**G: NON-TECHNICAL SUMMARY (NTS)**

NOTE: The Secretary of State considers the provision of a non-technical summary (NTS) is an essential step towards greater openness and requires one to be provided as part of the licence application in every case. You should explain your proposed project clearly using non-technical terms which will be understandable to a lay reader. You should avoid confidential material or anything that would identify you, or others, or your place of work. Failure to address all aspects of the non-technical summary may render your application incomplete and lead to it being returned.

This summary will be published (examples of other summaries can be viewed on the Home Office website at [http://scienceandresearch.homeoffice.gov.uk/animal-research/](http://scienceandresearch.homeoffice.gov.uk/animal-research/)).

**(WORD LIMIT: 1000 WORDS)**

Please complete the following:

<table>
<thead>
<tr>
<th>Project Title (max. 50 characters)</th>
<th>Preclinical drug development service for thrombosis disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Words (max. 5 words)</td>
<td>Thrombosis, anti-coagulant, combination studies</td>
</tr>
<tr>
<td>Expected duration of the project (yrs)</td>
<td>5</td>
</tr>
<tr>
<td>Purpose of the project (as in Article 5)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Translational and applied research</td>
</tr>
<tr>
<td></td>
<td>Regulatory use and routine production</td>
</tr>
<tr>
<td></td>
<td>Protection of the natural environment in the interests of the health or welfare of humans or animals</td>
</tr>
<tr>
<td></td>
<td>Preservation of species</td>
</tr>
<tr>
<td></td>
<td>Higher education or training</td>
</tr>
<tr>
<td></td>
<td>Forensic enquiries</td>
</tr>
<tr>
<td></td>
<td>Maintenance of colonies of genetically altered animals</td>
</tr>
</tbody>
</table>

Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed):

The purpose of this project is to generate scientifically valid and quality assured data in applicable animal models with clients who have the requirement to investigate the blood coagulation process.

The key questions:

1) Can we define the variables in the current models of bleeding and thrombosis?

2) Once these variables have been identified can we refine the models to produce robust and reproducible models?

---

1 Delete Yes or No as appropriate.

2 At least one additional purpose must be selected with this option.
Once we have established and refined our models our objective is to deliver 2 novel anti-coagulants into Phase I clinical trials.

What are the potential benefits likely to derive from this project (how science could be advanced or humans or animals could benefit from the project)?

By providing our experience and expertise as a service to companies, we will obtain data in refined and validated models of thrombosis to which they would not typically have access. This will expedite novel antithrombotic drugs moving into Phase I clinical trials. These agents will have an improved antithrombotic profile without the increased risk of bleeding. Acute arterial thrombosis is the proximal cause of most cases of heart attacks and 60% of strokes, collectively the most common cause of death in the developed world.

What species and approximate numbers of animals do you expect to use over what period of time?

Rodents: Rats - 5000 in total over the lifetime of this project licence (5 years). For mice of which some may be genetically modified 8750 in total over the lifetime of this project licence (5 years). Rabbits – approximately 500 in total over the lifetime of this project licence (5 years).

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?

We aim to refine the animal models described in this licence to minimise any limiting clinical signs whilst maintaining appropriate statistical power. In the majority of cases the primary end point measurements will be bleeding times and formation of thrombi which will mostly be done under terminal anaesthesia. For measurement of bleeding times in normal conscious animals and in those with genetic bleeding disorders we expect the level of severity to be moderate with blood loss being the primary adverse effect. The humane end points we have identified for the other procedures in conscious animals such as administration of test agents and blood sampling would put the likely level of severity at either mild or moderate. At the end of any study all animals will be killed by a suitable Schedule 1 method (rodents and rabbits) or for some rabbits exsanguination under terminal anaesthesia.

Application of the 3Rs

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

   Models of disease involve complex biological responses and therefore cannot be replicated in vitro. Wherever possible, through review of scientific articles, non-animal methods and existing animal data will be used to advise our clients on how to reduce animal use. However, regulatory and ethical guidelines for entering human clinical studies require a degree of animal experimentation, which cannot therefore be avoided if new therapeutic options are to be developed. Since such experimentation is an inevitable consequence of the current regulatory regime in the UK, our focus has been on refinement and reduction, reducing the animal welfare burden of each study that has to be performed.

2. Reduction
   Explain how you will assure the use of minimum numbers

   Although this application is for a Service Project Licence, a unique selling point for our service is our focus on reducing the number of animals required. We
ensure the use of the minimum number of animals by using best practices in terms of study design and statistical analysis. We take great care to reduce the variability in all of the procedures that we carry out, both when working with the animals and in the subsequent analysis of samples. Our novel combination study designs, which are a focus of this licence application, also reduce animal use. Efficacy, pharmacokinetic and safety data for an agent can be obtained from the same study. Careful study design and planning can reduce the animals required to obtain the same data by 50%. By combining several objectives in to a single study we reduce the animal welfare burden, while retaining or improving data quality (since all the data is obtained simultaneously from a single group of animals).

We also carefully monitor the number of animals supplied by our own breeding programme to ensure minimal wastage. If a programme of work on a particular GA strain is no longer required then the strain would be cryopreserved so that they can be re-derived for future studies.

3. 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. The models outlined in this application have been carefully selected to mimic certain aspects of the blood coagulation process seen in human diseases. We will use our expertise to identify biomarkers as validated end-points in the models we offer. We have conducted this process previously and the selection of the optimal biomarker panel together with an appropriate multivariate statistical analysis framework, reduced the animal-to-animal variability markedly, and reduced the number of animals required to achieve the same statistical power by ~30%. Prior to conducting work in animals, we ask our clients to provide us with data to justify the expectation of efficacy in a particular model and bring to our attention to any likely adverse effects of their test agents.

<table>
<thead>
<tr>
<th>For Office Use Only</th>
<th>Yes</th>
<th>No</th>
<th>Date due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Will the project be subject to Retrospective Assessment?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 The retrospective assessment should be completed, agreed with the establishment AWERRB, and submitted to the Home Office within 3 months of the date (or when the project terminates if earlier).

Version 1.4