HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

# Guide to
# Project Applications under Scientific Animal Protection Legislation

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## CONTENTS

## 1 SCOPE

This guidance is intended to assist applicants in completing and submitting a valid 'Application for a project authorisation under scientific animal protection legislation' which must be submitted as part of the project authorisation process. The legislation governing this process is 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).

## 2 INTRODUCTION

In accordance with Article 36 of the Directive and Regulation 24 of the Regulations, projects shall not be performed without prior authorisation from the Health Products Regulatory Authority (HPRA). A project authorisation application form must be submitted and approved in order for work to commence on any project involving the use of animals for research, regulatory or educational purposes.

Article 37 of the Directive and Regulation 25 of the Regulations set out mandatory requirements regarding the information to be submitted to the HPRA as part of an application for project authorisation. Note that an application for a project authorisation must be made to the HPRA, whether or not the project in question has been approved by the user establishment's ethics committee, another regulatory body or any other committee, organisation or person. Project applications will only be accepted from personnel based in user establishments authorised in accordance with the Regulations.

## 3 DEFINITIONS

Refer to Appendix I for relevant definitions relating to the application form.

## 4 APPLICATIONS FOR A PROJECT AUTHORISATION

The application should be completed by the user or project manager on behalf of the user. The user or project manager may be the person responsible for the conduct or supervision of the project procedures.

The project manager must hold a valid individual authorisation (for the purpose of project management) or have submitted an individual authorisation application (pursuant to Part 8 of the Regulations) to the HPRA at the time of applying for a project authorisation. The HPRA will be unable to grant an authorisation for the proposed project until all individuals named within the project application form have been issued with an individual authorisation.

Note that any substantial changes to be made to an ongoing project which was licensed by the Department of Health before 31 December 2012 must be applied for through the HPRA as a new project authorisation. The application must include all of the original project information for procedures yet to be conducted as well as details of the proposed changes. A cover letter should be provided outlining the situation as clearly as possible. A copy of the existing Department of Health project licence should also be provided. The changes to the project may not be implemented until a new HPRA project authorisation has been granted.

The HPRA endeavours to complete the evaluation of project applications within 40 working days. Project applications may be fast-tracked to a 21 working day timeline; however, a supplementary fee is required. As per the Directive and Regulations the HPRA reserves the right to extend the time taken to make a decision regarding an application for a project authorisation to 55 working days when justified by the complexity or the multi-disciplinary nature of the project concerned. However, the HPRA expects this to be a rare occurrence to be considered for exceptional cases only. When such a situation arises, the HPRA will notify the applicant of the additional time required to evaluate the project application prior to the completion of the original timeline outlined by the HPRA upon receipt of the application.

Timeframes may be extended if applications are incomplete or incorrect. Queries raised during the evaluation or a delay in applicants submitting responses to queries may also cause timeframes to be extended.

## 5 SECTION A - PROPOSED AUTHORISATION HOLDER (I.E. USER)

Provide details of the proposed authorisation holder (i.e. user). In an academic setting, the user should be the project manager. In a commercial setting, the user may be the commercial entity.

## 6 SECTION B - PROJECT MANAGER AND BREEDER/SUPPLIER/USER ESTABLISHMENT DETAILS

### 6.1 Project manager and deputy project manager details

Where the project manager is not based in the user establishment where the project or procedures are authorised to be conducted and/or cannot exercise responsibility for day-to-day compliance with the project authorisation and the legislation, a deputy project manager(s) must be appointed by the project manager to undertake all necessary responsibilities during the relevant period of absence. This situation may occur when the overall project manager moves between locations for a substantial period of time when the project is taking place.

In such cases, the deputy project manager undertakes the responsibilities of the project manager for compliance with the project authorisation and the legislation. The deputy project manager(s) must also have an individual authorisation for the purpose of project management.

The suitability of the proposed project manager and deputy project manager(s) (where relevant) must be substantiated through submission of a CV (setting out education, training and experience). A CV template can be found on the 'SAP Guides and Forms' section of www.hpra.ie. Each CV should include a list of any publications on which the proposed project manager or the deputy project manager(s) (where relevant) is an author, together with any additional information which reflects their successful completion of previous animal studies, or which illustrates their suitability to be a project manager or deputy project manager(s).

Note that where a deputy project manager(s) is appointed for the day-to-day management of a project, the project manager ultimately retains legal responsibility for the project.

### 6.2 User establishment details

Procedures must only be performed in an authorised user establishment as part of a valid project authorisation. Information on the user establishment where procedures are proposed to take place must be completed on the form. The HPRA will be unable to grant an authorisation for the proposed project until all user establishments named within the project application form have been issued with a user establishment authorisation. The precise address at which the project will take place must also be provided in the case that the user establishment authorisation refers to multiple sites.

In the case of collaboration between two or more different user establishments on the same project, provide details of the names and authorisation number(s) of each of the user establishments.

An exemption to carry out procedures other than at an authorised user establishment may be granted on the basis of scientific justification. Examples of additional locations include a commercial farm, wild life park or river basin (depending on the species involved). Work carried out at these locations must be conducted in association with an authorised user establishment.

## 7 SECTION C - PROJECT INFORMATION

### 7.1 Project information

Additional details on some of the terms used in section C are given below.

### 7.1.1 Regulatory requirements

The project is being performed solely to confirm regulatory safety or toxicological or quality requirements using established methods in conformity with the demands of a competent regulatory authority.

### 7.1.2 Production or diagnostic purposes

The project is being performed to verify compliance of a batch of a medicinal product with a European monograph, before releasing the medicine to a market; or where animals are used for the production and maintenance of infectious agents, vectors and neoplasms or other biological material.

### 7.1.3 Neuromuscular blocking agents

In accordance with Regulation 19(4) of the Regulations, a user shall not give an animal used in a procedure any drug to stop or restrict the animal from showing pain unless an adequate level of anaesthesia or analgesia is used and a scientific justification for the use of the drug in such a procedure is established.

The project protocol should provide details regarding how the neuromuscular blocking agents will be used, including the anaesthetic and analgesic regimen, the methods available to ventilate the lungs and the methods used to assist in monitoring the depth of anaesthesia (see section 10.2 below).

### 7.1.4 Approval from an establishment ethics committee

Indicate if the project has been approved by a user establishment's ethics committee. If the project has prior ethics committee approval from the user establishment's ethic committee, provide copies of the following documentation:

- the project application as approved by the ethics committee.
- the project protocol as approved by the ethics committee.
- the letter of approval of the ethics committee that identifies any conditions for the conduct of the proposed project.
- report outlining project queries that have been raised and addressed as part of the ethical review process. Alternatively, correspondence to and from the ethics committee relating to the project in which queries have been raised and addressed should be submitted. Please note e-mail correspondence is acceptable.
- signature of approval from a biostatistician, where possible.

