

National Competent Authorities for the implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes

Working document on specific articles in Directive 2010/63/EU

Brussels, 6-7 October 2011

The National Contact Points of the Member States responsible for the implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes and the Commission agreed to discuss a number of articles contained in the Directive with a view to finding a common approach throughout the EU.

The consensus on the understanding of the articles discussed at the meeting of 6-7 October 2011 is presented below to promote uniform implementation and application of the Directive.

This document covers the following articles:

- Article 1(5) - Practices that are exempted from the scope of the Directive
- Article 3 - Definitions for a procedure and project
- Article 16 - Use, re-use and continued use
- Article 40 - Multiple generic projects
- Article 41 - Complex or multi-disciplinary projects

Disclaimer:

The following is intended as guidance to assist the Member States and others affected by this Directive to arrive at a common understanding of the provisions contained in the Directive. All comments should be considered within the context of Directive 2010/63/EU on the protection of animals used for scientific purposes.

Only the Court of Justice of the European Union is entitled to interpret EU law with legally binding authority.

Article 1(5) - Practices that are exempted from the scope of the Directive

Background

Directive 2010/63/EU establishes measures for the protection of animals used for scientific or educational purposes.

Article 1(5) lists a number of practices which are exempted from the requirements of the Directive. These are as follows:

- (a) non-experimental agricultural practices;
- (b) non-experimental clinical veterinary practices;
- (c) veterinary clinical trials required for the marketing authorisation of a veterinary medicinal product;
- (d) practices undertaken for the purposes of recognised animal husbandry;
- (e) practices undertaken for the primary purpose of identification of an animal;
- (f) practices not likely to cause pain, suffering, distress or lasting harm equivalent to, or higher than, that caused by the introduction of a needle according to good veterinary practice.

The terms “non-experimental, agricultural and clinical veterinary practices” were used under the previous Directive 86/609/EEC.

Article 1 describes the Subject matter and Scope of the Directive with paragraph 5 of this Article describing the circumstances under which this Directive would not apply.

In determining whether or not an investigation falls within the scope of the Directive the key question to address is: Is the study to be undertaken for a scientific or educational purpose involving live vertebrates (including foetal forms of mammals in the last third of development and independently feeding larval forms) or live cephalopods?

If the answer is yes, then the clauses in Paragraph 5 needs to be reviewed to determine whether or not there is an exemption from the scope of the Directive.

If the practices are being undertaken as part of routine agricultural, animal husbandry or veterinary practice to manage health, welfare and care practices, are being applied for the primary purpose of identification, or are unlikely to cause pain, suffering, distress or lasting harm, these do not fall within the scope of Directive 2010/63/EU.

(a) Non experimental agricultural practice

Agriculture can be defined as the production of food, feed, fibre and other goods by the systematic raising of domesticated plants and animals. Agriculture covers all activities essential to food/feed/fibre production, including all techniques for raising and "processing" livestock. Agriculture includes agronomy, animal husbandry, and aquaculture. Agriculture practices are simply practices used in agriculture to facilitate farming.

A number of Council Directives set requirements for the protection of animals kept for farming practices [for example general standards are contained in 98/58/EC, and minimum standards set for calves in 2008/119/EC, pigs in 2001/88/EC and 2001/93/EC, laying hens in 1999/74/EC, and chickens kept for meat production in 2007/43/EC].

Examples of agricultural practices include disbudding/dehorning of cattle, castration of lambs, pigs and cattle, debeaking in poultry, nutritional manipulation of weight in broiler replacement breeders, rearing and weaning practices in dairy and veal calves, restraint around parturition e.g. pigs and advanced breeding techniques for agricultural purposes, such as embryo transfer and vasectomy to, for example, improve health or genetics of the flock or herd.

Simple observational studies of commercial agricultural practices which do not include any additional practices/interventions which may cause pain, suffering, distress or lasting harm do not fall within the scope of Directive 2010/63/EU.

