Applying for the use of experimental animals in FOTS, guidance document.

This document represents the experience of KPM on good and suboptimal ethical applications, and guidance about what the Norwegian Food Safety Authority (Mattilsynet or MT) will expect from an ethical application. This document follows the heading titles and format found in the current FOTS.

The guidance includes the changes and requirements that are expected with the new provisions to the animal welfare act (Forsøksdyrforskriften) that was effective from 1/7-2015. Mattilsynet will authorize the use of research animals based on the ethical applications submitted in FOTS. When initiated, each ethical application obtains a unique number code, also known as the FOTS-id. The outline and administrative routines of FOTS are expected to change, but when and how is not yet certain. The OUS form used for local evaluation and feed-back to the applicant is enclosed at the end of this document.

An English version of FOTS can be chosen during log-in by clicking on the English flag.

NB// until FOTS is updated with new features to accommodate the required information in the FOTS form, applicants are expected to submit the project summary (A2) and severity category (A5) as separate attachments to the FOTS form.

Applying for ethical approval in FOTS, new experiments

A General information

1 Working title:
2 Application summary: *The application summary will be published and should not included sensitive information related to IP or scientific interests or information that is otherwise intended to be exempt from public access. Use lay terms for a general description of the project/experiment. The summary must describe the following:* *I. The purpose of the experiment/project* *II. The expected adverse effects on the animals* *III. The expected scientific benefits or benefits for society* *IV. The number of animals and species* *V. How will the requirements for 3R be accomplished by the experiment/project*
3 Applicant:
4 Institution where the experiment/project will be conducted: *The link between the applicant and the institution will be decided by the FOTS user name and password that was used for FOTS access.*
5 Severity category (prospective): *The applicant must prospectively evaluate and classify the experiment(s) according the degree and duration of pain, fear, lasting harm or other adverse effects. Individual cumulative severity during the procedure, the type of handling and/or lack of ability to express natural behavior (including restricted standards of housing and care) must be incorporated in the evaluation.* *Note that evaluation of severity classification includes more parameters than just pain. Please note that experiments that will result in long lasting severe pain, fear or oter adverse effects, that cannot be ameliorated, is not allowed (§ 13).* *Experiments are characterized into the following 4 severity categories: Non-recovery, Mild, Moderate and Severe. See Forsøksdyrforskriftens Vedlegg B, where examples on experiments in the different categories are listed. The severity categories are defined as follows:* *I. Non-recovery: Procedures which are performed entirely under general anaesthesia from which*

the animal shall not recover consciousness.

II. *Mild: Procedures on animals as a result of which the animals are likely to experience short-term mild pain, suffering or distress, as well as procedures with no significant impairment of the well-being or general condition of the animals.*

III. *Moderate: Procedures on animals as a result of which the animals are likely to experience short-term moderate pain, suffering or distress, or long-lasting mild pain, suffering or distress as well as procedures that are likely to cause moderate impairment of the well-being or general condition of the animals.*

IV. *Severe: Procedures on animals as a result of which the animals are likely to experience severe pain, suffering or distress, or longlasting moderate pain, suffering or distress as well as procedures, that are likely to cause severe impairment of the wellbeing or general condition of the animals*

It is noted that many previous FOTS-applications, when the user had no fixed severity classifications, have indicated unrealistic assessments of the severity and longevity of pain and adverse effects. The number of severity categories is now markedly reduced and examples of severity classification of different animal models are given in Vedlegg B, Forsøksdyrforskriften. The applicant is advised to assess the severity classification realisticly and seek advice from person med særskilt kontrollansvar if needed.