### 7.1.5 Expected duration of project work

The maximum period for which a project can run is 5 years.

### 7.1.6 Expected start date of project

Projects cannot be conducted prior to approval being granted by the HPRA. Projects are expected to commence within one year from the date of HPRA authorisation. Where the project does not commence within one year of the date of HPRA project authorisation, a project amendment for the purpose of extending the start date of the project must be submitted to the HPRA.

### 7.1.7 Total number of animals to be used

If multiple species are being used in the project, the total number of animals to be used for each species must be provided.

### 7.1.8 Details of individuals carrying out procedures

All personnel planning to carry out procedures must hold a valid individual authorisation for the purpose of carrying out procedures within the relevant user establishment; therefore the individual authorisation number of each person must be provided. If an individual authorisation number has not been assigned, indicate the date that the application for individual authorisation was submitted. If the project manager and/or deputy project manager(s) will be carrying out procedures, they should also be listed in this section of the form. The HPRA will be unable to grant an authorisation for the proposed project until all individuals named within the project application have been issued their individual authorisation.

Where the proposed project is a collaboration between two or more user establishments, individuals require an individual authorisation for each user establishment at which they plan to carry out procedures on live animals. Further information can be found in the HPRA 'Guide to New and Amendment Applications for Individuals under Scientific Animal Protection Legislation'.

# 8 SECTION D - PROJECT PURPOSE

## 8.1 Project details

This section will assist the HPRA in the project evaluation as required by Article 38 of the Directive and Regulation 31 of the Regulations.

A separate completed project application form must be provided for each separate project proposed. The purpose of any sub-projects included within the project must contribute to the overall objective of the project. It is strongly suggested that projects be kept relatively short and focussed on a particular purpose where possible. Complex projects which comprise

multiple studies that must be conducted in a certain sequence, and whose design is likely to be affected by the results of studies yet to be generated during the project are less likely to be approved by the HPRA under a single 'umbrella' project approval. In this case, each sub-project must be applied for as a separate project.

The HPRA may allow the authorisation of multiple generic projects carried out by the same user if such projects are to satisfy regulatory requirements or if such projects use animals for production or diagnostic purposes with established methods. It is possible that regulatory studies of similar design would fall into this category of approval, but additional information on the nature of the study types (e.g. is the same process used for each study) would need to be provided. Moreover, the HPRA may require details of the test products involved and may limit the duration of any such approval.

When detailing the **purpose** of the project, include the overall project objective(s), clearly setting out the predicted scientific benefits or educational value and/or any justification of the proposed project design from a scientific, educational or legal/regulatory viewpoint. Include information to show that the project is designed so as to enable procedures to be carried out in the most humane and environmentally sensitive manner possible. The degree of detail required depends on the type of project envisaged.

Provide information on the current state of scientific knowledge i.e. whether this is leading edge research (where little information is already available) or relates to new research of an existing and well-defined research area. Provide information on how the objectives of this project differ from findings of previous studies in this area, the merits of the proposed study design and overall value compared to previously conducted studies, so that the HPRA can evaluate whether the predicted harm to the animals is justified by the expected outcome. Evidence of the relevant literature regarding the research performed must be provided. On request, the applicant must provide the HPRA with access to cited references listed here.

Scientific **benefits** may be defined as the gains, insights into disease controls or advances achieved for humans or other target species resulting from animal studies. This information is absolutely essential for the HPRA to conduct a harm-benefit analysis of the project. A project proposal will be considered unacceptable when the harms outweigh the benefits. For example, if the harms to the animals are severe, and the expected benefits low, the outcome of the project evaluation by the HPRA will be a refusal. When describing the potential benefits, the following considerations should be incorporated in the details provided:

- What previously unknown information will be obtained?
- What will the benefit be?
- Who will it benefit?
- How will it benefit them?
- When is this benefit expected to be realised?

General statements (e.g. to find a treatment for cancer) may not be sufficient.

The ultimate benefits of basic/fundamental research to humans, animals or the environment may not be fully known at the time of applying for a project authorisation; however, the following should be clearly outlined:

- the hypothesis
- supporting evidence for the hypothesis
- previous work in the area and the specific knowledge gap(s) that will be filled by the proposed project
- if possible, who/what may ultimately benefits from the work (humans, animals or the environment) and how

Details of the planned **dissemination of results** (e.g. publication plan) should be provided to aid the harm-benefit analysis.

**Feasibility** and resource information are requirement for all projects. These will provide information to support the contention that, if approved, there are sufficient resources available to allow the project to be completed expertly and in conformity with the terms and conditions of any project authorisation granted. Information provided should include:

- the experience, training and expertise of those involved in the project
- availability of the necessary facilities, equipment and reagents
- financial resources available to complete the project (it is expected that financial resources will be obtained prior to submitting a project authorisation application.)

Note that some of the above-mentioned required information may not be required in the same level of detail for projects carried out for regulatory requirements, or which use animals for production or diagnostic purposes with established methods.

## 8.2 Purpose of the project

Choose all relevant project category headings and provide sub-fields if required (see Appendix II for details). These categories have been established by the Directive and the Regulations. Please send any queries relating to completion of the project purpose section to sap@hpra.ie.

### 8.2.1 Basic research

Basic research includes studies of a fundamental nature including physiology. It also includes:

- studies that are designed to add knowledge about normal and abnormal structure,
- functioning and behaviour of living organisms and environment as well as fundamental studies in toxicology,
- investigations and analyses that are focused on a better or fuller understanding of a subject, phenomenon or a basic law of nature instead of on a specific practical application of the results,
- studies relating to the creation of a new genetically altered animal line.

Select if the animals are intended to be used for the creation of a new genetically altered animal line (including crossing of two lines) and intended to be used for the purposes of basic research (e.g. developmental biology, immunology) according to the purpose for which they are being created.

All animals carrying the genetic alteration during the creation of a new line must be included within the project application form. Include animals used in creation e.g. for superovulation, vasectomy and embryo implantation in the project application. Non-genetically altered (wild type) offspring will not be required to be included within the project application form.

The creation of a new genetically altered line requires a project authorisation until such time as the line becomes 'established'. A new line of genetically altered animals is considered to be 'established' when transmission of the genetic alteration is stable, which will be a minimum of two generations, and a welfare assessment has been completed.

