HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Practices ~~Outside~~ outside the Scope of Scientific Animal Protection Legislation

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This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.

1 INTRODUCTION

This guide is intended to clarify when studies or practices involving animals may fall outside the legislation governing the protection of animals used for scientific purposes i.e. Directive 2010/63/EU ('the Directive') and S.I. No. 543 of 2012, as amended by S.I. No. 434 of 2013 and S.I. No. 174 of 2014 (hereafter referred to as 'the Regulations'). It may be used in situations where an applicant seeks HPRA confirmation on whether a project/study falls within the scope of the legislation (i.e. requires authorisation) or falls outside the scope of the legislation (i.e. does not require authorisation).

2 CONSIDERATION OF SITUATIONS OUTLINED IN THE LEGISLATION

Article 1(5) of the Directive and Regulation 4 of the Regulations outline specific situations where the Directive will not apply. These are considered individually below:

2.1 Non-experimental agricultural practices

Agriculture covers all activities essential to food/feed/fibre production, including all techniques for raising and 'processing' livestock as well as for aquaculture. Non-experimental agricultural practices are practices used in agriculture to facilitate farming. Examples include disbudding/dehorning of cattle, castration of lambs, rearing and weaning practices in calves and embryo transfer. Examples in aquaculture include some tagging practices, stripping and weighing of fish. These practices do not fall within the scope of the legislation. Furthermore, some experimental studies in agriculture do not fall within the scope of the legislation if they do not cause pain, suffering, distress or lasting harm, such as an observational study to compare the effects of intensive and extensive rearing systems on production and behavioural indices in growing pigs. However, in cases where injections are to be administered as part of the study, whether to deliver a drug or to take a sample of blood or tissue, or where a surgical procedure is performed (e.g. to insert a rumen fistula), a project authorisation would be required.

2.2 Non-experimental clinical veterinary practices

The practice of veterinary medicine is defined in Regulation 53 of the Veterinary Practice Act, 2005 (No. 22 of 2005). It includes 'carry[ing] out treatment, whether surgical or medical in nature... [as well as] performing a surgical procedure'. Within the context of this document, all procedures conducted by a veterinary practitioner in relation to the practice of veterinary medicine (as defined by Regulation 53 of the Veterinary Practice Act, 2005), and that are carried out in a veterinary premises (defined by Regulation 105 of the Veterinary Practice Act, 2005) are regarded as outside of the scope of the Directive.

Examples include:
- taking blood samples from an animal on a farm, or animals within a herd, to assist in clinical management e.g. for disease diagnosis,
- taking a series of biopsies from an animal for diagnosis of disease and monitoring the efficacy of treatment,
- imaging to assist in diagnosis and monitoring, and
- administering veterinary treatment, including to animals undergoing scientific procedures when the treatment is for the animal's benefit and is not part of a scientific procedure.

However, it should be noted that scientific research studies on animals carried out by veterinary practitioners are not necessarily outside the scope of scientific animal protection legislation, as these may not in the fall under the umbrella of routine veterinary practice.

2.3 Veterinary clinical field trials required for the marketing authorisation of a veterinary medicinal product

The HPRA understands a 'clinical trial' to mean a study which aims to examine under field conditions the safety or efficacy (or both) of a veterinary medicinal product under normal conditions of animal husbandry or as part of normal veterinary practice for the purpose of obtaining a marketing authorisation or a change thereof.

The EU guidance on 'Good Clinical Practice for the Conduct of Clinical Trials on Veterinary Medicinal Products in the European Union' under Directive 81/852/EEC as amended differentiates between pre-clinical studies (such as pharmacokinetic studies) and those conducted as clinical trials. The EU Commission advice is that the conduct of pre-clinical trials falls within the scope of scientific animal protection legislation and requires HPRA project authorisation. The HPRA is also the competent authority for veterinary clinical field trials under S.I. No. 361 of 2014 and this involves a separate application process.

It is important to note that studies in the target species intended to elucidate pharmacodynamic effects, or to establish proof of concept of a new innovative drug or therapy, as well as determination (titration) of dose studies, animal model studies and tolerance studies conducted at multiples of the recommended dosage in the target animal are regarded as pre-clinical tests. Additionally, confirmation of dose studies carried out under laboratory conditions or in artificially diseased or infected animals also falls within the scope of scientific animal protection legislation.