For example, a study to compare the effects of intensive and extensive rearing systems on production and behavioural indices in growing pigs. Study consists of simple observations on commercial farms using different rearing systems (which comply with national/EU legislation), and subsequent comparison of behaviour and production records.

(b) Non experimental clinical veterinary practice

Clinical veterinary practice can be defined as procedures and techniques performed by veterinary surgeons in the course of their professional duties which ensure the health and welfare of animals committed to their care.

Examples include

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

(c) Veterinary clinical trials required for the marketing authorisation of a veterinary medicinal product

During the development of veterinary medicines, a great deal of work will have been performed on animals authorised under 2010/63/EU.

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. Pharmaceutical companies need to generate these data in order to support an application for a marketing authorisation.

Directive 2001/82/EC details the requirements for veterinary clinical trials. Animals used in such trials are under veterinary care and appropriate clinical care, including alternative treatments, is provided should the test product prove ineffective or animal welfare is compromised.

(d) Practices undertaken for the purposes of recognised animal husbandry

Animal husbandry may be defined as the system of taking care of domestic animals, including those held and used in laboratories.

This definition encompasses all husbandry and care practices including housing conditions and colony management, monitoring reproductive, growth and health indices. *N.B. Further information will be made available on legal interpretation of "recognised" husbandry.*

For example:

- Single housing of males may be necessary to minimise aggression;
- Vaginal swabbing (mice/dogs) or blood sampling (dogs) to determine stage of oestrus and optimum time for mating;
- Single housing on grid floors to check for mating plugs (rats & mice);
- Weighing fish under general anaesthesia to monitor growth to facilitate dietary and stocking management;
- Management of diet (composition, quantity and availability) to meet requirements of animals – e.g. managing obesity in older animals; infrequent feeding of snakes to mimic biological needs.

Simple observational comparisons of different animal husbandry practices, which do not include any additional practices/interventions which may cause pain, suffering, distress or lasting harm, do not fall within the scope of directive 2010/63/EU. For example, a study to compare the effects of cage changing frequency on growth rates and behaviour in mice.

(e) Practices undertaken for the primary purpose of identification of an animal

Animals are identified for a number of reasons, for example - 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.

Practices undertaken for the primary purpose of identification are not within the scope of the Directive.

This should not be confused with the requirements of Article 32. For animals used within the scope of the Directive, there is a requirement that each dog, cat and non-

human primate shall be provided with a permanent individual identification mark in the least painful manner possible (Article 32).

For reasons of good welfare, consideration should be given to the method chosen for identification, and should be the most refined technique appropriate to the need. For example, where it is only necessary to identify an animal for a short period of time, the use of a non-toxic dye or fur clipping would not cause any pain or discomfort. Alternatively, there may be a legal requirement in farm species for two separate methods to be employed, for example an ear tag and a transponder.

(f) Practices not likely to cause pain, suffering, distress or lasting harm equivalent to, or higher than, that caused by the introduction of a needle according to good veterinary practice

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 Directive.

Annex VIII provides some examples of equivalent “thresholds” for other classes of procedure, such as dietary manipulations and psychological stress:

- assessing body composition by non-invasive measures and minimal restraint;
- monitoring ECG with non-invasive techniques with minimal or no restraint of habituated animals;
- application of external telemetry devices that are expected to cause no impairment to socially adapted animals and do not interfere with normal activity and behaviour;
- breeding genetically altered animals which are expected to have no clinically detectable adverse phenotype;
- adding inert markers in the diet to follow passage of digesta;
- withdrawal of food for <24h in adult rats;
- open field testing.

In addition it is important to note that a series or combination of “below threshold” techniques *together* may have the effect of causing an animal pain, suffering, distress or lasting harm. Using the food withdrawal as an example, if this was repeated frequently, it is likely that there would be adverse welfare consequences for the animal. Similarly, multiple or cumulative minor changes to an animal’s environment may cause sufficient disturbance to the animal to be considered a mild procedure.