A project authorisation is required for 'established' genetically altered lines that produce offspring that may possess a harmful phenotype. The project purpose 'maintenance of colonies of established genetically altered animals, not used in other procedures' should be selected and not 'basic research'. A project authorisation will not be required for 'established' genetically altered lines that produce offspring that are not at risk of developing a harmful phenotype as a result of the genetic alteration.

### 8.2.2 Translational and applied research

This describes the translational and applied research with any of the following aims:

(i) the avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality or their effects in human beings, animals or plants,

(ii) the assessment, detection, regulation or modification of physiological conditions in human beings, animals or plants, or

(iii) the welfare of animals and the improvement of the production conditions for animals reared for agricultural purposes.

This category does not include studies required for regulatory submissions. However, efficacy testing during the development of new medicinal products must be reported under this category.

This category should be selected if the animals are intended to be used for the creation of a new genetically altered animal line (including crossing of two lines) and intended to be used for the purposes of translational or applied research (e.g. cancer research, vaccine development) according to the purpose for which they are being created.

All animals carrying the genetic alteration during the creation of a new line must be included within the project application form. Animals used in creation, such as for superovulation, vasectomy and embryo implantation, should also be included within the project application form. Non-genetically altered (wild type) offspring will not be required to be included within the project application form.

The creation of a new genetically altered line requires a project authorisation until such time when the line becomes 'established'. A new line of genetically altered animals is considered to be 'established' when transmission of the genetic alteration is stable, which will be a minimum of two generations, and a welfare assessment has been completed.

A project authorisation is required for 'established' genetically altered lines that produce offspring that may possess a harmful phenotype. For these projects, the project purpose 'maintenance of colonies of established genetically altered animals, not used in other procedures' should be selected and not 'translational and applied research'. A project authorisation will not be required for 'established' genetically altered lines that produce offspring that are not at risk of developing a harmful phenotype as a result of the genetic alteration.

### 8.2.3 Regulatory use and routine production

This describes the use of animals in procedures performed with a view to satisfying legal requirements for producing, placing and maintaining products/substances on the market, including safety and risk assessments for food and feed.

This also includes animals used in the manufacturing process of products if the manufacturing process requires regulatory approval (e.g. include animals used in the manufacturing serum-based medicinal products within this category).

The efficacy testing during the development of new medicinal products is excluded and should be reported under the category of 'translational and applied research'.

### 8.2.4 Protection of the natural environment in the interests of the health or welfare of human beings or animals

This purpose includes studies aimed at investigating and understanding phenomena such as environmental pollution, loss of biodiversity, and epidemiology studies in wild animals. It excludes any regulatory use of animals for ecotoxicology purposes.

### 8.2.5 Preservation of species

This includes actions in relation to a life-threatening or debilitating condition in which human beings are endangered, and no other species or alternative method would suffice in order to achieve the aims of the procedure.

### 8.2.6 Higher education or training for the acquisition, maintenance or improvement of vocational skills

This includes training to acquire and maintain practical competence in techniques as required under Article 23(2) of the Directive and Regulation 43 of the Regulations. For further information on this type of project, see the HPRA's Guide to Use of Animals for Educational Purposes under Scientific Animal Protection.

### 8.2.7 Maintenance of colonies of established genetically altered animals, not used in other procedures

This category has been as set out by the European Commission and refers to animals required for the maintenance of colonies of genetically altered animals of established lines with an intended harmful phenotype and which have exhibited pain, suffering, distress or lasting harm as a consequence of the harmful genotype. The intended purpose for which the line is being bred is not recorded.

All animals required for the maintenance of such a colony should be included within the project application, including the number of breeding pairs required and number of offspring expected. However this excludes all animals needed for the creation of a new genetically altered line and those used in other procedures (other than creation/breeding).

### 8.2.8 Forensic inquiries

This includes the use of animals by forensic pathologists for legal investigations.

## 9 SECTION E - NON-TECHNICAL PROJECT SUMMARY

A non-technical project summary (NTPS) must be provided to the HPRA for all projects, including projects relating to regulatory and diagnostic testing of chemicals or biological substances. The NTPS is an integral part of a project application. Some of the same headings listed within in the NTPS form are also listed within the project authorisation application form. However, the information specified in the project authorisation form is intended to assist the HPRA in the conduct of the project evaluation and is more technical and detailed than the summarised and non-technical information that will appear in the NTPS. The content of the NTPS should be in simplified lay language only, as the NTPS will be published on the HPRA website for public viewing in accordance with Regulation 33(4) of the Regulations. Refer to the 'Guide to Completing a Non-Technical Project Summary under Scientific Animal Protection Legislation', at www.hpra.ie for further information.

## 10 SECTION F - EXPERIMENTAL DESIGN

The information given in this section relates to the project design and conduct.

### 10.1 Project design - procedure

For each procedure to be carried out, detailed information on the technique involved must be given in the table provided. Each procedure must be numbered in chronological order.

This table can be expanded by copying and pasting sections as many times as required depending on the total number of procedures to be conducted.

An explanation of the terms is provided below:

| | |
|---|---|
| Procedure number | Number each procedure in chronological order. |
| Name of procedure | Name each procedure accurately. For example,<br>- 'intravenous injection of therapeutic substance' (substances should be named where possible),<br>- 'surgical implantation of tumour cells' (location should be named),<br>- 'induction of EAE by subcutaneous injections of inflammatory adjuvant' (adjuvant used should be named where possible). |
| Description/details of procedure | More detailed information about the technique(s) to be performed for that procedure should be provided (e.g. surgical details where relevant). |
| Justification/relevance of procedure | For each procedure to be performed as part of the project, provide details on the relevance of each procedure to the overall project objective. Where substances are being administered, both the route of administration and the substance being administered should be justified. Where an animal model of disease is being used, justification for this model over other available models should be included. |
| Species | Provide information on the species on which the procedure is to be performed. If multiple species are proposed for use in a single procedure, please add a separate procedure for each species. |