6 Previous experience with comparable procedures: *No/Yes. It is relevant and recommended that the applicant includes the experience of the applicant and all participants when answering this question*

7 Experiments/procedures funded by: *Den Norske Kreftforening/ EU/EØS-midler/ Forskningsrådet/På oppdrag fra offentlig etat/På oppdrag fra privat bedrift/ Annen finansieringskilde. All applications are expected to hold the same quality, irrespective of funding source. Applications supported by large and important funding institutions are sometimes seen to have very brief, sometimes even incomplete, applications. While funding by EU and/or Forskningsrådet obviously is an indicator of relevance, it is important to realize that funding from these sources does neither constitute an approval nor an evaluation of specific experimental animal projects.*

8 Planned start and end dates: *The applicant is adviced to apply for sufficient project time. Projects tend to take more time than planned and the approved project time is really without any ethical consequence. Applications can be approved for up to 4 years. Application fees, including fees for changes, will be implemented during 2015.*
Starting date should not be prior to application submission, as it will imply that the project was started prior to submission.

B Public access

Product sensitive details are very seldom required in an ethical application. Generic information on the type and class of test substance are most often sufficient. The sections of the application that is to excempt from Open Files act must be specified – the entire application cannot be excempt.

1 Do the information in the application contain information that should be kept from public access? *Yes/No*

2 If yes, please refer to relevant act(s) and regultion(s) (example: Open files act, article 13, 1st paragraph together with Public administration act, article 13, 1st paragraph, 2nd point): *Enter mentioned paragraphs, if relevant*

3 If yes, which information do you want to keep from public access?
Keep in mind that 1) all registered users at an approved animal facility has reading access to all FOTS-id at the facility, 2) Mattilsynet will rarely need sensitive information in their review of and decision on an ethical application. Information related to the type/class of test substance will often be a sufficient and

equally relevant substitute for sensitive information. The applicant must specify which parts of the application that is to be kept from public access -the entire application cannot be expected to be excempt from public access. Note that MT will not consider your wish for public access excemption until a demand for public access is raised. If such demand is raised, MT will decide on public access after conferring with the applicant.

C Applicant and participants

1 Institution:

Name	Position and education	Course on animal experimentation
Responsible applicant		
Participant X		
Participant Y		

All persons involved in planning or conduction of the experiment are to be registered here, Forsøksdyrforskriften cf. article 7, 2. paragraph. Such persons must be added as project participants in an institution before they can be added as project participants in an application.
Forsøksdyrforskriften requires that all persons planning, conduction and/or participating in animal experiments have sufficient skills and required training within the field and species in question. The rules and regulations regarding animal experimental course is changing, but the current requirements for category C and B personnel is upheld for the time being. All participants that will perform the practical or experimental interventions with the animals must be registered as participants in the FOTS id in question and must be registered with an animal experimentation course that is valid and suitable for their role in the experiment. The responsible applicant must send name, telephone number, mail address, education and lab animal course documentation (pdf copy of the course certificate and documentation of the required practical training) to the named animal care and welfare officer (person med særskilt kontrollansvar) for all participants that has not previously been registered in FOTS. If the lab animal course is non-Norwegian course or a course not accredited by FELASA, please include an official course description and other relevant details (course length (days/hours), lab animal species involved, practical training) with the course certificate.
It is generally better to include too many than too few participants, in order for the application to reflect reality and avoid the need for later changes. However, personnel that only handle animal cadavers or organs after termination and/or personnel that only assist in data capture (e.g. imaging), without handling live animals, are not considered participants in relation to Forsøksdyrforskriften and are hence not relevant to include in an ethical application.

D Background and purpose

1 Give a short presentation of the background and purpose of the experiment (max 500 words), in a common language for lay people to understand. Describe the hypothesis to be tested. If the experiments are required by law by public authorities, please refer to the relevant acts and regulations: It is acceptable and normal that early phase projects often are descriptive and/or explorative by nature, with few or no defined hypothesies. All other projects, and particularly projects describing continuation of ongoing research project, are expected to describe one or more hypothesies that warrant the activity and provide context to the study design and practical performance. Results achieved and their interpretation are relevant to include when applying for continuation of a project, particularly when the need for continued study and the study design are based on such previous results and interpretations. *Where relevant,*

literature references are important to include in the text and as electronic attachments.

