Home Office

NON-TECHNICAL SUMMARY

Safety and efficacy assessment for fish medicines

Project duration

Years **5**
Months **0**

Project purpose

- (b) Translational or applied research with one of the following aims:
  - (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants.
- (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 purpose (b)
- (d) Protection of the natural environment in the interests of the health or welfare of man or animals.

Key words

vaccine, safety, pharmaceutical, fish, efficacy

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.

Objectives and benefits

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

What is the aim of this project?

This Project Licence covers the *in vivo* testing required to demonstrate that medicines destined to be used to treat farmed fish are effective and safe to the fish themselves and the consumer.

Severe diseases caused by infectious disease agents (bacteria, viruses and parasites) cause significant losses of farmed fish. Such diseases causesignificant welfare problems for the animals concerned, a waste of resource inputs, and economic losses, constraining the sustainable development of this important industry. Veterinary medicines and vaccines are needed to treat or prevent these diseases, but their effectiveness and safety to the animal, to the consumer and to the environment must be established first. Whilst much of this can be done by *in vitro* methods not using animals, it is still necessary to confirm that a candidate treatment truly protects or treats the target animal species from the disease concerned and is safe for such use. The final stage of consumer safety, to protect consumers from unacceptable veterinary residues and to determine the minimum length of time between last treatment and slaughter, must be tested in the animal itself, because currently available artificial systems do not offer sufficient guarantee of consumer safety.

The fish species used under this project will be the farmed fish that the treatments are designed to protect, or treat, thus ensuring the results are fully transferrable to potential use in the field.

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?

The results of the tests carried out under this Project Licence will help improve / maintain the availability of aquatic medicines, vaccines and feed additives, and thus markedly assist in maintaining the welfare of the more than two billion fish on fish farms in Europe. In addition, they will also support efforts to protect consumer safety by provision of incurred residue materials for testing laboratories looking to developing analytical methods to detect the presence of legally and illegally used medicines in fish meat destined for human consumption.

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?

The types of animals to be used will be fish species, principally Atlantic salmon and rainbow trout. Other species will also be used, such as sea- bass, carp, tilapia, wrasse, lumpfish and other cyprinids and, turbot and dab. Numbers are difficult to predict as these will depend on the numbers of products to be tested over project, types of testing required and, in particular, the size of fish to be used. An estimated range is approximately 7,000-40,000 over the 5 years .

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?

For most of the safety tests, no adverse effects are likely. For the efficacy testing, this will involve exposing fish to harmful pathogens, which will result in severe disease symptoms, including mortality. However, care will be taken to identify humane endpoints where possible to reduce suffering to a minimum

Application of the three Rs

1. Replacement

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

For much the work done under this Project License to test candidate veterinary medicines, EU and UK regulations typically require use of live animals, since the objective is to determine the safety and efficacy of the product in the whole animal. The whole animal in most cases needs to be the intended target species for the veterinary medicine.

This also applies to studies where we will look to expose fish to illegal medicines in support of testing programmes that help confirm that fish sold to the public is free of illegal contaminants. We need to be sure that the laboratories running the testing have access to samples of fish tissues that have been dosed ('incurred') with these drugs in a way that fully mimics the way they would accumulate in nature. At this time, these studies must still be carried out on the whole animal

However, advice and guidance from advisory bodies, along with published information, will be continually monitored throughout the duration of this licence and where non-animal testing is accepted by regulators these will be adopted in keeping with the principles of replacement.

2. Reduction

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

The minimum numbers of animals to be used are as defined by the relevant regulations, or, where this is not mandated, by consultation with our statistical services group in each case, to ensure the minimum statistically valid number of fish, consistent with the need to provide robust data, are used. This also includes a careful check of the published literature to ensure the work planned does not duplicate other work that has already been undertaken. Cefas staff also regularly discuss planned tests with the regulators themselves (e.g. the UK's Veterinary Medicines Directorate) to ensure the most appropriate studies are undertaken, consistent with the principles of the 3Rs. This all helps to avoid unnecessary use of fish.

For each and every experiment involving live animals (fish), we then write a Study Plan which includes:

- A statement of the objective(s)
- A description of the experiment, covering such matters as the experimental treatments, the size of the experiment (number of groups, number of animals/group), and the experimental material
- How the 3Rs are addressed.

The protocols are then reviewed by our local Animal Welfare and Ethical Review Body (AWERB) to ensure the studies are ethically justifiable and adhere to the principles of the 3Rs. No study can take place until it has obtained clearance from both the statistical services group and the AWERB.

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 target species used will typically be the farmed species to eventually be treated with the products, this may also be as mandated under relevant legislation. These include salmonids (Atlantic salmon and rainbow trout), sea-bass, tilapia and carp. Although these will form the majority (certainly in terms of numbers) of experimental fish, the list cannot be exhaustive; other species may become important during the life of this licence (e.g. lumpfish).

Stocking density and population size will be considered to ensure expression of normal feeding and social behaviours, and to minimise anti-social (aggressive) behaviour.

The fish themselves will typically be purchased from normal fish farm stock (or reared from eggs in house), usually from a site with an established disease history as disease-free fish in compliance with relevant regulations.

Suffering will be minimal in the protocols assessing the safety of medicines, as most of the procedures listed will be no greater than mild. Where preliminary tests with candidate products are required, and there is not good toxicology data available for the target species, it is possible that occasional moderate reactions will be observed. A literature review will be undertaken to determine test doses that are unlikely to cause any adverse reaction. In practice, it is unlikely that adverse effects that would even be considered moderate will be observed in these protocols.

Other than that, methods used under those protocols are identical to those that will be used by veterinary practitioners when applying antibiotic therapy (or other pharmaceutical treatment) to control disease. No adverse effects are expected and if any occur the trial will be terminated immediately.

Where the fish are dosed with an illegally used veterinary medicine or environmental contaminant, a literature review and consultation with aquaculture health and other experts will always be undertaken first to establish a likely safe dose believed representative of practice. Where such published data or information are scarce, a pre-test will be carried out with a small number of fish (10 or fewer) applying a

dose believed representative of practice. This is final confirmation that the proposed dose is safe before exposing much larger numbers of fish to produce incurred residue material.

Severe protocols

Challenging fish with pathogens or toxic substances, as is undertaken for many of the vaccine and medicine efficacy tests, often results in the death of the challenged fish. In some cases, where European and UK law require it, there will be no option but to use death as an endpoint (e.g. European Pharmacopoeia monographs for fish vaccines). It is otherwise proposed to use infection or moribundity as alternative end-points to mortality for other studies performed under these protocols. On occasion, particularly for vaccine tests, it will also be possible to monitor the host response of treated fish by serological or other methods. Where this is scientifically justified, this alternative approach will be followed. In those cases, treated (e.g. vaccinated) fish will be sampled at intervals and blood samples examined to follow the host response to the vaccine. Efforts will be made to influence EU and UK regulators to mandate the use of alternative criteria to death as an end-point, where published guidance specifies the use of death.