| | |
|---|---|
| Life stage or age | Provide the life cycle stage or age of the animal. Examples of life stages include embryo, larval, neonate or adult. |
| Number of animals to be used | The number of animals proposed to undergo the procedure. |
| Duration of procedure | Provide information on the length of time that the procedure will take per animal. If the procedure is a single injection which induces a disease process, the duration should not be the length of time it takes to administer the injection, but rather the length of time the animal will experience suffering due to the disease induction (e.g. the injection of an arthritis-inducing agent). |
| Frequency of procedure, including the total maximum number of times an individual animal will undergo the procedure | Provide information on the total number of times each animal will undergo the procedure as part of the project. For example, if an animal is undergoing a procedure weekly, information must be provided on how many weeks in total this procedure will be conducted and the maximum number of times an animal will undergo the procedure. For example if a procedure is to take place weekly over a six week period, the entry should state 'weekly for a total of six weeks; a total of six times per animal', rather than simply 'weekly'. If within the project different groups of animals are scheduled to undergo a given procedure at different frequencies, please give the range and worst case scenario (i.e. highest frequency) at which any animal will experience the procedure. |
| Proposed severity classification | Procedures are classified as 'non-recovery', 'mild', 'moderate' or 'severe' based on the criteria set out in Article 15 and Annex VIII of Directive 2010/63/EU. |
| Adverse effect(s) | Describe in detail any potential effect(s) of the procedure that will impact negatively on animal welfare, and the likelihood that the adverse effect(s) will occur. Where substances are being administered, both the adverse effects of the route of administration and the adverse effects of the substances being administered should be included. |

| | |
|---|---|
| Humane endpoints | All procedures must have clearly defined procedure-specific humane endpoints, directly related to the adverse effects, describing the stage at which animals will be removed from a study for welfare reasons. If an animal welfare score sheet is used to determine humane endpoints, this should be provided with the application. All projects with procedures classified as 'severe' will require an animal welfare score sheet. |
| Pain-relieving methods | List any methods of reducing pain such as the use of analgesic and/or other methods. |
| Details of anaesthesia | If anaesthesia (e.g. general, sedation, local or topical) is being used please provide this information here. If anaesthesia is not being used, justification must be provided. |
| Additional refinements | In addition to pain-relieving methods and anaesthesia, additional procedure-specific refinements should be outlined. |
| What is the fate of the animals at the end of the procedure? | State the fate of the animals at the end of the procedure i.e. 'euthanised', rehomed', 'rehabilitated and set free', 'continued use under this project authorisation', 're-use in another project authorisation' or 'other' fate of the animals not captured herein. In the case of 'other' please provide details. |
| If the fate of the animals is euthanasia, please state the method of euthanasia | Name the method of euthanasia to be used at the end of the procedure. If the method is a not an approved method as per Annex IV to Directive 2010/63/EU, provide justification for the use of this method. In the case of food-producing animals that are to be allowed to enter the food-chain, information on compliance with consumer requirements (MRL and withdrawal periods) should be provided. |

The predicted **overall severity** of the project should be entered as mild, moderate, severe or non-recovery. The overall severity should take into account all the procedures animals will undergo, the potentially cumulative nature of multiple procedures and the contingent harms (e.g. from transport, housing, handling) to the animals. Where there are numerous groups of

animals that experience different levels of overall severity, the worst case scenario should be entered. For example, if 80% of animals are expected to experience an overall severity of 'mild' and 20% of animals are expected to experience an overall severity of 'severe', the overall severity of the project should be entered as 'severe'. Where relevant, a breakdown of percentages relating to severity should be provided.

**Unexpected adverse effects** which occur must be reported to the designated veterinarian and/or the animal welfare body without delay. If, during the course of an authorised project, the severity classification of a procedure is found to exceed that originally authorised, this should be reported to the animal welfare body immediately and recorded as a project deviation. Project deviations involving increased severity classification of a procedure will require a project amendment application. Refer to the 'Guide to Amendment and Renewal Applications under Scientific Animal Protection Legislation' for further information.

**Euthanasia** should not be listed as a procedure within the project application form and instead should be captured under the question 'What is the fate of the animals at the end of the procedure', where relevant. However, non-recovery procedures (e.g. surgery carried out under terminal general anaesthesia) must be included as a procedure. This includes procedures such as cardiac puncture and cardiac perfusion carried out under general anaesthesia.

The appropriate **breakdown of procedures** within a project is evaluated on a case-by-case basis. It is generally advisable that procedures conducted as part of a single surgery are listed as one procedure only, which encompasses the entire surgical experience for the animal. Generally, the use of anaesthesia and/or analgesia should not be listed as a separate procedure and details should be captured under the questions 'List details of ~~P~~pain relieving methods, ~~and/or~~ including analgesia' and/or 'Provide details of anaesthesia', where relevant.

In most cases **individual housing** of animals is considered a procedure that requires a HPRA project authorisation. When individual housing is planned as part of a project, this should be listed as a procedure within the project application form. If individual housing is not listed as a procedure within a HPRA project authorisation and it transpires during the course of the project that individual housing is required, a project amendment application must be submitted to request the addition of individual housing as a procedure to the HPRA project authorisation.

Assigning the appropriate severity classification for individual housing is evaluated on a case-by-case basis; however factors taken into consideration include the species of animal, age, duration, frequency and any relevant refinement measures proposed. Refinement measures should include visual, auditory and olfactory contact with other animals, as well as additional environmental enrichment. Refer to Appendix III for assistance in assigning the appropriate severity classification for individual housing before review by the HPRA (Appendix III is intended as a guide only and is subject to periodical revisions).

There are certain scenarios in which single housing is not considered a procedure. These scenarios may include:
- individual housing of solitary animals
- separation of animals for routine husbandry purposes (e.g. to prevent fighting)
- temporary isolation to allow recovery from surgery

If in doubt, contact the HPRA for advice (contact details below). A classification request form is available on the HPRA website, which should be completed in order for the HPRA to determine if a project authorisation is required for the study planned.
For procedures which may result in the induction of an **animal model of disease** (including, but not limited to, tumour formation), one procedure should encompass both the initiation of the disease (e.g. injection of cells) and disease progression (e.g. tumour formation). If the induction of the disease involves a surgical procedure which has a different severity classification to the disease progression, these should be entered as two separate procedures. When assigning a proposed severity classification, any subsequent disease progression as a result of the initial induction of the model of disease should be taken into account.

**Ear-punching** where the primary purpose is identification of an animal is not considered to constitute a 'procedure' under the legislation. Ear-punching where the primary purpose is DNA testing is considered to be a 'procedure' under the legislation and will require a project authorisation. If the animals have a harmful phenotype, a project authorisation for the purpose of breeding these animals is required and the ear-punching can be included as a procedure within this application.

**Food restriction/fasting** of animals is considered a procedure that requires a HPRA project authorisation, including but not limited to the following scenarios:
- 16 hours fasting of mice, young hamsters and rats under 100 grams
- 24 hours fasting of rats, rabbits, dogs and cats over 100 grams

A project authorisation may also be required if animals are subjected to repeated periods of food deprivation shorter than detailed above. Food restriction should be avoided in ferrets, guinea pigs and shrews. The duration of fasting should be kept to the absolute minimum required to achieve the scientific benefits of the project.

