HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Project Applications under 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.

CONTENTS

1 SCOPE

This guidance is intended to assist applicants in completing and submitting a valid Health Products Regulatory Authority (HPRA) '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 (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 HPRA. A project authorisation application form must be submitted and approved 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 either the project authorisation holder (user) or project manager on behalf of the user.

The project manager must hold a valid individual authorisation (for the purpose of project management in the relevant species) 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 the project manager and any deputy project manager(s) named within the project application form have been issued with an individual authorisation for the purpose of project management.

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. 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.

It should be noted that the above timelines do **not** include the time taken for the receipt and validation of the applications by the HPRA. Applications are not validated as eligible for HPRA scientific animal protection (SAP) evaluation until all necessary documentation has been provided and, where necessary, the correct fee paid. Further, the time taken by applicants to respond to queries is not part of the evaluation timeline (the system 'stops the clock' on applications for the duration of the period when satisfactory responses to queries are awaited).

5 APPLICATION FORM: SECTION A - PROJECT TITLE AND PROPOSED PROJECT AUTHORISATION HOLDER (I.E. USER)

Provide the project title and details of the proposed authorisation holder (i.e. user). The project authorisation holder can be a person or a legal entity. The user's address, Eircode, email address and telephone number should be provided.

6 APPLICATION FORM: SECTION B - PERSONNEL AND BREEDER/SUPPLIER/USER ESTABLISHMENT DETAILS

6.1 Project manager and deputy project manager details

The project manager is responsible for the overall implementation of the project and its compliance with the project authorisation. If 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 must be appointed by the project manager to undertake all necessary responsibilities during the relevant period of absence. This situation may occur, for example, when the overall project manager moves between locations for a substantial period of time when the project is taking place. More than one deputy project manager may be appointed if required.

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 must also have an individual authorisation for the purpose of project management.

The suitability of the proposed project manager and deputy project managers (where relevant) must be substantiated through submission of a CV (setting out education, training and experience). A CV template can be found in the SAP submission documents section of the HPRA

website, however the HPRA will accept CVs in other templates. 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, where any of their work has translated, e.g. into clinical trials, or any other relevant information which illustrates their suitability to be a project manager or deputy project manager.

Note that where a deputy project manager(s) is appointed for the day-to-day management of a project, the project manager retains ultimate responsibility for the overall implementation of the project and its compliance with the project authorisation.

For information relating to requirements for individuals who will be carrying out procedures, please see Appendix II.

6.2 Details of previous project authorisations

Details of all HPRA project authorisations held by the project manager **and** the deputy project manager(s) in the past five years must be listed here.

6.3 User and collaborating establishment details and additional locations

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 entered 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 user establishment authorisations. If the user establishment authorisation refers to multiple sites, the precise site at which the project will take place must be provided.

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

Additional locations are unauthorised locations such as a commercial farm, wildlife park or river basin. An exemption to carry out procedures other than at an authorised user establishment may be granted on the basis of scientific justification.

7 APPLICATION FORM: SECTION C - PROJECT INFORMATION

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

7.1 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.

7.2 Production or diagnostic purposes

This is where animals are used for the production and maintenance of, for example, infectious agents, or other biological material such as blood-based products.

7.3 Neuromuscular blocking agents

A neuromuscular blocking agent (NMBA) is a drug that produces paralysis of the skeletal muscles. 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. Special care is necessary when using neuromuscular blocking agents systemically because they specifically block neuromuscular transmission, causing paralysis, yet have no significant central effects and therefore will not induce analgesia, unconsciousness, or even sedation. The use of NMBAs is therefore quite challenging and requires concomitant skill in the delivery and monitoring of anaesthesia, hence the HPRA requirement for rigorous and robust justification for their use in any project. Furthermore, permission for the use of NMBAs is granted on an individual level, and each member of personnel intending to use NMBAs under a given project authorisation must also hold individual authorisation to do so.

The project protocol should provide details regarding how the NMBAs 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, as well as information on the skill and expertise of those delivering anaesthesia.

7.4 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, 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

- The 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 (email correspondence is acceptable)
- The signature of approval from an experienced statistician, where possible

7.5 Expected duration of project work

The maximum period for which a project can be authorised is 60 months. Projects authorised for periods of less than 60 months can be renewed at a later date; however, projects authorised for 60 months cannot be renewed.

7.6 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. The project amendment application form and guide can be found in the SAP submission documents section and Guidance documents section, respectively, on the HPRA website.

7.7 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.

