Private & confidential: *Please be aware that the contents of this form may be made public resulting from the "Freedom of information Act". Personal details will not be released.*

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 programme of work clearly using non-technical terms which can be understood by 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 will 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 www.gov.uk/research-and-testing-using-animals.

Word limit; 1000 words

Project Title	Immunogenicity of biologics
Key Words	immunogenicity, IgG, biologics
Expected duration of the project	5 year(s) 0 months

Purpose of the project (as in ASPA section 5C(3))

Purpose	
Yes	(a) basic research;
	(b) translational or applied research with one of the following aims:
Yes	(i) avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality, or their effects, in man, animals or plants;
No	(ii) assessment, detection, regulation or modification of physiological conditions in man, animals or plants;
No	(iii) improvement of the welfare of animals or of the production conditions for animals reared for agricultural purposes.
No	(c) 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 paragraph (b);
No	(d) protection of the natural environment in the interests of the health or welfare of man

	or animals;
No	(e) research aimed at preserving the species of animal subjected to regulated procedures as part of the programme of work;
No	(f) higher education or training for the acquisition, maintenance or improvement of vocational skills;
No	(g) forensic inquiries.

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

Protein immunogenicity, is the ability of proteins to be recognised as foreign (and potentially harmful) by the immune system and therefore removed. The problem of immunogenicity is very important for a new type of drug "biologics" that are widely used in inflammatory diseases like arthritis (the top 5 best selling drugs in 2015 were biologics). Biologics are proteins, often antibodies, which are good drugs because they are very specific, so only act on the target tissue, and do not have "off-target" effects or toxicity. However, although these drug proteins are usually engineered so that they should not look foreign to the patient's immune system, in many patients the drug protein is recognised as foreign and so the immune system responds like it was an infection, producing antibodies to get rid of the drug protein. These anti-drug antibodies mop up the drug so it does not work any more and can no longer be used to treat the patient. The focus is on understanding how changes to the shape of the protein (its folding), especially those that lead to the protein clumping, result in a stronger immune response to the drug protein, in order to help design better drugs that might avoid this problem.

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)?

Biologics are increasingly widely used and are very effective in the treatment of many immune and inflammatory diseases such as arthritis and psoriasis which are very unpleasant for the sufferer. The testing under this project will help understand how they sometimes cause immune responses that prevent their use, so will help to develop better drugs which do not have this problem so that more patients can be treated safely

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

The project will last for 5 years. Animal numbers are as follows Mouse : 1575

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

All of these studies will be conducted using mice. The mice will be dosed by intraperitoneal injection with test proteins, sometimes with adjuvant (materials that enhance immune responses), or with test proteins that have been modified. The animals will have booster injections of the same materials at weekly intervals for up to 4 weeks by the same route. At the end of the experiment they will be killed humanely and immune tissue (lymph nodes or spleen) and blood taken. The animals will usually show nothing more than minor discomfort from dosing. They are expected to eat, drink and groom normally after these procedures. The animals will be expected to develop an immune response to the injected drug proteins. In our experience the immune response to these types of materials does not cause any noticeable damaging effects but it is possible, although very unlikely, when using new materials that an allergic reaction could occur. Allergic reactions would happen immediately (within minutes) after repeat dosing and signs of an allergic reaction would be blueing of the skin and respiratory distress. On the day of dosing the experimenter stays with the animals for 1 hour after dosing (which is done at the beginning of the day) and they are checked at several times more on that day. If they have an allergic reaction that did not resolve within a couple of minutes they would be humanely killed. It is also possible, but very unlikely, that the proteins used might have some inherent toxicity or be contaminated in some way, such as with bacterial products like endotoxin. Again this effect was not seen under the previous licence with these types of drug proteins. Doses used are relatively small (usually a maximum of 2.5 mg) and the materials that will be used do not usually cause damage unless the specific target of the antibody crossreacts with mouse tissue and could cause a “cytokine storm”. This effect would be most likely seen on first dosing and occur fairly rapidly. For every new protein, and every type of treatment to the protein, sighting studies using one mouse will be conducted where animals are always dosed at the beginning of the day and checked four times more on the day of injection for any sign of adverse effects (piloerection, hunched posture etc). If they had signs that persisted for more than an hour they would be humanely killed. All animals are humanely killed at the end of procedures.

Application of the 3Rs

Replacement

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

Replacement

The immune systems of mice and humans are very complex with many different parts working at different times and in different ways together and alone. Parts of the immune system can be modelled in test tubes in isolation but it is not yet possible to study the immune system as a whole in this way, so we require animals with an immune system like humans. The immune system of mice is very well studied, and is sufficiently similar to

human to be appropriate for this work. The work is conducted in parallel with investigations on human antibody responses to biologic drugs. A substantial part of the investigations are conducted ex vivo with the tissue/serum obtained.

Reduction

Explain how you will ensure the use of minimum numbers of animals

Reduction

All experiments will be designed in order to achieve the scientific objectives whilst using the minimum number of animals. In typical experiments many outcomes are obtained per mouse. Cells and serum are stored for future analyses if alternative end points become apparent from subsequent investigations or from the published literature.

Refinement

Explain the choice of animals 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.

Refinement

Mice are used for these studies. This species are considered to be of the lowest neurophysiological sensitivity available that will allow the study aims to be achieved. For the majority of studies the severity limit is mild (with the exception of sighting studies as the materials will be unknown) and the procedures are not expected to cause anything but mild discomfort during the injection. Sighting studies will be conducted with a single animal for any new material/preparation to ensure there are no unexpected effects caused by the new material. Animals will be routinely group housed with congenic animals from the same stock date and will have environmental enrichment. In an improvement on previous practice, individual mice used for sighting studies will also be identified and remain with cagemates for the duration of the study. Advice on general animal welfare and for specific concerns about the health/well being of the animals will be sought from animal unit staff including a veterinary specialist who is available to advise on any ill health issues and appropriate care for the animals.