For studies involving the feeding of **unauthorised feed additives to food-producing animals**, a classification request may be required in order for the HPRA to determine if a project authorisation is required. A classification request form is available on the SAP Guides and Forms section of the HPRA website. The study may also need to be registered with the Department of Agriculture, Food and the Marine. The Department of Agriculture, Food and the Marine should be contacted regardless of whether or not a HPRA project authorisation is required.

### 10.2 Project protocol document

A project protocol must be provided as a separate document. A HPRA project protocol form/template is not available, as due to the diverse nature of projects, there is no format that will satisfy all projects. The project protocol should be as detailed as possible and the overall format of the project protocol should best capture the details of the proposed project.

The project protocol should contain detailed descriptions of each procedure listed within the project application form. Any relevant details for each procedure that may not have been captured within the application form (e.g. more detailed SOPs and/or photographs) should be captured within the project protocol.

In addition to the details of each individual procedure, the flow of procedures for the overall project and per experimental group must be outlined. The overall experience of individual animals and/or groups of animals should be made clear.

Illustrations/schematics/tables/flowcharts should be provided to capture the flow of procedures for each group of animals.

A breakdown of the total number of animals must be clearly accounted for within the project protocol. For project applications consisting of a number of sub-projects, a breakdown of the animal numbers for each sub-project is required. The number of animals for each experimental group within each sub-project must also be clearly broken down.

If the project has been approved by a user establishment's ethics committee, the protocol initially submitted should only contain information that has been approved by the ethics committee. However, please be aware that even if the information required is already outlined within the ethical documentation provided, a project protocol must be submitted as a separate document for each project application, as modifications may be required during the evaluation and for any future amendment applications.

## 11 SECTION G - ANIMAL INFORMATION

### 11.1 Application of methods to replace, reduce and refine the use of animals

This section relates to the application of methods to replace, reduce and refine the use of animals.

The HPRA is dedicated to achieving:

- **Replacement:** a scientifically satisfactory method or testing strategy, not involving the use of live animals, instead of a procedure.
- **Reduction:** a reduction in the number of animals to a minimum without compromising the objectives of the project.

- **Refinement:** refinement of breeding, accommodation and care of animals used for scientific purposes, as well as the refinement of methods used in procedures through eliminating or reducing to the minimum any possible pain, suffering, distress or lasting harm to the animals.

When providing a justification for the numbers of animals to be used, include any statistical parameters used to calculate the sample group size. If an experienced biostatistician has been consulted, details of their level of involvement should be provided, for example, if they were involved at the initial stages of designing the project through to submitting the application to the HPRA, or if it was approved by a biostatistician as part of the local ethics committee review.

### 11.2 Information on animal species

Provide information on the animal species and strains to be used in the project, including information regarding the status of the animal's origin. If more than one animal species, life stage, animal strain/breed or genetic line is to be used, a separate table must be completed for each.

An explanation of the terms is provided below:

| | |
|---|---|
| Species | Provide information on each animal species to be used in this project. If multiple species are proposed for use, complete a separate table for each species. |
| Life stage or age | Provide the life cycle stage or age of the animal species. Examples of life stages include embryo, larval, neonate or adult. |
| Strain / breed | Describe the specific strain/breed of the animal species to be used. For example if the species is mouse, the strain may be C56BL/6. If the species is cattle, the breed may be Holstein Friesian. |
| Genetic status | Select the relevant genetic status. |
| Genetic alteration (if GA) | If the animals are genetically altered, please specify the gene(s) that have been altered and any impact on the phenotype. |
| Supplier establishment | Provide the name and authorisation number of the registered breeder/supplier from whom the animals were sourced, if they are a species from Annex 1 of the Directive and sourced within the Republic of Ireland. |

| | |
|---|---|
| Country of origin | Provide the country from which the animals were sourced.<br>If animals are a species from Annex 1 of the Directive and are sourced outside of the Republic of Ireland, information on the source of the animals and a certificate confirming authorisation and registration of that breeding/supplying establishment under Directive 2010/63/EU (or other non-EU legislation) should be provided. |
| Have these particular animals been previously used in a project (i.e. will this be a 'reuse' of these animals)? | Animals may only be re-used in new projects subject to the conditions set out in Regulation 21 of the Regulations and Article 16 of the Directive. If the animals have been used in previous studies, the following conditions of re-use must be met:<br>- the re-use of the animals must be in accordance with veterinary advice, taking into account the life-time experience of each animal (e.g. approved by the designated veterinarian at the user establishment),<br>- the animal's general state of health and well-being must be fully restored,<br>- the actual severity of the previous procedure(s) must be mild or moderate and further procedures must be mild, moderate or non-recovery. |
| Number of animals to be used | Provide the total number of animals to be used in the project for each species/life stage/strain/breed/genetic alteration. |

## 12 SECTION H – DECLARATION AND UNDERTAKING

The declaration and undertaking must be signed by the applicant (i.e. the user or the project manager on behalf of the user). The user establishment's compliance officer must also sign a declaration and undertaking in the relevant section. If a collaborating user establishment has been entered under section B, the compliance officer of the collaborating user establishment must also sign the relevant declaration and undertaking.

In the event of the project authorisation being granted, by signing the declaration and undertaking these persons are assuming the responsibility for the overall implementation and compliance of the project with the legislation and with respect to fulfilment of the conditions

and obligations as set out in the declaration and undertaking in their user establishment. They are also confirming they will comply with any conditions which may be imposed in the authorisation itself in their user establishment.

## 13 MAKING AN APPLICATION

A project authorisation application consists of the following:
- a complete and signed project application form
- the CV of the proposed project and deputy project managers
- a detailed project protocol
- the non-technical project summary form (in Word format)
- ethics review application and supporting institutional ethics committee approval information, including any report/correspondence in which concerns have been raised and addressed (where applicable)
- certificate confirming authorisation and registration of breeding/supplying establishment as required under Directive 2010/63/EU (or other non-EU legislation) for source of animals (if sourced outside the Republic of Ireland)
- a completed 'Fee Application Form for Scientific Animal Protection' and the appropriate fee (where relevant)
- animal welfare score sheets (where relevant)

A covering letter may also be provided. This is not a requirement, however should be provided in situations where the project application has been prompted by the inability to amend an existing Department of Health project licence (see section 4 above; a copy of the relevant Department of Health project licence should also be submitted in these cases). Signed copies of all application forms must be submitted to the HPRA through submission of a hard copy or scanned original document.