8 APPLICATION FORM: SECTION D - PROGRAMME OF WORK

8.1 Purpose of the project

Choose the most relevant project category heading (see Appendix III for a visual overview of the project purposes and categories and Appendix IV for a more detailed description) and select sub-fields from the drop-down lists, if required. These categories have been established by the European Commission for reporting purposes.

In some projects it is possible that more than one project purpose may be appropriate – for example, if the first part of the study is more of a fundamental nature, this would be 'basic research', and if the second part of the study is a therapeutic study, this would be 'translational and applied research'. When reporting the animal numbers in the annual statistical returns to the HPRA, each group of animals should be reported only once, and under the most relevant project purpose.

8.2 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 authorisation.

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 study design relevant 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.

Information must be provided 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. When detailing the overall purpose of the project, include the project objective(s), clearly setting out what is hoped to be achieved from this project, as well as any justification of the proposed project from a scientific or legal/regulatory viewpoint. Include information on how this project is novel, compared to previous studies in this area. Provide information on how the objectives of this project differ from findings of previous studies in this area, and 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.

Scientific **benefits** may be defined as the potential gains, insights into disease, or advances achieved for humans, other species, or the environment 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 ineligible for approval if the harms are determined to outweigh the benefits. For example, if during a project evaluation it is determined by the HPRA that the proposed harms to animals to be used in the project are severe, and the expected benefits are minor or questionable, then the harm-benefit analysis for this application will not be favourable, and 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:

- A description of the potential benefits, ensuring that they are realistic
- Whether the potential benefits will be obtainable within this project, or if a further project will be required, e.g. projects which aim to establish a disease model, before using those models in another project to evaluate treatments for that model
- The potential advances in scientific knowledge which could be obtained, and the value of this knowledge
- Why these potential benefits are important
- Who will potentially benefit
- An estimation of when any potential benefits may be expected to be realised
- A description of how the benefits are likely to be realised (e.g. by your research group, other researchers, the pharmaceutical industry, clinicians, human patients or animals)

Note: general or very broad statements (e.g. to find a treatment for cancer) are not 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 and the supporting evidence for the hypothesis, including any relevant preliminary data from prior studies or *in vitro* experiments
- Previous work in the area and the specific knowledge gap(s) that will be filled by the proposed project
- The expected impact and strength of the research and its expected contribution to the field

Details of the planned **dissemination of results** (e.g. publication plan) should be provided to aid the harm-benefit analysis. A publication plan should include plans to publish negative results (should that be the outcome of the study) to reduce publication bias which is a current challenge facing the future of science.

Feasibility and resource information are requirements 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 and will be in place for the entire duration of the project)

9 APPLICATION FORM: SECTION E - NON-TECHNICAL SUMMARY

A non-technical summary (NTS) must be provided to the HPRA for all projects and is an integral part of a project application. The information in the NTS is intended to be clear, concise and understandable to the layperson (e.g. a teenager/young adult with very basic scientific knowledge). It should be noted that the information specified in the project authorisation application 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 NTS. The NTS is anonymous and therefore identifying information such as academic institutions/faculties in which the research will be carried out should **not** be included. The content of the NTS should be written in the **third person only** (i.e. terms such as 'our research group' and 'we' should be avoided) and in simplified lay language only (assume a reading age of 12). The NTS will be submitted for publication to the European Commission's open access ALURES EU NTS Database, in accordance with Regulation 33(45) and (6) of S.I. No. 543 of 2012 as amended by S.I. No. 324 of 2020.

In November 2020, the European Commission developed a common template for the submission of NTSs, and a guidance document has been published to assist users in completing submissions. The NTS template is available in the SAP submission documents section of the HPRA website and the guidance document can be found on the EU Publications Office website. The HPRA 'Guide to Technical Specifications for Completion of Non-technical Project Summaries' which can be found in the SAP Guidance documents section, provides information in technical specifications required for entering data in the European Commission template. When drafting the NTS, the following general points apply:

- The summary should accurately capture the details of the project.
- Acronyms and abbreviations should only be used after their meaning has been clarified and explained in full.
- All the benefits that could potentially be accrued should be clearly stated to adequately explain why the proposed work is important.
- References and citations should be removed.
- Detailed information about statistical calculations should be removed and replaced with a lay persons' explanation of the design of the study
- Information should be anonymous and names of places or people removed.
- Applicants should adhere strictly to specified character counts.

The NTS must be tested on the European Commission File Quality Control module prior to submission to confirm there are no validation errors. Submissions will be returned to applicants for correction if they are deemed unsuitable for publication, and the project evaluation 'clock stopped' until a satisfactory NTS is received.