E Research animals

1 Animal species, Strain/Line, Sex, Weight at start, Weiht at end, Age: *If more than one strain/line is needed, these should be registered on separate pages in FOTS. This is especially required when several GM lines with known or possible phenotypic alterations of clinical relevance will be used.* *Note that the Ministry of Health approved the KPM animal facilities for enclosed use of GM animals under the requirement that notification of the use of GM animal lines ("GMO-melding") must be enclosed with all FOTS-id where the animal lines are used. Attachments of relevant "GMO-meldinger"are hence required before applications are send to MT for review. Also note that a "GMO-melding" can include many GM lines and that a "GMO-melding" for one or more lines can be reused in subsequent etical applications, as long as the institution and the responsible person for the facilities listed in the "GMO-melding" are still valid.*
2 Number of animals: *The total number of animals must comply with the calculated number of animals needed, including animals in excess of the calculated number (see Calculating number of animals).*
3 Number of reused animals (cf. paragraph 17)/Reuse not applicable: Note that Forsøksdyrforskriften has changed markedly on reuse, requiring special need and arguments for allowing reuse. *Note that multiple planned prosedyres does not represent reuse.*
4 Experience with this species: *No/Yes. It is relevant and recommended that the applicant includes the experience of the applicant and all participants when answering this question (provided that the experienced participants actually participate in performing the study)*
5 Duration for the individual animals. State the expected duration of the entire experiment for the individual animal in days, hours, minutes (e.g. 5, 0, 0): *It is the <u>maximum</u> duration of the experiment for individual animals that is to be recorded. Assumptions, averages or the time for doing the surgical intervention alone will be erroneous and misleading information. Information about the duration for the individual animal is vital for review of the application, both before and afterapproval.*
Animals with a deviant phenotype: Do the animals have any congenital or hereditary disease/illness or other abnormalities related to their phenotype that may impair their welfare (e.g. diabetes, autoimmun disease, increased tumor incidence, dental defects)? *All animal strains with known hereditary disposition to a deviating phenotype, including animals with genetic defects that do not arise from genetic modification, are to be considered.Note that "No altered phenotype", meaning no <u>clinically observable</u> adverse effects from the genetic modification is the most common presentation of GM animals. This is important to include this information in the ethical application. If the clinical effects of the altered phenotype depends on the age of the animal, the progression of the alterations and the maximum time that the animals are allowed in the study or to live should be stated*
6 Describe wich precautions, efforts and/or treatments the animals will be given in order to safeguard their wellbeing and welfare and when this will be relevant: *Actions can range from altering of the diet, altering the routines of monitoring to termination. If the clinical effect of the deviant phenotype is dependent upon the age of the animal, the age at which the animals will be used and/or terminated must be defined.*
7 Sedation, analgesia and anesthesia: *Anesthesia and analgesi is to be described in terms of active ingredient, concentration, dose (mg/kg or similar), route, frequency and duration of administration. The frequency and duration of analgesia treatment is very important information, frequently lacking. Several variants of common anesthesia mixtures are known in the literature (at least 3 different mixtures containing Zoletil are known). When using mixtures of anestethetic agents, the dosing volume (ml/kg) and the mixing recipe and/or the concentration of active ingredients (mg/ml) must be described. Doublecheck*

that the anesthesia and analgesia protocol concouers with the despcription in the Materials and Methods section. It is noted that the use of anesthesia and analgesia is very important information during application review. Information on this topic is quite often incomplete and the applicant is advised to apply appropriate focus on this anesthesia and analgesia. The table function intended for describing anesthesia and analgesia will be removed from the FOTS system and should no longer be used.