Article 3 - Definitions for a procedure and project

Project

According to the Directive, a **project** means a programme of work having a defined scientific objective and involving one or more procedures.

Projects can vary in size and complexity, for example, from the work of a single scientist consisting of a single blood harvest procedure in a single species, to an entire department's drug discovery programme, which involves many scientists, multiple complex procedures and a wide range of species.

Procedure

According to the Directive, **procedure** means any *use*, invasive or non-invasive, of an animal for experimental or other scientific purposes, with known or unknown outcome, or educational purposes, which may cause the animal a level of pain, suffering or distress or lasting harm equivalent to, or higher than, that caused by the introduction of a needle according to good veterinary practice.

Within a project, procedures will be performed to meet a defined scientific purpose. Procedures may be simple or complex depending on the purpose.

The purpose may be achieved by using a single step procedure (for example withdrawal of blood), but much more commonly requires a number of steps used in combination to achieve a single outcome, and which requires the use of the same animal (for example antibody production would generally require a number of antigen injections to stimulate antibody production, and a number of blood samples to achieve the desired outcome).

Examples of Procedures

A single subcutaneous injection of a test substance may be given in a pharmaceutical project to attain the objective of understanding the drug distribution within the body tissues. The animal is then killed by a method listed in Annex IV.

This project comprises of one procedure (the injection of the test substance) which may cause the animal pain, suffering, distress or lasting harm.

In contrast, a procedure to assess the effect of the test substance on blood pressure using telemetry would require a number of separate technical steps to be carried out to meet this single scientific purpose (multi – step procedure).

The animal would need to be anaesthetised, blood pressure transducer implanted and, following a suitable recovery period, administered the test substance by subcutaneous injection. The animal is then killed by a method listed in Annex IV.

In this example three steps namely anaesthesia, surgical implantation of blood pressure transducer and injection of the test substance) need to be used in combination

to meet the single scientific purpose of understanding the effects of the substance on blood pressure.¹ All the steps need to be made in the correct sequence and using the same animal to achieve the objective of the study – neither omitting a step nor using a different animal at any stage would allow the objective to be met.

¹ In this example, each step, *if used in isolation to meet a single scientific purpose*, would be considered a “procedure” as each may cause the animal 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.

Article 16 – Use and re-use

Use

The “use” of an animal within a project extends from the time the procedure (or first procedure/technique in a series) is applied to it, to the time when the observations, or the collection of data (or other products) for a particular scientific purpose (usually a single experiment or test), are completed.

Re-use

“Re-use” is a term to indicate the subsequent use of an animal which has already completed a procedure (or series of procedures/techniques) for a particular scientific purpose.

Article 16 on re-use defines it as a use *when a different animal on which no procedure has previously been carried out could also be used*. Article 16 also defines the circumstances under which an animal may be re-used.

Continued Use

This is a term not included in the Directive, but can be used to describe the situation when the single “use” of an animal extends over more than one project or across different procedures within the same project. This arrangement can simplify project applications and avoid undue repetition.

Example 1 - Re-use

Purpose 1: to obtain sheep blood to make diagnostic plates for bacteriology.

Purpose 2: to determine the effect on blood parameters in sheep of a test dietary supplement, which may have adverse effects.

First use

A sheep is used on the first procedure to obtain a blood sample for use in preparation of diagnostic plates.

Second use

The same animal is then used on a second unrelated project to study the metabolism of a dietary supplement, blood samples are taken for analysis and other non-invasive measurements are made.

The two studies are not related.

Any naive sheep could have been used for the second study. Use of the sheep for the dietary study would constitute re-use of that animal.

Example 2 – Re-use

Purpose: The use of a sheep on more than one occasion to provide blood samples for use in preparation of diagnostic plates.

The first blood sample obtained by jugular venepuncture constitutes the first use – the purpose is attained.

As a different animal could be used on each occasion, the second sample (procedure) and each subsequent sample (procedure) is classified as re-use. There is no scientific need to take multiple samples from the same animal.