10 APPLICATION FORM: SECTION F - EXPERIMENTAL DESIGN

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

10.1 Details of procedures

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:

Term	Explanation of term
Procedure number	Select a procedure number from the drop-down list.
Procedure name	Name each procedure accurately to convey the experience of the animal. For example: - 'IV injection of therapeutic substance' (class of substance should be named where possible) - 'surgical implantation of tumour cells to induce tumour growth' (location of implantation should be named) - 'induction of EAE by SC injections of inflammatory adjuvant' (adjuvant used should be named where possible) - 'breeding and maintenance of genetically altered line of kidney disease'
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.

Term	Explanation of term
Species	Provide information on the species on which the procedure is to be performed.
Life stage or age	Provide the life cycle stage or age of the animal. Examples of life stages include embryo, larval, neonate, adolescent or adult.
Number of animals to be used	The number of animals proposed to undergo the procedure (including any additional required for attrition where relevant).
Frequency of procedure (how many times will the procedure be performed?)	Provide information on the maximum total number of times each animal will undergo the procedure as part of the project. Examples include: - 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. - 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. Please include the time which will elapse between each frequency (i.e. 'four times over a total of two weeks', rather than 'four times').

Term	Explanation of term
Duration (how long will the procedure take and how long will the animal be affected for?)	Provide information on the length of time that the procedure will take per animal. If the procedure is a surgery, provide the duration of the surgery (e.g. 'two hours') and the duration of any intended impacts on the animal (e.g. 'four weeks of neurological deficits'). 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 may have a duration of eight weeks).
Proposed severity classification	Select a severity from the drop-down list. Procedures are classified as 'non-recovery', 'mild', 'moderate' or 'severe' based on the criteria set out in Article 15 and Annex VIII to Directive 2010/63/EU. The European Commission guidance documents on severity assessment containing illustrative examples for the process of severity classification is also a useful reference in prospective severity classification.
Adverse effect(s)	Describe in detail any potential effect(s) (physical and emotional) of the procedure that will impact negatively on animal welfare, and the percentage likelihood that each 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.
Attrition rate	Estimate the percentage of animals that may not reach the pre-determined end-point of the experiment and outline the reasons (e.g. being culled early due to reaching humane endpoints, anaesthetic deaths, failure of animal model) and give a breakdown of the estimated percentages of animals that fall into each of these categories.

Term	Explanation of term
Humane endpoints	All procedures must have clearly defined procedure-specific humane endpoints, directly related to the adverse effects, describing the criteria which will determine when animals will be removed from a study for welfare reasons (e.g. weight loss of ≥20 percent, ulceration of tumour, etc.). If an animal welfare score sheet is used to determine humane endpoints, this must be provided with the application. All projects with procedures classified as 'moderate' or 'severe' will require an animal welfare score sheet (and in some instances procedures with an assigned severity of 'mild' may also require a scoresheet).
Details of anaesthesia	If anaesthesia (e.g. general, sedation, local or topical) is being used, provide relevant details of agents to be used here (including dosages). If anaesthesia is not being used, justification must be provided.
Details of analgesia	Provide details of analgesia including dosing regimens. If analgesia is not being used, justification must be provided.
Additional refinements	Other than pain-relieving methods and anaesthesia, additional procedure-specific refinements should be outlined. These refinements do not need to be novel refinements devised specifically for this project. It is important to include refinements which have already been identified through prior experience or literature research (e.g. provision of heat to avoid hypothermia associated with anaesthesia). Please note that refinements are a legal requirement. Entries of 'not applicable' are not acceptable.
What is the fate of the animals at the end of the procedure?	Select the fate of the animals at the end of the procedure from the drop-down list.

Term	Explanation of term
If the fate of the animals is euthanasia, choose the method	Select the method of euthanasia to be used at the end of the procedure from the drop-down list. If the method is 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 (maximum residue level and withdrawal periods) should be provided. The use of decapitation for rodents will also require justification, as this method should only to be used if other methods are not possible.

The predicted **overall severity** of the project should be selected from the drop-down list as non-recovery, mild, moderate, or severe. The overall severity should consider all the procedures animals will undergo, their phenotype if genetically altered (i.e. they may be purchased with a harmful phenotype from another supplier), 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 percent of animals are expected to experience an overall severity of 'mild' and 20 percent 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.