The HPRA requests that project applications and their accompanying documents are named appropriately. Each document should begin with the unique user establishment number of the authorised user establishment where the proposed project is to be carried out. This should be followed by an underscore and the letters 'PAN' (this stands for project application number, as a number will not yet have been assigned to new project applications). This should be followed by an underscore and one of the following words/phrases:
- Application form: to be used for the project application form
- CV: to be used for the project manager CV
- CV2: to be used for the deputy project managers CV (where applicable)
- PP: to be used for the project protocol
- NTPS: to be used for the non-technical project summary
- FEE: to be used for the completed Fee Application Form for Scientific Animal Protection
- COR: to be used for the certificate confirming authorisation and registration of breeder / supplier establishment where animal(s) are bred / supplied in the country of original (if the animal are sourced outside of the Republic of Ireland)

- ECR: Ethics committee approval document, ethics committee review and/or accompanying documentation (where applicable)
- Score sheet: to be used for the animal welfare score sheet (where applicable)
- Appendix (where applicable)
- Cover letter (where applicable)
- DoH: to be used for a Department of Health project licence in situations where the project authorisation (if granted) is to replace an existing Department of Health project licence (where applicable).

The following is an example of how the files should be named for a hypothetical project application from a hypothetical user establishment with the establishment number AE12345.

| DOCUMENT | FILE NAME |
|---|---|
| Project application form | AE12345_PAN_Application form |
| The project manager's CV | AE12345_PAN_CV |
| The deputy project manager's CV | AE12345_PAN_CV2 |
| Project protocol | AE12345_PAN_PP |
| Non-technical project summary | AE12345_PAN_NTPS |
| Certificate of registration | AE12345_PAN_COR |
| Animal welfare score sheet | AE12345_PAN_Score sheet |
| Cover letter | AE12345_PAN_Cover letter |
| Ethics committee application | AE12345_PAN_ECR1 |
| Ethics committee approval document | AE12345_PAN_ECR2 |
| Ethics committee correspondence | AE12345_PAN_ECR3 |
| Fee application form | AE12345_PAN_FEE |

Any supporting documents included with the application should also be named appropriately. In the example given above, the supporting documentation from the ethics committee are numbered sequentially after the letters 'ECR'.

If multiple projects are submitted simultaneously, number each project after 'PAN' for example 'PAN1'and 'PAN2'.

## 14 ADMINISTRATIVE DETAILS

Due to the possible sensitive nature of information contained in project applications, the HPRA provides a secure online system to enable submission of applications and data. This system is known as CESP – the Common European Submission Platform. It is recommended that each establishment nominates one individual to register with CESP. Applicants should liaise with the nominated person within their establishment to organise submission of applications. Nominated persons can contact cesp@hma.eu for further information.

Applications can also be submitted by standard e-mail to sapsubmit@hpra.ie.

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 validation.
Send hard copy applications to:

Receipts and Validation Section
Health Products Regulatory Authority
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2

Applications that do not include the necessary information are not eligible for HPRA evaluation. If an application is incomplete, the applicant will be notified as quickly as possible via the e-mail address on the application form.

Queries in respect of application requirements or communications relating to project applications submitted can be made by telephone, fax, e-mail or by post to the address below:

Scientific Animal Protection Section
Veterinary Sciences Department
Health Products Regulatory Authority
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2

Tel: +353 1 676 4971
Fax: +353 1 676 7836
E-mail: sap@hpra.ie

Fees:
Project applications submitted with prior ethical approval and for evaluation on the standard 40 working day timeline (as described above) are not subject to fees. Applications submitted without prior ethical approval and/or requesting fast-track to a 21 working day timeline for evaluation (as described above) are subject to fees and the evaluation process will not begin without the appropriate fee. Please see the 'Guide to Fees for Scientific Animal Protection', which can be found under SAP Guides and Forms at www.hpra.ie.

## APPENDIX I DEFINITIONS

**Compliance officer** – the person indicated in Regulation 44 of the S.I. who is responsible for ensuring compliance with the provisions of S.I. No. 543 of 2012.

**Project manager** – the person who holds a project manager authorisation pursuant to Part 8 of S.I. No. 543 of 2012 and is responsible for the overall implementation of the project and its compliance with the project authorisation. The project manager shall ensure that:

a) any unnecessary pain, suffering, distress or lasting harm that is being inflicted on an animal in the course of a procedure is stopped,
b) the project is carried out in accordance with the relevant project authorisation and
c) in the event of non-compliance, the appropriate measures to rectify it are taken and recorded.

**Additional location** – an additional premises, other than the authorised establishment, where procedures and/or methods of euthanasia are conducted in accordance with S.I. 543/2012 e.g., a commercial farm, wild life park or river basin (depending on the species involved). Procedures and/or methods of euthanasia carried out at these locations must be conducted in association with the relevant authorised breeder/supplier/user establishment.

**Breeder** – any natural or legal person breeding animals referred to in Annex I to Directive 2010/63/EU with a view to their use in procedures or for the use of their tissue or organs for scientific purposes, or breeding other animals primarily for those purposes, whether for profit or not.