8 Other medication: *Remember to add all test substances, drugs and chemicals that the animals will be exposed to. Dose levels are always relevant, but remember to also include information on dosing volume.*

9 If neuromuscular blockers are to be used, a scientific justification is required: *"Animals must not be administered drugs that abolish the expression of pain unless a suitable anaesthesia or analgesia is provided. Scientific documentation of the need and proposed procedyre, including details of anesthesia, analgesia and monitoring routines, must be submitted" (§ 14 in the provisions). The prior expert opinion by FDU should remain a guiding document for users that contemplate the use of NMB agents (see http://www.mattilsynet.no/fdu/prinsippavgjorelser/article54868.ece).*

10 Pain and discomfort. The experiment will result in severe pain, or longlasting moderate pain and analgesia cannot be used: *No/Yes*

11 Justification for the omission of analgesia:
Animals that may experience pain at the end of anesthesia must be given pre-emptive and post-operative analgesia as appropriate. If the use of analgesia is incompatible with the scientific purpose of the study, the omission of analgesia in general or classes of analgetics must be described in the application (conf Forsøksdyrforskriften § 14, 4. Led, og Appendix B, 3f). Omission of analgesia will affect severity classification!

12 Justification for the animal model choice:
Confer Forsøksdyrforskriften Appendix A1 - species, strain/line, sex, age, special traints, genetic modifications

F Calculating number of animals

1 Describe the rationale and justification for the number of animals that will be used. Pilot experiments must be performed in case of uncertant population size, confer Forskriftens § 6, 2. ledd. Seek statistical help if you are in doubt.
The justification and prospective calculations on the required number of animals is often insufficient or missing. Describing the statistical methods that is intended to be applied on the obtained results is a misunderstanding – calculating the number of animals is a prospective analysis. Delayed processing of the ethical application is likely if animal numbers are not justified by prospective calculations. If insufficient data are available for prospective statistical analysis, a logical estimate or a pilot study is required. If (pilot-) studies with the same or similar animal models are previously performed, existing study results are expected to be used for prospective calculation of required number of animals.

Calculating the number of animals in breeding projects can obviously be difficult. The input that the applicant has used in his/her estimation (fertility, genetics and how it affects the number of offspring with the desired genotype and number of offspring required for experiments, analysis or colony maintenance) must be included.Calculating the number of animals in a breeding project is otherwise considered to be an estimate. NB - an estimate does not imply that an open end number of animals can be used – it just implies that the allowed maximum number of animals was derived by estimation.
The breeding protocol represents a deviation from the use of reaserach animals in in vivo experiments, where the prospective calculation of the required number of animals is expected with a higher degree of precision. It is hence recommende to separate ethical applications for breeding of animals and in vivo use of animals (also if the animals used are bred in-house).

In some experiments (e.g. surgical interventions, post mortem processing of organs), a certain degree of surgical failure or data loss is expected when the operated animal or organ does not comply with defined inclusion criteria. A certain number of extra animals, in addition to the calculated numer of animals, will hence be needed to compensate for used but excluded animals. It is acceptable to apply for extra animals, in addition to the calculated number, provided that the extra animals are justified and reasonable and that this is written explicit in the application. Do not describe the need for 100 animals and apply for 110 without explaining why an extra 10 animals are needed.
2 Describe all experimental groups and group sizes. Attach a table when needed *Note that tables copied directly into FOTS and table-like organization of data directly in FOTS becomes chaotic nonsense in a print-out. Tables are often very illustrative, but include Word- or Excell tables as Attachments.*
3 Which statistical method was used for prospective calculation of animal numbers? *Power analysis/Ressource equation/Other method/Not applicable*
4 If "Power analysis"/"Ressource equation": Which input has been used? If "Other method": Describe in detail the statistical method used. If "Not applicable": Describe why statistics cannot be applied. *It is not sufficient to only tick off Power analysis or Resource equation. These are not magic choices that releave the applicant for the required calculations. If Power analysis, Ressource equation or similar prospective metod of calculation has been used, input parameters and justification for the chosen values of these parameters should be included. For Power analysis, input parameters would be Size of the effect of biological interest, Variation, Desired Power of experiment (usually > 0.8), Significance level (usually assumed to be 0.05, Alternative hypothesies (usually assumed to be 2-tailed).* *Again, note that plans for retrospective analysis of the results obtained are entirely without relevance to describe here!*