10.2 Points to note

- **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. The administration of anaesthesia and/or analgesia should not be listed as a separate procedure and details should be captured under the relevant fields, i.e. details of anaesthesia/details of analgesia, 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. 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 to mitigate against isolation and boredom in animals that are individually housed should include visual, auditory and olfactory contact with other animals, as well as additional environmental enrichment, and for some species, human interaction (e.g. dogs and cats). Refer to Appendix V for assistance in assigning the appropriate severity classification for individual housing before review by the HPRA (Appendix V is intended as a guide only and is subject to periodic revisions – final decisions on the prospective severity of individual housing procedures will be taken on a case-by-case basis taking into consideration the whole experience of the animal on study).

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

  If in doubt, contact the HPRA for advice (see contact details below in section 14).

- For procedures which may result in the induction of an **animal model of disease** (for example, tumour formation), one procedure should encompass both the initiation of the disease (e.g. injection of cells) and disease progression (e.g. tumour development).

- **Ear-punching**, where the primary purpose is identification of an animal, is not considered to constitute a 'procedure' under the legislation. However, ear-punching which is not being performed for the purposes of identifying the animal but rather the primary purpose is DNA testing (genotyping), and any subsequent collection of tissue when the animal is already identifiable, is considered to be a 'procedure' under the legislation and will require a project authorisation. If the animals have a harmful phenotype, or have an unknown phenotype (because a new line is being created), the **breeding and/or maintenance of these animals** is considered a procedure and should be included as a procedure in Section F. The genotyping can be a part of this procedure within the application. For more information on this topic, refer to section 12 of this guide.

- **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 or more of fasting of mice, young hamsters and rats under 100 grams
  - 24 hours or more of 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 for the HPRA to determine if a project authorisation is required. A classification request form can be found in the SAP submission documents section of the HPRA website. The study may also need to be registered with the Department of Agriculture, Food and the Marine (DAFM). DAFM should be contacted regardless of whether or not a HPRA project authorisation is required.

10.3 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 and their chronological order for each group of animals.

A clear breakdown of the total number of animals must be included 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 to the HPRA 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 APPLICATION FORM: SECTION G - THE 3RS AND WELFARE MONITORING

11.1 Application of the 3Rs

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. Where replacement is not possible, animal use must only be permitted where justified and where the expected benefits outweigh the potential adverse effects.
- **Reduction**: Appropriately designed and analysed animal experiments that are robust and reproducible, and truly add to the knowledge base.
- **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 (and sex) of animals to be used, include any statistical parameters used to calculate the sample group size. If an experienced statistician 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 statistician as part of the local ethics committee review. The NC3Rs website is an excellent resource to assist in optimal experimental design and includes information on experimental design supports such as the Experimental Design Assistant (EDA), and the ARRIVE Guidelines to maximise the quality and reliability of published research. These resources should be consulted in the design phase of all studies.

11.2 Animal welfare monitoring arrangements

Provide details about how the welfare of the animals will be monitored and scored throughout the project, including details on the use of score sheets. It is important to note that the word 'monitor' is not interchangeable with the word 'score', with 'monitor' referring to daily health observations and 'score' referring to the use of the score sheets. Details about who will monitor and score on the animals should be included. The frequency and duration of both general daily monitoring and scoring should also be included.

12 APPLICATION FORM: SECTION H - ANIMAL INFORMATION

12.1 Animals to be used

Provide information about the animals to be used in the project, i.e. if they are listed in Annex I to Directive 2010/63/EU, and whether they have been bred specifically for use in scientific procedures, if they are wild animals, endangered animals or stray/feral animals. The HPRA may grant exemptions for the above, but only based on scientific justification.

12.2 Animal species and strains

Provide information on the animal species and strains to be used in the project, including information regarding the status of the animals' 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:

Term	Explanation of term
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, adolescent 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; or if the species is cattle, the breed may be Holstein Friesian. For genetically altered animals, it is recommended to provide full details of the transgene and any reference identifiers for the strain.
Genetic status	Select the relevant genetic status from the drop-down list. Please note, the European Commission defines genetically altered animals as genetically modified (transgenic, knock-out and other forms of genetic alteration) **and** naturally occurring or induced mutant animals. Therefore, animals do not have to have been intentionally genetically modified to be classified as genetically altered.