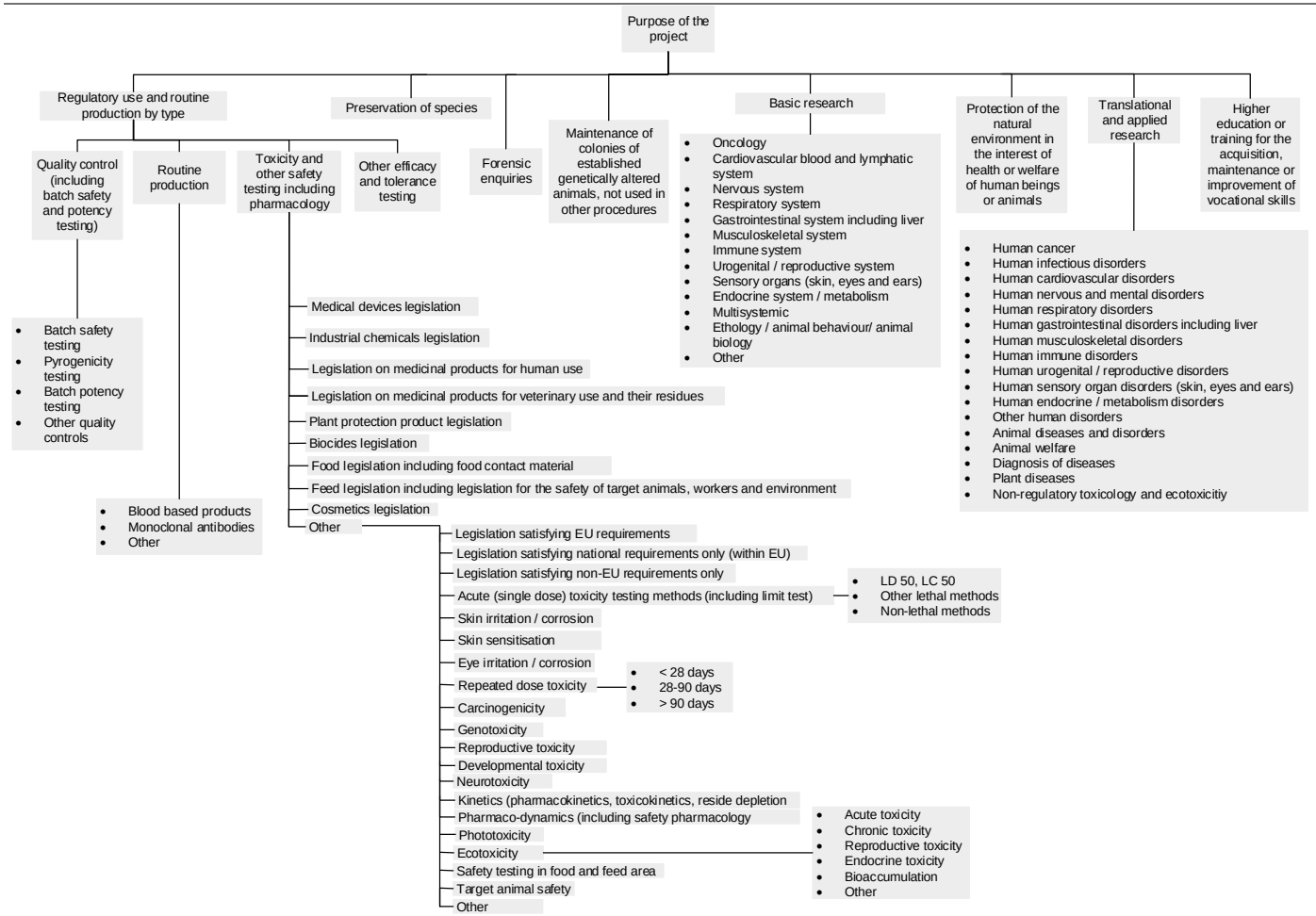
**Supplier** – any natural or legal person, other than a breeder, supplying animals with a view to their use in procedures or for the use of their tissue or organs for scientific purposes, whether for profit or not.

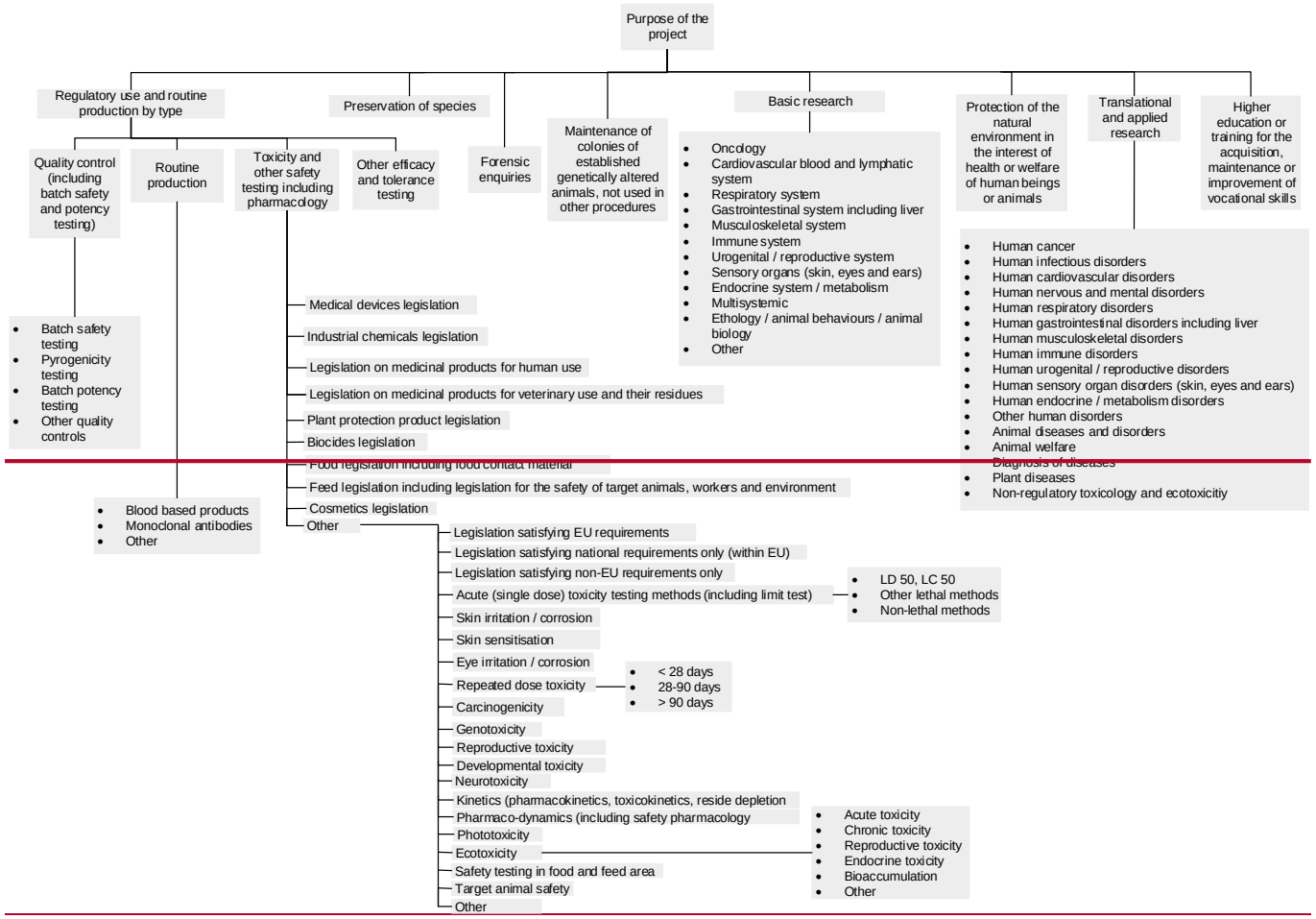
**User** – any natural or legal person using animals in procedures, whether for profit or not.