Example 3 - Use and continued use

Purpose: To determine the effects of genetic defect X in mice by measuring changes in blood parameters with age and undertaking a histological analysis of adult brain structure.

Use

This could be undertaken within a single study.

Step 1 - Production and genotyping of GM mouse

Step 2 - Blood sampling

or

Continued use

Split between a procedure (on the same or different project) under which the mouse with the genetic defect was produced and genotyped (Step 1), with the use continued under a second procedure (Step 2), possibly on a different project, on which the sampling and final preparation for histology are carried out.

In this example Step 1 may be on a project at an establishment that specialises in breeding mice with genetic alterations (under a generic project authorisation) and Step 2 on the project of the scientist studying that particular genetic defect.

Example 4

More complicated situations

Depending on the scientist's intention and the specific design of the study, it may not be immediately clear whether some studies should be regarded as re-use or continued use.

Example:

If the metabolism of a series of drugs is studied in an individual animal this will constitute continued use if serial-data from individual animals which had been used for each preceding study is needed to interpret each subsequent study (a within animal design) and data from a different animal would not have satisfied the scientific objective.

However, if each study is to be interpreted independently of the others and without reference to earlier findings (and therefore any animal could have been used) this will constitute re-use. What actually happens to the animal is the same in each series of studies, but the way in which data are analysed determines whether the subsequent use is regarded as re-use or continued use.

Article 40 - Multiple generic projects

Some classes of projects involve a series of standard procedures being applied for a particular purpose. These are sometimes referred to as “multiple generic projects”. The procedures are generally well-established and the likely consequences on the animals are well-understood and can be minimised appropriately. There are unlikely to be particular novel or contentious issues raised during project evaluation. As in the case of simplified administrative procedure under Article 42, the procedures considered under multiple generic projects are required to satisfy regulatory requirements or needed for production or diagnostic purposes with established methods.

Regulatory toxicology projects are required to deliver certain data for the evaluation of the safety of novel compounds on man, animals and the environment. The Directive 2010/63/EU includes articles which limits the use of animals, but at present, and for the foreseeable future there will remain a need for some such studies. There is generally a prescribed list of requirements for each class of compound which need to be followed to meet the needs of regulatory requirements such as for the production and marketing of pharmaceuticals, chemical substances or for testing the safety of food and feed additives. The animal studies remain reasonably consistent for each class of compound, and the scientific objective remains the same.

Other examples which could be included in this category are projects for antibody production (using well established procedures applying minimum severity procedures) to provide a high quality product for use in specified areas e.g. disease diagnostic kits, and for projects with the objective of producing defined genetically modified lines for a particular purpose e.g. manipulation of genes involved in immune function.

Project evaluation of multiple generic projects should look into the availability of alternative methods taking into consideration the types of compounds to be tested as well as the ways reduction and refinement can be applied in the context of standardised methods.

As with any scientific study, before any animals are used within the framework of such an authorisation, the person responsible for the project must be able to demonstrate that the use of animals is justified for each individual study, that no alternatives could be used, that the minimum numbers of animals are used consistent with the scientific objective and that each study has been designed to reduce to the minimum any pain, suffering, distress or lasting harm.

It is advisable in the framework of the project authorisation of multiple generic projects to draw the attention of the person responsible for the authorised project to the obligation to replace, reduce and refine methods throughout the course of the project to ensure that any changes in the availability of alternatives are duly considered, and utilised as soon as practicable.

Article 41 - Complex or multi-disciplinary projects

Projects vary significantly in their scale and scope; may involve many procedures; may require a variety of species including non-human primates; may include severe procedures likely to have a significant impact on the animals; may raise novel scientific issues or introduce novel issues with regard to animal use.

Projects with many complicated objectives and procedures, which raise unusual (out of the ordinary issues) with regard to the use and care of animals, in particular where high severity is expected, are likely to require more time for detailed consideration during the project evaluation, and in these circumstances there is the provision within Article 41 to extend the period for the authorisation decision to be made.