Term	Explanation of term
Genetic alteration (GA)	If the animals are classed as genetically altered, describe the phenotype and details on any adverse effects of the genetic alteration, including the chronology of their development. Please note if you are breeding or maintaining genetically altered animals with an established harmful phenotype, or creating a new line, the breeding of these animals should be captured as a procedure in Section F. For the creation of a new genetically altered line, all animals carrying the genetic alteration must be included in the breeding procedure, including those used for colony maintenance breeding. Wild-type animals used solely as breeders are not required to be included, however all offspring, regardless of genotype, should be included. Animals used for superovulation, vasectomy and embryo implantation should also be included. For the breeding and maintenance of established lines of a known phenotype, all animals carrying the genetic alteration should be included (i.e. animals which are homozygous and heterozygous for the transgene, even for strains with recessive mutations). Note that breeding of harmful lines by crossing het x het or het x wild-type to reduce (or eliminate) the risk for expressing a harmful phenotype still requires authorisation. Guidance on the reporting of genetically altered animals in annual statistical returns is detailed later in Appendix IV.
Refinements and monitoring arrangements	If the phenotype is harmful, details should be provided about the refinements that will be put in place to ensure animal welfare. Details about the monitoring/scoring arrangements and the humane endpoints which will be implemented should also be included. A score sheet should be included, if relevant.
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 I of the Directive.
Country of origin	Provide the country from which the animals were sourced.

Term	Explanation of term
Reuse	Reuse refers to animals that have already been used in a previous experiment/project. Animals may only be reused 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 reuse must be met: (i) the reuse of the animals must be in accordance with veterinary advice, considering the life-time experience of each animal (e.g. approved by the designated veterinarian at the user establishment), (ii) the animal's general state of health and well-being must be fully restored, (iii) the actual severity of the previous procedure(s) must be mild or moderate and further procedures must be non-recovery, mild or moderate. Applicants must clarify whether these conditions have been met or not, by selecting the actual severity of previous procedures and by selecting yes/no answers to the appropriate questions.
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.

13 APPLICATION FORM: SECTION I - DECLARATION AND UNDERTAKING

The declaration and undertaking must be signed by the proposed project authorisation holder (i.e. the user), the proposed project manager and the compliance officer(s).

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.

14 MAKING AN APPLICATION

14.1 Checklist

A project authorisation application consists of the following:
- A complete and signed project application form (minimum of three signatures required)
- An up to date/recent CV of the proposed project and any deputy project manager(s)
- A detailed project protocol
- The non-technical summary form (in Excel format)
- Ethics review application and supporting institutional ethics committee approval information, including any report/correspondence in which queries have been raised and addressed (where applicable)
- A completed 'Fee Application Form for Scientific Animal Protection' and the appropriate fee (where relevant)
- Animal welfare score sheets (where relevant)

A cover letter may also be provided; however, this is not a requirement.

14.2 Naming convention

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's CV
- CV2: to be used for the deputy project manager's CV (where applicable)
- PP: to be used for the project protocol
- NTS: to be used for the non-technical summary
- FEE: to be used for the completed fee application form for scientific animal protection
- 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)

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

DOCUMENT	FILE NAME
The project manager's CV	AE12345_PAN_CV
The deputy project manager's CV	AE12345_PAN_CV2
Project protocol	AE12345_PAN_PP
Non-technical summary	AE12345_PAN_NTS
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 to be submitted at the same time, a separate email or CESP submission should be used for each set of project application documents.

14.3 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 email to sapsubmit@hpra.ie.

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

Queries in respect of application requirements or communications relating to project applications submitted, but not yet evaluated, can be made by telephone or email.
Tel: +353 1 676 4971
Email: sap@hpra.ie

Queries or communications relating to the ongoing evaluation of a project should be made by emailing sapsubmit@hpra.ie.

14.4 Fees

Project applications submitted with prior ethical approval and for evaluation using 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 before receipt of the appropriate fee. Please see the 'Guide to Fees for Scientific Animal Protection', which can be found in the SAP Guidance documents section of the HPRA website.

APPENDIX I DEFINITIONS

Additional location – an additional premises, other than the authorised establishment, where procedures and/or methods of euthanasia are conducted in accordance with the Regulations, e.g. a commercial farm, wildlife 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.

Compliance officer – the person indicated in Regulation 44 of the Regulations who is responsible for ensuring compliance with the provisions of the Regulations.

Procedure – any use, invasive or non-invasive, of an animal for experimental or other scientific purposes, with known or unknown outcome, or for 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.

Project authorisation holder/user – any natural or legal person using animals in procedures, whether for profit or not.

Project manager – the person who holds an individual authorisation for the purpose of project management pursuant to Part 8 of the Regulations and is responsible for the overall implementation of the project and its compliance with the project authorisation. The project manager shall ensure that:

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

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.