The EU has published advice on the consensual approach of Member States and the Commission. The advice is that in the development of veterinary medicines, a great deal of work will have been performed on animals authorised under scientific animal protection legislation, but that there usually comes a point when it is necessary to test the efficacy and safety of new preparations in the target species under field conditions which requires a clinical field trial licence. Please refer to the HPRA 'Guide to ~~Clinical Field Trials for Veterinary~~

~~Medicinal Products~~clinical field trial licence applications under animal remedies legislation' for additional information on veterinary clinical field trial requirements.
~~Pre-clinical trials may involve safety and efficacy studies not conducted in the field, which would then fall within the scope of scientific animal protection legislation.~~

~~Veterinary clinical field trials should not be confused with regulatory testing which falls within the scope of scientific animal protection legislation. Regulatory testing refers to tests on animals that are required by legislation to manage risks to human and animal health and the environment. Regulatory testing is required to evaluate the safety, efficacy, and/or potential adverse health effects of new chemicals and products such as vaccines, medicines, food additives, pesticides, biocides, and chemicals, medical devices and other substances. It also encompasses tests on fish or birds which might be needed to evaluate the safety of a substance for the environment. This testing information provides the basis for risk assessment decisions to safeguard public and animal health. Whilst the performance of clinical trials and regulatory testing often has some common aims, such as confirming the safety and efficacy of the particular drug, there are a number of critical differences between them. In contrast to regulatory testing, the animals being used in a clinical field trial of a veterinary medicinal product will not normally be owned by or reside at a laboratory. The dose rates, methods of administration, time of dosing etc. of veterinary medicines used in clinical field trials will be those previously determined as appropriate to the age, species, breed, sex and size of the animal.~~

2.4 Studies involving unauthorised feed additives

Studies involving unauthorised feed additives, which do not involve pain, suffering, distress or lasting harm would be considered to fall outside the scope of the legislation. However, it should be noted that in order t~~T~~o ensure that consumer, animal and environmental safety is maintained, these studies ~~involving unauthorised feed additives~~ may ~~also~~ need to be registered with the Department of Agriculture, Food and the Marine ~~(DAFM) who will ensure~~. Therefore the ~~Department of Agriculture, Food and the Marin~~DAFM ~~e~~Department should be contacted when carrying out studies using unauthorised feed additives. ~~regardless of whether or not a HPRA Project Authorisation is required.~~

~~2.4~~2.5 Practices undertaken for the purposes of recognised animal husbandry

The term 'animal husbandry' is understood as the processes and activities undertaken for the health and welfare of animals (i.e. carried out for their benefit). The HPRA understands this definition to encompass all husbandry and care practices including housing conditions and colony management, and the monitoring of reproductive, growth and health indices. Some examples include: single housing of males in order to minimise aggression, vaginal swabbing of mice and dogs to determine stage of oestrus and optimum time for mating, routine vaccinations of domestic animals, worming and dietary manipulation in order to meet particular requirements (such as managing obesity in older animals).

Simple observational studies of different animal husbandry practices which do not cause pain, suffering, distress or lasting harm, do not fall within the scope of the legislation, for example a study to compare the effects of cage changing frequency on growth rates and behaviour in mice.

Genetic characterisation is not regarded as a recognised husbandry practice and would therefore fall within the scope of the legislation.

~~2.5~~2.6 Practices undertaken for the primary purpose of identification of an animal

Animals are identified for a number of reasons e.g. to facilitate identification of individual animals held in groups, to facilitate routine stock and breeding management and to facilitate tracing of animals for health and disease control. These practices do not fall within the scope of the legislation. Some examples include ear tagging or freeze branding of cattle, tattooing or microchipping of dogs. Furthermore, Article 32 of the Directive and Regulation 65 of the Regulations require that each dog, cat and non-human primate in an establishment should be provided with a permanent individual identification mark in the least painful manner possible.