G Alternatives/3R

Alternative, scientifically relevant methods not involving the use of animals should always be considered. Review relevant alternative methods and why these are rejected, considering the 3Rs ("Replacement, Reduction, Refinement").

1 Replacement: Why is it not possible to achieve the aim of this experiment without the use of animals? What alternatives have been considered and why were they rejected? *Replacement is obviously not available or relevant in some select cases. However, "Not relevant" is not a relevant fulfillment of the legal requirements to review alternatives. Formally speaking, alternatives are in many cases available, but they are most often not relevant. Your conclusion on suitability of alternatives can only be reviewed by MT if the nature of the alternative methods has been described.To fulfill the legal requirements and enabling MT and others to review the alternatives AND your conclusion on suitability, the alternatives must be presented as objectively and in depth as possible. Conclude with the up- and downsides of the available alternatives versus the applied use of research animals. It is insufficient for applicant to merely present his/her conclusion about little described alternatives.*
2 List the databases and search terms you have used, searching for alternatives.
3 Reduction: When the use of animals is unavioidable: Which efforts, steps and measures have you taken to minimize the number of animals and still achieve valid scientific results? *The most important measure will be a logic and transparent prospective calculation of animals needed.Critical review of how and when control animals are used could also be relevant (control animals are often included several times).*
4 Refinement: When the use of animals is unavioidable: Which improvements of the husbandry and the procedures have been implemented to minimize the pain, suffering, distress and lasting harm and

improve animal welfare, compared to previous comparable experiments? (Keywords: analgesia, anaesthesia, endpoints, environmental enrichment, surgical techniques, sampling techniques etc). *Experience from prior (pilot) experiments or literature must be used to reduce and refine future protocols and ethical applications.*

H Methods description

When writing ethical applications and performing animal experiments, one simple rule applies: *Write what you do and do what you write*. The description of you ethical application must enable MT to assess the technical performance of the experiment, how this will affect the animals and the obtained results and how the study will meet the described study objective. The technical performance of the experiment must be described in a clear and complementary text, enabling an objective assessment of study performance versus the ethical application by designated persons at KPM. It is recommended to include a coherent logic description of all planned procedures in chronological order in one of the text boxes, rather than mindless answering of the questions in all text boxes. The later often leaves the reader with little or no insight into the bigger picture.

1 Preparation of the animals before the actual experiment/intervention: *Training/preparing of the animals prior to study start? Use of metabolism cages or other type of physical restraint or reduced freedom of movement? Use of equipment that requires an activity that is not voluntary and/or normal (e.g. running on a treadmill)? Training and accommodation of the animals prior to study start should be described where relevant.*
2 Describe any purchase, transport, quarantine/acclimation, housing, environmental enrichment, feeding regime, tagging, weighing etc: *Method of ID marking and biopsy sampling must always be described, also if traditional ear tagging is used. Note that a method of biopsy that also results in ID marking must be the default method applied at KPM (see guideline for biopsy and ID marking of rodents). Note that cage groups should not be reorganized after acclimatization and the number of animals per cage should therefore be considered carefully when setting up til study plan.*
3 Describe the procedures (surgery, administration of test substance, physical treatments etc.) that will be applied to the animals during the experiment. You may also attach drawings, figures, protocols or timelines to this application. • *The provision has a general requirement for anesthesia when performing procedures on research animals. However, anesthesia can be omitted if anesthesia is considered more stressfull than the procedure itself or anesthesia is considered to be incompatible with the study purpose. Literature clearly document that physical restraint is very stressfull for rodents, and more so than minor rapid procedures. Only routine procedyres, that can be completed rapidly by skilled technique and require short periods of physical restraint, can be performed under physical restraint only. Routine SC/IP injection and standard blood sampling are examples of procedures that are performed best without anesthesia.When physical restraint or anesthesia will be used for sampling, injection and/or other procedures, describe the number and duration of (repeated) procedures, anesthesia and physical restraints that is planned.* • *Even if described in the Research animal section, it is recommended to include a complementary description of the methodology and timing of the anesthesia and analgesia protocol in context with the experimental procedure description. Anealgsia, observation time after conclusion of the surgical intervention and supportive therapy (heat, fluids, other). Ensure that method and dose levels of anesthesia and analgesia in the Methods description and Research animal sections are identical. Anesthesia and analgesia are central elements in the cost-benefit analysis and one of the topics that*