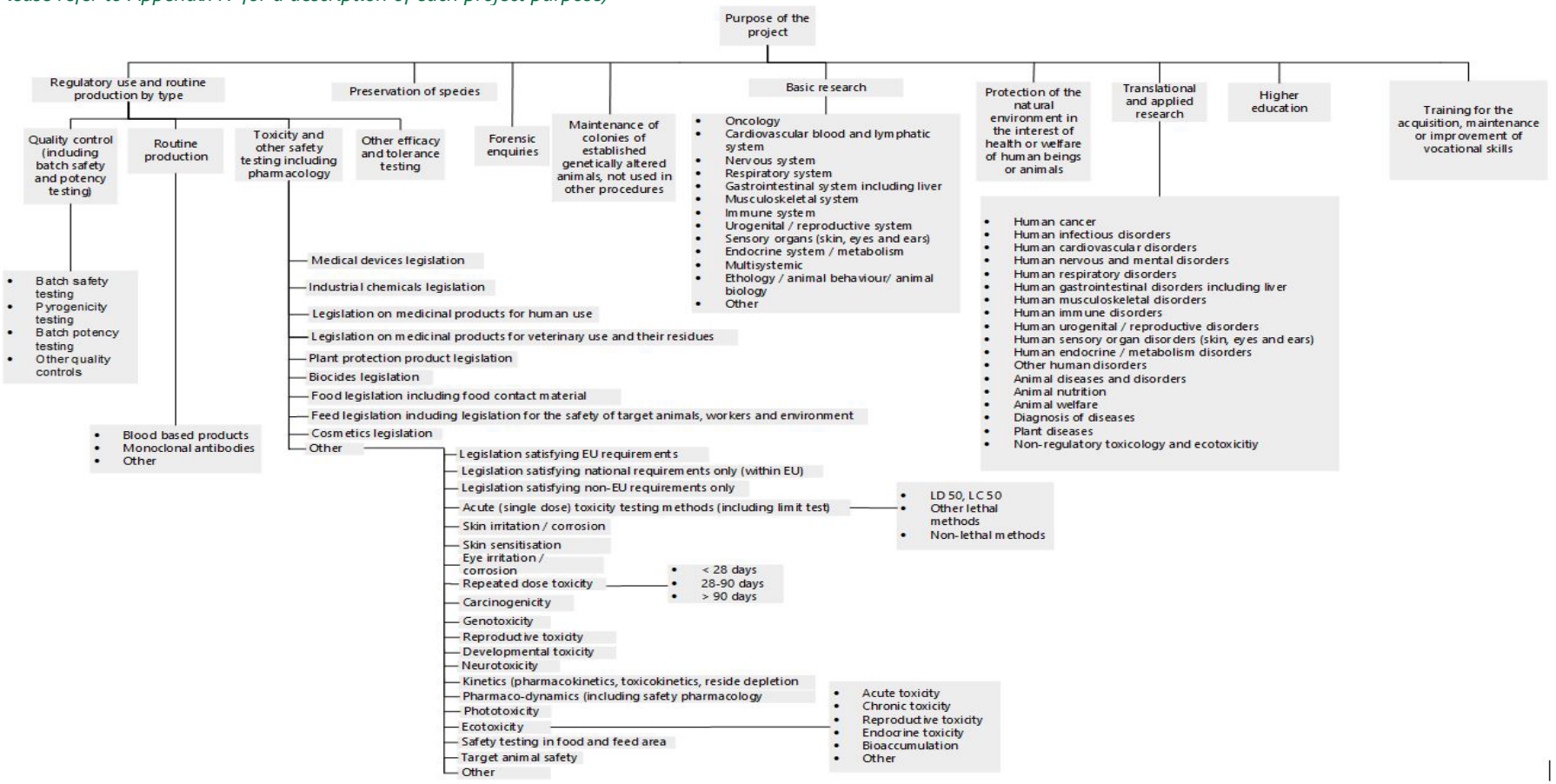
APPENDIX II DETAILS OF INDIVIDUALS CARRYING OUT PROCEDURES

There is no requirement for individuals who will be carrying out procedures to be named on the project authorisation document. It is important to note, however, that all personnel planning to carry out procedures must hold a valid individual authorisation for the relevant species, and within the relevant user establishment. It is ultimately the project authorisation holder's responsibility to ensure that all individuals working on a project hold the relevant individual authorisations. The project authorisation holder (or project manager, on behalf of the project authorisation holder) will be required to maintain a current and up-to-date register of personnel allowed to perform procedures under that project authorisation. This register should be readily accessible for the Compliance Officer and the HPRA inspectorate and should be tightly controlled.

