the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the Medicines and Healthcare products Regulatory Agency (MHRA) validation guidelines of GLP toxicity studies authentication methods, to produce data to evaluate the stability of potential medicinal substances in blood. The purpose of this work was to ensure the integrity of the blood collection used in GLP studies and the scientific integrity of the data generated from the blood sample.

Further supporting 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.

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.

What are the potential benefits that will derive from this project?

Bio-products provided will contribute invaluable scientific information to support and progress potential new medicines where there is currently an unmet clinical need. Conducting investigations using blood and/or tissues taken from animals reduces the number of potential new medicines requiring evaluation in living animals and can be used to establish whether conducting experiments on living animals would be beneficial.

The products are also used to aid the development of new medicines in man or animals when it is necessary to calibrate and validate many of the machines or testing systems used to support research. They may also be used to support other methods in research as an alternative to live animals.

Species and numbers of animals expected to be used

What types and approximate numbers of animals will you use over the course of this project?

Over a 5 year period:

Dogs: 275

Mice: 50

Guinea pigs: 50

Predicted harms

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

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected level of severity? What will happen to the animals at the end?

More than 85% of the animals used under this licence will be kept under general anaesthesia throughout the sampling procedures and will not be brought back to consciousness. They will be humanely killed while still under anaesthesia with an overdose of anaesthetic. Therefore these animals are not expected nor likely to experience any adverse effects.

The remainder (mainly dogs) are trained to donate small volumes of fresh whole blood at weekly or monthly intervals and these donors are not expected to suffer adverse effects as a result of the project (similar to taking a blood sample from a human). These dogs will continue to be used as donors for several years until they are retired. The dogs receive full clinical health checks by a veterinarian and experienced animal technicians. They will be retired if there are signs that their, normal health state is affected by the project, their age or health issues.

Training of donors is however not always possible and in the case of mice and Guinea pigs, to avoid the need for restraint of the donor and for handler safety, sedation prior to bleeding is performed.

Adverse effects from repeated blood collection are not expected under this project but could (rarely) include slight bruising, anaemia or uncontrolled bleeding. Any animal with anaemia or poor clotting mechanisms will be removed from the bio-

products donor pool. Adverse effects of the sedation are not expected. Any adversely affected animals will cease to be used and will be referred to the responsible veterinary surgeon who will determine the need for any treatment, consider its suitability for rehoming or if the animal should be humanely killed.

Retrospective assessment

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

In this project, 422 reuse procedures were conducted on beagles to draw small amounts of fresh blood without anaesthesia, to supply the research community. This group would have experienced mild discomfort when the needle was inserted for blood sampling. No other adverse reactions were observed.

A further 103 beagles and 8 ferrets were placed under general anaesthesia and required blood volumes withdrawn. After sampling was completed all animals were humanely killed via a suitable Schedule 1 method without regaining consciousness.

Replacement

State why you need to use animals and why you cannot use non-animal alternatives.

Drug research programmes rely, in part, on biological materials obtained from human or animal sources to validate and confirm disease-associated drug targets and the mechanisms of action for potential new medicines. This programme of work supports the replacement of using living animals by enabling the supply of high quality blood and tissue samples where living cells are needed for experiments due to the lack of appropriate cells from existing alternative sources or instances where it is not possible to use cell culture techniques.

There are a number of promising technologies in development which aim to utilise human cells to recreate the physiological functions of organs without using animals. However, these *in vitro* approaches do not yet offer an alternative to totally replace the need for research animals and authentic blood, blood products, body fluids and tissues to enable their use in all the investigations required to support the research and development of new medicines.

Retrospective assessment

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What, if any, non-animal alternatives were used or explored after the project started, how effective were they and are there any lessons worth sharing with others?

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. During each request for blood products researchers were required to validate the reason non-animal alternative products could not be used to support their research. If non-animal alternative products have been confirmed as available by the researchers, the request for the supply of blood products was rejected.

Reduction

Explain how you will assure the use of minimum numbers of animals.

The number of animals used is minimised by using proven collection techniques including taking blood under non-recovery anaesthesia to ensure that large volume, non-clotted samples can be obtained.

Tissue requests will be co-ordinated in order to supply multiple samples from one animal (e.g. whole blood, pancreas, femurs and liver) to a number of requesters for their individual purposes. This reduces the total number used.

The project aims to provide blood components and tissues of the highest quality as this improves the significance of test results in studies involving animals and can often lead to improved scientific knowledge and a reduction in the overall number of animals.

The project can reuse animals and this means that multiple samples can be obtained from a smaller number of donors thereby reducing the need to kill animals for the purpose of taking each sample.

The use of blood products, tissues and organs that are obtained from animals that are not suitable for direct use in research reduces the total numbers of live animals required for research

Retrospective assessment

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

Previous knowledge and experience in the production and supply of laboratory animal bioproducts 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 or house a larger groups of blood donor dogs for the purpose of taking blood samples. If other researchers needing blood products were able to use such supply project licences, this would reduce the number of animals needed for their projects, resulting in a decrease in the number of animals used in research overall.

Refinement

Explain the choice of species and why the animal model(s) you will use are the most refined, having regard to the objectives. Explain the general measures you will take to minimise welfare costs (harms) to the animals.

Where there is scientific need to preserve tissue integrity/architecture or obtain high volume and quality blood samples, then taking samples under appropriate and well maintained non-recovery anaesthesia is considered the most refined approach and we have refined the technique so that we will cause the minimum amount of discomfort and distress to the animal when we anaesthetise it.

Persons taking samples are well trained in the techniques involved to ensure high quality samples are obtained quickly & effectively with minimal impact on animal welfare.

The choice of donor species is driven by the scientific needs of research scientists. When it is prudent to sedate the donor prior to sampling (if the donor cannot be readily trained or if it would be hazardous for the person taking the sample), then a second drug is used to reverse the sedative and thereby speed up recovery from sedation.

By only using donor dogs from the colonies we house, we ensure they are kept in appropriate longterm housing. The reuse of animals in a donor pool means they are used for a minimum 1 year in ferrets and several years for dogs. The animals benefit in the long term by being housed in appropriate socially enriched housing, cared for by trained staff. This housing is in the holding rooms of the general population and they therefore benefit from being in busy, familiar surroundings with social contacts of other dogs.

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With the knowledge you have now, could the choice of animals or models used have been improved at all? How did you minimise harm to animals during the project?

The project was performed under 2 protocols. 1 for blood sampling from animals under non recovery general anaesthesia, which is deemed the least invasive method in causing suffering, distress, or lasting harm to the animals.

The other being performed on donor beagle dogs used to supply low volumes of dog blood as fresh as possible to perform regulated assays where currently no surrogate matrix is available. Beagles under this protocol were only considered for sampling suitability after they had received training to sit calmly on an examination table and acclimatized to manual restraint and the sound of the clippers. After blood sampling they received food treat reward making the process easier and reducing stress associated with the techniques when future live sampling is required.

Staff were also trained in suitable techniques for handling and restraining of donor beagle dogs during sampling. Staff required to perform sampling had been trained

and assessed for competency by a qualified NVS and PIL holder overseen by the NTCO for the techniques required to perform live sampling.

Prior to each sampling request, a PILH or NACWO checked and ensured the blood volume requested was 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 health checks whilst also considering each donors lifetime history allowing for a full clinical assessment to evaluate its suitability and continuation for re-use under this protocol.

Additionally, once a month each blood donor dog was 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 were carried out for each donor dog, to ensure these parameters remain within the required limitations.