Free ranging wildlife (i.e. the animals are not kept in captivity in an establishment, or if so, only for a very short period of time) can be identified by non-invasive or radio-collaring means outside of the scope of the legislation, provided they do not cause pain, suffering, distress or lasting harm, but any invasive identification such as microchipping is regarded as a procedure under the legislation. ~~This is due to the cumulative effect of the stress of capture plus the stress of invasive identification on a wild animal.~~

~~2.6~~2.7 Practices not likely to cause pain, suffering, distress or lasting harm equivalent to, or higher than, that caused by the introduction of a needle in accordance with Good Veterinary Practice

When conducted in isolation, practices undertaken for a scientific or educational purpose which do not reach a threshold of pain, suffering, distress or lasting harm equivalent to or higher than that caused by the introduction of a needle according to Good Veterinary Practice do not fall within the scope of the legislation. Some examples include monitoring ECG with non-invasive techniques with minimal or no restraint of habituated animals and breeding genetically altered animals which are expected to have no clinically detectable adverse phenotype.

Annex VIII of the Directive provides other examples for procedures that do not fall within the scope of the legislation. It is important to note that a series or combination of 'below threshold' procedures together may have the effect of causing an animal pain, suffering, distress or lasting harm which is equal to or exceeds the threshold, and therefore would fall under the scope of the legislation. However this is reviewed on a case-by-case basis.

~~2.7~~2.8 Other practices outside the scope of the legislation

Although not mentioned specifically in the legislation, the HPRA regards the following practices as outside the scope of the legislation and therefore does not require a project authorisation:

- The use of choice chamber tests and food-preference tests for animal behaviour studies.
  The use of non-human vertebrate animals for food preference tests would also fall outside the scope of this legislation, provided the activity did not have the capacity of causing pain, suffering, distress or other lasting harm and that the animals concerned were not taken from the wild.

- The hatching of chicks from eggs kept in an incubator.
  Although chicks are included as 'animals' under the legislation, the observation and monitoring of such animals (including hatching) while housed under conditions of good husbandry would be out of scope of the legislation as no procedure with the likelihood of causing pain, suffering, distress or lasting harm would be considered to have taken place. Again, care should be taken that animals are not handled in a way that is harmful to their development or causes them fear and anxiety. Chicks that are bred from genetically modified lines or where eggs are manipulated to introduce new genes fall within the scope of the legislation and require a project authorisation.

- The use of frog spawn in glass tanks to facilitate observational studies.
  Some species of frogs (*Xenopus laevis, Xenopus tropicalis, Rana temporaria* and *Rana pipiens*) come under the scope of the legislation at the stage that the larvae become capable of independent feeding. However, the observation of spawning in a situation similar to a natural pond is considered to be out of scope of the legislation.

- The use of an aquarium or vivarium or small mammal cage in laboratories for direct observation of animal behaviour including species of fish, reptile, amphibia, arthropod or small mammal such as hamster. The observation and monitoring of fish in an aquarium or animals in small cages that are housed under natural conditions would not constitute a 'procedure' under the legislation and so would fall outside the scope of this legislation.

3 CLASSIFICATION OF PROJECT/STUDIES BY THE HPRA

It may not be clear in every situation whether certain studies, procedures or trials fall within the scope of the legislation. Applicants can request an opinion from the HPRA on the classification of their study prior to submitting a full application for project authorisation by completing a 'Classification ~~R~~request for a pProject/~~S~~study under scientific animal protection legislation' form. This will inform the applicant if their study falls outside the scope of the legislation, or falls within ~~its scope~~its scope. Applicants can therefore utilise this classification

process to avoid the risk of not complying with the national legislative requirements by performing procedures without the necessary HPRA project authorisation.

~~If the application cannot be submitted electronically, applications will be accepted in hard copy by post. Applications that arrive by post must be electronically scanned by the HPRA resulting in additional processing time for evaluation.~~
~~Send hard copy applications to:~~
~~Scientific Animal Protection Section~~
~~Health Products Regulatory Authority~~
~~Kevin O'Malley House~~
~~Earlsfort Centre~~
~~Earlsfort Terrace~~
~~Dublin 2~~

3.1 Applying for classification of a study by the HPRA

To apply for classification of a project/study download the 'Classification Request for a Project/Study under Scientific Animal Protection Legislation' form from www.hpra.ie and submit the signed and completed form to sap@hpra.ie. In order to arrive at a classification decision, the HPRA must be in receipt of sufficiently accurate information about the study. Please append the study protocol and any other relevant information to the classification request form.