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. Further information can be found in the HPRA 'Guide to New, Renewal and Amendment Applications for Individuals under Scientific Animal Protection Legislation' in the SAP Guidance documents section of the HPRA website www.hpra.ie.

APPENDIX III PURPOSE OF PROJECTS

(Please refer to Appendix IV for a description of each project purpose)



APPENDIX IV PROJECT PURPOSE DESCRIPTIONS

1. Basic research

Basic research refers to studies of a fundamental nature including:
- physiology,
- 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, and
- 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.

Projects conducted for basic research purposes can be classified into the following sub-fields.
- 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

Genetically altered animal lines

If the project is for the creation of a new genetically altered animal line (including crossing of two existing lines) and these animals are intended to be used for the purposes of basic research (e.g. developmental biology, immunology), select the basic research purpose for which they are being created. However, if they are being bred and maintained for research that is considered translational in nature, then translational and applied research should be selected as the primary project purpose rather than basic research.

Points to note

- The subfield 'oncology' should be chosen for any basic oncology research regardless of the target system.
- The subfield 'musculoskeletal system' should be chosen for basic dentistry research.
- The subfield 'multisystemic' should only include basic research where more than one system is the primary interest, such as research into some infectious diseases.
  The subfield 'other basic research' should only be selected if the research is not related to an organ/system already listed. It is rare that this should be chosen, as the pre-defined categories should cover most types of basic research.

2. Translational and applied research

Translational and applied research refers to animals used for any of the following aims:
- the avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality or their effects in human beings, animals or plants,
- the assessment, detection, regulation or modification of physiological conditions in human beings, animals or plants, and
- the assessment of 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, but does include discovery toxicology and investigations to prepare for the regulatory submission and method development. Efficacy testing during the development of new medicinal products must be reported under this category.

Projects conducted for Translational and applied research purposes can be classified into the following sub-fields.
- 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 nutrition
- Animal welfare
- Diagnosis of diseases
- Plant diseases
- Non-regulatory toxicology and ecotoxicity

Genetically altered animal lines

If the project is for the creation of a new genetically altered animal line (including crossing of two existing lines) and these animals are intended to be used for the purposes of translational and applied research (e.g. human cancer), select the translational and applied research purpose for which they are being created. However, if they are being bred and maintained for the purposes of basic research (e.g. immunology), basic research should be selected instead.

Points to note

- The subfield 'human cancer' should be chosen for any human cancer research regardless of the target system.
- The subfield 'human infectious disorders' should be chosen for all research on human infectious disorders regardless of the target system.
- The subfield 'diagnosis of diseases' includes, amongst others, animals used in the direct diagnosis of diseases such as rabies and botulism, but excluding those covered under regulatory use.
- The most relevant subfield shall be chosen for animals used for the production and maintenance of infectious agents and other biological material produced for the purposes of translational and applied research.
- The subfield 'other human disorders' should only be selected if the research is not related to an organ/system already listed. It is rare that this should be chosen, as the pre-defined categories should cover most types of applied research.

3. Regulatory use and routine production

Regulatory use refers to the use of animals in procedures performed with a view to satisfying legal requirements for producing, placing and maintaining products/substances on the market.

Projects conducted for regulatory use and routine production purposes can be classified into the following sub-fields:

- Quality control including batch safety/potency testing, pyrogenicity testing or other quality controls
- Routine production including blood-based products, monoclonal antibodies or other products
- Toxicity and other safety testing including pharmacology including legislation for medical, industrial chemical, plant protection, biocides, food and feed and cosmetics or other toxicity and safety testing satisfying EU requirements. It also covers legislation on medicinal products for human and veterinary use and their residues.
- Other efficacy and tolerance testing

This includes safety and risk assessments for food and feed tests carried out in respect of products/substances for which a regulatory submission was foreseen but ultimately not made, for instance because they were deemed unsuitable for the market by the developer and thus failed to reach the end of the development process.

Routine production refers to animals used in the manufacturing process of products if that manufacturing process requires regulatory approval (for example, animals used in the manufacturing of serum-based medicinal products).