most often give rise to questions and requests for change. The applicant is hence adviced to choose an anesthesia that is fit for purpose include a complementary description.

- *Describe experimental groups, preferably with an attached table. A table that provides an overview of experimental groups, dose levels, dosing and sampling interval and observation time will provide clarity. Describing the experimental groups and above information as text only will create little clarity and cannot be recommended.Note that animals dosed with different dose levels or identities of test substances should not be housed in the same cage after dosing.*
- *Technical description of*
- *surgical interventions*
- *injections*
- *sampling of blood, including methodology and details related to volume per sampling, number of samples and frequency of sampling.*
- *sampling of other tissues than blood (including organs at or after termination).*
- *Ethical applications with surgical interventions as central elements are often missing information on other procedures that are planned. It is important to include all activities and procedures in the Methodology description (e.g. behavior studies, special diets etc).*
- *Details regarding dosing volume and dose of active substance per dosing, number of dosages, route of administration and speed of injection (ml/min by IV injections). Assumed clinical effects at the chosen dose levels should be stated when the test substances are likely to cause adverse or toxic reactions.*
- *Attachments may supplement and expand the information supplied, but should not be a substitute for submitting a complementary text in the ethical application form.*

4 Which parameters will be monitored and which samples will be taken during the experiment? *The data sampled will set the study purpose in context*

5 Describe the follow-up and supervision of the animals during the experiment (before, under and after procedures). *Described possible adverse effects. When relevant, a plan for monitoring must be described, detailing monitoring frequency at critical periods and planned actions. The provision requires minimum 1 daily inspection of the animals and more than 1 inspection per day may be required at critical periods of an experiment. Planned actions are often described very briefly, or not at all. In experiments classified as moderate or severe, a plan for monitoring and action (i.e. score sheet) must be included. Score sheets should be included only when adverse effects qualify to these severity scores and adverse effects are anticipated. In other experiments where little or no adverse effects are anticipated (e.g. non-recovery and mild), score sheets should generally not be included. On the design of score sheets, see the principle statement by FDU regarding"Belastende forsøk i smågnagere" at* http://www.mattilsynet.no/fdu/incoming/article87694.ece .

6 Describe the method for euthanasia and why this method is chosen, confer Forsøksdyrforskriften § 16 and Vedlegg C. When using pharmaceuticals, state the correct generic name, commercial name and dose: *Note that approved methods of killing animals (including requirements) are described in Vedlegg C to the provisions. Any method of killing that deviates from those described in Vedlegg C must be explicitly described in the ethical application and approved prior to use. The description must include a scientific rationale for the choice of method and why the methods in Vedlegg C cannot be used. When animals are killed by an anesthetic overdose, active ingredient and dose level must be stated. Note that KCl is not included in Vedlegg C and that decapitation can only be used if "other methods are not possible". In reality, this means that the choice to kill animals by decapitation requires a scientific rationale (e.g. harvest of brain or brain stem).*
Killing of rodents, rabbits and neonate dogs by concussive/ percussive blow to the head and killing rabbits by electrical stunning is described as approved methods in Vedlegg C. These methods of killing animals are grossly inappropriate and are absolutely NOT approved as method of killing at IMB.