3.2 Completing the classification request form

The 'Classification Request for a Project/Study under Scientific Animal Protection Legislation' form requests information in respect of the applicant, the project or study as well as other administrative information. These are considered further below.

3.2.1 Section A, Applicant Details

Information and contact details for the applicant should be provided here. This information will be used by the HPRA in case of any follow up questions that might be required before a decision can be made. Where the applicant is based in a breeder/supplier/user establishment that has already been authorised by the HPRA ~~or registered by the Department of Health~~ for scientific animal purposes, it would be useful for the HPRA to have details of the breeder/supplier/user establishment concerned.

3.2.2 Section B, Details of Request

In order for the HPRA to reach an opinion, full but succinct information on the study is needed. The applicant should describe the proposed project/study in 500 words or less. Information on the species and numbers of animals to be used should be provided. The applicant should clarify the basis on which the proposed project/study may fall outside the scope of the legislation by selecting the relevant category. Where the applicant is unsure

which category may be relevant, the box labelled 'Other' should be checked. In any case, the applicant should briefly outline the reasons why the project/study may fall outside the scope of the legislation.

3.2.3 Section C, Checklist and Signature of Applicant

The applicant should sign the application form, having confirmed that Sections A and B have been completed and that the study protocol and other supporting information deemed relevant to the HPRA assessment have been appended to the form.

3.3 The classification process

The application details and associated study protocol and information are assessed by the Scientific Animal Protection Section in the Veterinary Sciences Department to determine whether the project/study:

- is outside the scope of scientific animal protection legislation
- falls within the scope of the legislation and requires an application in order to obtain a project authorisation from the HPRA.

The classification query may be referred to HPRA experts for an opinion if necessary.

3.4 Duration of the classification process

Usually, provided the applicant has provided clear and comprehensive information as detailed in the application form, the HPRA can give an opinion within 15 working days of receipt of the application. In the case of applications which are novel or complex, necessitating consultation with HPRA experts, the procedure to complete the evaluation may take up to 28 working days.

3.5 Administrative details

Applications should be sent electronically to sap@hpra.ie; however if the application cannot be submitted electronically, applications will be accepted in hard copy by post. Applications that arrive by post must be electronically scanned by the HPRA resulting in additional processing time for evaluation.

Send hard copy applications to:
Scientific Animal Protection Section
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4 SUMMARY

For the purposes of this guide, the HPRA concludes that the following trials, studies or practices fall outside the scope of scientific animal protection legislation:

- General nutritional trials (which tend to be observational only) where the animals' nutritional needs are met in full, no procedures are conducted.
- Procedures that are carried out for an animal's benefit by a veterinary practitioner in a veterinary premises in relation to the treatment of animals under his/her care, and are not conducted as part of a study.
- Veterinary clinical trials carried out on final formulations of a veterinary medicinal product on the target species at the recommended dosage and under field conditions (i.e not utilising artificial disease models). These are trials that are being conducted under Good Clinical Practice conditions, and involve animals which are privately owned, i.e. not owned by the breeder/supplier/user establishment, which are under the responsibility of an investigator and under the care of a veterinary practitioner.
- Procedures carried out as part of non-experimental agricultural practice e.g. castration.
- Procedures carried out as part of recognised animal husbandry practices e.g. vaginal swabbing.
- Certain procedures for identification of an animal e.g. ear tagging.
- Practices undertaken for a scientific or educational purpose which do not reach a threshold of pain, suffering, distress or lasting harm equivalent to or higher than that caused by the introduction of a needle according to Good Veterinary Practice.

For the purposes of this guide, the HPRA concludes that the following trials, studies or practices fall within the scope of scientific animal protection legislation:

- Practices likely to cause the animal a level of pain, suffering, distress or lasting harm equivalent to or higher than that caused by the introduction of a needle according to Good Veterinary Practice.
- Studies on wildlife that use an invasive procedure to identify the animals involved.
- Preclinical trials including pharmacokinetic studies, toxicity studies, tolerance studies etc.

It is the express responsibility of the person or establishment planning to carry out a study to ensure compliance with the relevant legislation. Failure to comply with the legislation may result in penalties, fines or prosecution as specified in the Regulations.