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

Points to note

- The subfield 'quality control' refers to animals used in the testing of purity, stability, efficacy, potency and other quality control parameters of the final product and its constituents and any controls carried out during the manufacturing process for registration purposes, to satisfy any other national or international regulatory requirements or to satisfy the in-house policy of the manufacturer.
- The subfield 'other efficacy and tolerance testing' covers efficacy testing of biocides and pesticides as well as the tolerance testing of additives in animal nutrition. This also covers dose-range-finding studies when carried out with a view to satisfy legislative requirements.
- The subfield 'toxicity and other safety testing' covers studies carried out on any product or substance to determine its potential to cause any dangerous or undesirable effects in humans or animals as a result of its intended or abnormal use, manufacture or as a potential or actual contaminant in the environment.
- The subfield 'target animal safety' refers to testing that ensures that a product for a specific animal can be used safely on that species, but excludes batch safety testing which is covered under 'quality control'.

4. Protection of the natural environment in the interests of the health or welfare of human beings or animals

This project purpose refers to 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.

5. Preservation of species

Preservation of species refers to research where the primary aim is preserving a species of animal.

6. Higher education

Higher education refers to animals used for delivering theoretical knowledge within a higher education programme.

7. Training for the acquisition, maintenance or improvement of vocational skills

Training for the acquisition, maintenance or improvement of vocational skills refers to animals used for training to acquire and maintain practical vocational skills, such as animals used in the training of medical doctors and veterinarians.

This purpose should also be chosen for projects where the sole purpose is to provide training to acquire and maintain practical competence in procedures (e.g. drug administration techniques, blood sampling). For further information on this type of project, see the HPRA's 'Guide to Use of

Animals for Educational Purposes under Scientific Animal Protection Legislation' which can be found in the SAP Guidance documents section of the HPRA website.

8. Maintenance of colonies of established genetically altered animals, not used in other procedures

This project purpose 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 equivalent to, or higher than, that caused by the introduction of a needle in accordance with good veterinary practice. Details on the use and authorisation of genetically altered animals can be found in the Framework for the genetically altered animals under Directive 2010/63/EU on the protection of animals used for scientific purposes. The HPRA considers any line which receives a score in any category of the relevant welfare assessment template in **Part 3** of the Framework to harbour a harmful phenotype, meaning that project authorisation is required for its breeding and maintenance.

All transgene-carrying 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, that could potentially carry the harmful gene. This category should only be selected for existing lines (i.e. not for the creation of a line) and when these animals are not being used within this same project application for other research purposes.

Points to note regarding the reporting of genetically altered animals

For all prospectively authorised creation and breeding procedures, the following should be considered when reporting animals in the annual statistical returns:

- Did the animal demonstrate a harmful phenotype?
- Was invasive genotyping required, when tissue taken for the primary purpose of identification could not be used?
- Did the animal undergo subsequent procedures (including terminal non-recovery procedures e.g. transcardial perfusion)?

If the answer is 'yes' to **any** of the above:

- Animals should be reported with a **genetic status** as 'Genetically altered with a harmful phenotype' and under **EU submission** as 'EU-Yes', ensuring to select the highest severity experienced by the animal in the **actual severity** column.

If the answer is 'no' to **all** of the above:

- Animals should be reported with a **genetic status** as 'Genetically altered with a harmful phenotype' but under **EU submission** as 'EU-No' with an **actual severity** of 'non-recovery', to represent that they were animals with the potential to develop a harmful phenotype as a result of their genetic alteration, but under your care they did not experience such harms (e.g. due to being heterozygous for a recessive mutation, or being euthanised before a harmful phenotype could develop).

9. Forensic enquiries

Forensic enquiries refer to tests as part of forensic investigations and the production of materials, for example, antisera, for use in forensic investigations where this is not being carried out to meet a regulatory requirement.

APPENDIX V SEVERITY CLASSIFICATIONS FOR SINGLE HOUSING

Species	Mild	Moderate	Severe
Metabolic caging (rodents)	< 24 hours	1-5 days	> 5 days
Metabolic housing (other species)	Severity is determined on a case-by-case basis during project evaluation		
Dogs	4 hours - 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	24 hours - 1 month	> 1 month	
Rats	12 hours - 1 month	> 1 month	
Mice	24 hours - 1 month	> 1 month	
Guinea pigs	24 hours - 1 month	> 1 month	
Ferrets	24 hours - 1 month	> 1 month	
Rabbits (young or female)	24 hours - 1 month	> 1 month	
Sheep	24 hours - 1 month	> 1 month	
Cattle	1 week - 6 months	> 6 months	
Pigs	1 week - 6 months	> 6 months	
Zebrafish	8 days - 6 months	> 6 months	

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.