7 Criteria for humane endpoints, i.e. setting of clear, predictable and irreversible criteria that allow early termination of the experiments before the animals experience significant harm whilst still meeting

the experimental objectives. *Humane endpoint, i.e. clinical symptoms that indicate serious and unnecessarily severe strain and/or impending death, must be pre-defined and as specific as possible.Subjective and little specific HE are very often seen and give no guidance on interpretation and action. "The animals will be killed if the suffer unnecessarily"is an example of a meaningless HE.* *Humane end points are also relevant in non-recovery experiments (e.g. inability to maintain the animal in stable surgical depth anesthesia) and breeding experiments (deviations from normal clinicalstate/physiology). Unless the breeding animals are rare and truly unique animals, the tolerance for deviating clinical status will be very limited. "Not applicable" is therefore not an option for HE.*
8 Which actions will be taken if animals reach the humane endpoint (examples: treatment of symptoms, reduced exposure or euthanasia)? *Therapy by analgesia, antibiotics or killing is typical actions. If actions other than killing are planned, more frequent monitoring must be part of the plan. Monitoring in itself is not an action.*

I Attachments to the ethical application

The provisions to the law on genetically modified organisms and the law on environment, health and safety requires that GMO notifications and EHS risk evaluations are included in all ethical applications where these are relevant. The ministry of health also requires that KPM keeps a record of all acitivity that include GMO and that ethical applications are only approved if valid GMO notifications are included. A copy of a valid GMO notification must hence be attached to ALL ethical applications where GMO is used, also when a given GMO line has been included in previous ethical applications. An EHS risk evaluation form must be included in all ethical applications. Applications that are missing required GMO notifications and EHS risk evaluation forms will be returned to the user.

Applying for change in previously approved FOTS id

Any change of an approved project that may have a negative impact on animal welfare must be applied for and approved by MT, conf Forsøksdyrforskriften § 6. Changes that are considered to have no negative impact on animal welfare require notification only. FOTS has been updated with 2 options; Application for minor changes and Notification of change. When minor changes of previously approved FOTS id are needed, the applicant must describe 1) Purpose of the change, 2) the required changes, 3) why the changes are considered to have no negative impact on animal welfare (Notification) and 4) update project summary (if relevant) in either "Application for minor changes" or "Notification of change".

KPM personell with special responsibility for animal welfare decide if a project change must be applied or notified to MT and document their decision in the FOTS id. The applicant submits notification or application to MT according to these instructions

Guiding document on typical changes

Change	Assessment	Comment
Extension of project end date	Application	Extending the project end date has no negative effect on animal welfare and could be notified. However, changing the end date of an approved project requires an authority that only MT has. Note that the project period and the maximum length of the procedures for individual animals are 2 separate issues.
Expanded animal numbers	Application	Expanding the animal numbers will have an overall negative effect on animal welfare.
Altered composition of animal lines and genotypes within same species. No change in total animal numbers within species in question	Notification	If the desired change is a relative change between different animal lines, with or without altered phenotype, and the previously described severity classification is not altered.
Altered composition of animal lines and genotypes within same species. No change in total animal numbers within species in question	Application	If the desired change will increase the number of animals in a higher versus a lower severity category compared to the original application.
Altered anesthesia/analgesia	Most often notification	Notification requires that the qualitative effects of the altered anesthesia and analgesia remains as previously described.
Including new participant	Notification	Requires that the participant can document the required comtence and education.
Including new test substance	Variable	Assumed/known effects of the intended new test substance versus the previously approved test substance(s) are essential. Notification is only an option if similar test substances were included in the original FOTS id and the identity and effects of the new test substance can be considered to be comparable to the test substances or family of test substances previously approved.