**Procedure** – 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, distress or lasting harm equivalent to, or higher than, that caused by the introduction of a needle in accordance with good veterinary practice. This includes any course of action intended, or liable, to result in the birth or hatching of an animal or the creation and maintenance of a genetically modified animal line in any such condition, but excludes the killing of animals solely for the use of their organs or tissues.

**Project** – a programme of work having a defined scientific objective and involving one or more procedures.

## APPENDIX II PURPOSE OF PROJECTS


Purpose of the project
Regulatory use and routine production by type
Quality control (including batch safety and potency testing)
Routine production
Toxicity and other safety testing including pharmacology
Other efficacy and tolerance testing
Preservation of species
Forensic enquiries
Maintenance of colonies of established genetically altered animals, not used in other procedures
Basic research
Protection of the natural environment in the interest of health or welfare of human beings or animals
Translational and applied research
Higher education or training for the acquisition, maintenance or improvement of vocational skills
Batch safety testing
Pyrogenicity testing
Batch potency testing
Other quality controls
Blood based products
Monoclonal antibodies
Other
Medical devices legislation
Industrial chemicals legislation
Legislation on medicinal products for human use
Legislation on medicinal products for veterinary use and their residues
Plant protection product legislation
Biocides legislation
Food legislation including food contact material
Feed legislation including legislation for the safety of target animals, workers and environment
Cosmetics legislation
Other
Legislation satisfying EU requirements
Legislation satisfying national requirements only (within EU)
Legislation satisfying non-EU requirements only
Acute (single dose) toxicity testing methods (including limit test)
LD 50, LC 50
Other lethal methods
Non-lethal methods
Skin irritation / corrosion
Skin sensitisation
Eye irritation / corrosion
Repeated dose toxicity
< 28 days
28-90 days
> 90 days
Carcinogenicity
Genotoxicity
Reproductive toxicity
Developmental toxicity
Neurotoxicity
Kinetics (pharmacokinetics, toxicokinetics, reside depletion
Pharmaco-dynamics (including safety pharmacology
Phototoxicity
Ecotoxicity
Acute toxicity
Chronic toxicity
Reproductive toxicity
Endocrine toxicity
Bioaccumulation
Other
Safety testing in food and feed area
Target animal safety
Other
Oncology
Cardiovascular blood and lymphatic system
Nervous system
Respiratory system
Gastrointestinal system including liver
Musculoskeletal system
Immune system
Urogenital / reproductive system
Sensory organs (skin, eyes and ears)
Endocrine system / metabolism
Multisystemic
Ethology / animal behaviour/ animal biology
Other
Human cancer
Human infectious disorders
Human cardiovascular disorders
Human nervous and mental disorders
Human respiratory disorders
Human gastrointestinal disorders including liver
Human musculoskeletal disorders
Human immune disorders
Human urogenital / reproductive disorders
Human sensory organ disorders (skin, eyes and ears)
Human endocrine / metabolism disorders
Other human disorders
Animal diseases and disorders
Animal welfare
Diagnosis of diseases
Plant diseases
Non-regulatory toxicology and ecotoxicitiy


Purpose of the project
Regulatory use and routine production by type
Preservation of species
Forensic enquiries
Maintenance of colonies of established genetically altered animals, not used in other procedures
Basic research
Protection of the natural environment in the interest of health or welfare of human beings or animals
Translational and applied research
Higher education or training for the acquisition, maintenance or improvement of vocational skills
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Routine production
Toxicity and other safety testing including pharmacology
Other efficacy and tolerance testing
Batch safety testing
Pyrogenicity testing
Batch potency testing
Other quality controls
Blood based products
Monoclonal antibodies
Other
Medical devices legislation
Industrial chemicals legislation
Legislation on medicinal products for human use
Legislation on medicinal products for veterinary use and their residues
Plant protection product legislation
Biocides legislation
Food legislation including food contact material
Feed legislation including legislation for the safety of target animals, workers and environment
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LD 50, LC 50
Other lethal methods
Non-lethal methods
Skin irritation / corrosion
Skin sensitisation
Eye irritation / corrosion
Repeated dose toxicity
< 28 days
28-90 days
> 90 days
Carcinogenicity
Genotoxicity
Reproductive toxicity
Developmental toxicity
Neurotoxicity
Kinetics (pharmacokinetics, toxicokinetics, reside depletion
Pharmaco-dynamics (including safety pharmacology
Phototoxicity
Ecotoxicity
Acute toxicity
Chronic toxicity
Reproductive toxicity
Endocrine toxicity
Bioaccumulation
Other
Safety testing in food and feed area
Target animal safety
Other
Oncology
Cardiovascular blood and lymphatic system
Respiratory system
Gastrointestinal system including liver
Musculoskeletal system
Immune system
Urogenital / reproductive system
Sensory organs (skin, eyes and ears)
Endocrine system / metabolism
Multisystemic
Ethology / animal behaviours / animal biology
Other
Human cancer
Human infectious disorders
Human cardiovascular disorders
Human nervous and mental disorders
Human respiratory disorders
Human gastrointestinal disorders including liver
Human musculoskeletal disorders
Human immune disorders
Human urogenital / reproductive disorders
Human sensory organ disorders (skin, eyes and ears)
Human endocrine / metabolism disorders
Other human disorders
Animal diseases and disorders
Animal welfare
Diagnosis of diseases
Plant diseases
Non-regulatory toxicology and ecotoxicitiy

## APPENDIX III SEVERITY CLASSIFICATIONS FOR SINGLE HOUSING

| | Mild | Moderate | Severe |
|---|---|---|---|
| Metabolic caging (all species) | <24hr | 1-5 days | >5days |
| Dogs | 4 hrs - 1 month | >1 month | Single housing may be considered severe in scenarios where appropriate refinements are not in place, however this is determined on a case-by-case basis during the project evaluation |
| Cats | 24hrs - 1 month | >1 month | |
| Rats | 12hrs - 1 month | >1 month | |
| Mice | 24hrs - 1 month | >1 month | |
| Rabbits (young or female) | 24hrs - 1 month | >1 month | |
| Ferrets | 24hrs - 1 month | >1 month | |
| Sheep | 24hrs - 1 month | >1 month | |
| Pigs | 1wk – 6 months | >6 months | |
| Cattle | 1wk – 6 months | >6 months | |
| Guinea pigs | 24hrs – 1 month | >1 month | |

Please note that the severity of single housing is evaluated on a case-by-case basis. The severities outlined above are based on a 'best case scenario' whereby animals receive all suitable refinements. This table is intended as a guide only and is subject to revision.