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Technical information animal experimentation

Safety testing 4.01

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1. Objective and legal framework

The aim of this information is to standardise the submission of applications in the approval procedure for animal experiments in the field of safety testing. These animal studies are classified into groups for which separate applications must be submitted in each case.

- The content details regarding the animal experiments provide the authorities with an improved overview for assessing the applications and help to ensure that unnecessary studies and studies using outdated methodology can be avoided.
- The administrative effort is reduced to what is objectively essential.
- The information is coordinated with the forms that have been in use for animal experiments since 2008 and thus allows a more detailed statistical analysis in the field of safety tests.

This information applies to all animal studies that are carried out in the context of safety tests and risk assessments of substances and products. Such studies require approval by the authorities[1], who review the basic conditions for conducting all tests[2].

Animal experiments that inflict pain, suffering or harm on the animal, subject it to great fear or substantially impair its wellbeing must be kept to an absolute minimum[3]. In various safety tests, impairment of the animal's wellbeing is to be expected and is unavoidable in view of the nature of the experiment.

Details are set forth in the ordinance on animal experiments[4].

If suitable, validated alternatives to animal experiments are available and are recognised for registration purposes, they must be used (see: chapter 3).

The reliability of animal experiments for investigating the potential hazards of substances and products must be reviewed according to the assessment criteria of the animal welfare ordinance[5]. The application (Form A)[6] must be submitted in detail according to the application units defined in the corresponding information, so that the applications for approval of animal experiments can be reviewed and statistics[7] compiled. For a complete set of statistics, further details on safety tests carried out must be made at the time of reporting (Form C).

The framework for the experimental design of a safety test animals is described in the relevant national and international guidelines. However, the most detailed experimental design depends heavily on the test substance, and must accordingly be described in exact detail.

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1 Animal Welfare Act (TSchG) of 16 December 2005: Art. 18 and Art. 13

2 Animal Welfare Act (TSchG) of 16 December 2005: Art. 17

3 Animal Welfare Act (TSchG) of 16 December 2005: Art. 20

4 FVO ordinance on animal experiments dated 12 April 2010

5 Animal Welfare Ordinance (TSchV) of 23 April 2008: Art. 137

6 FVO animal experiment forms

7 Animal Welfare Act (TSchG) of 16 December 2005: Art. 36 and FVO ordinance on animal experiments dated 12 April 2010: Art. 147

2. Uses and hazards

2.1. Pharmaceuticals

Safety testing and quality control of active substances and excipients, products or end-products and devices for use in human and veterinary medicine.

The tests must be geared to national and international conditions, e.g. the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[8, 9], the US FDA[10, 11], the European Medicines Agency (EMA)[12, 13] and the European Union (EU)[14].

National and international directives and laws point out that, where it makes sense to do so, validated alternative methods are to be used for toxicity studies (see: chapter 3).

Further important requirements are set forth in the pharmacopoeias. Amongst other things, these list test methods which to some extent also concern safety tests (e.g. test for genotoxic impurities) and quality controls. These reference works include, for example, the Swiss pharmacopoeia, the European Pharmacopoeia[15] [commercially available], the US Pharmacopeia – National Formulary (USP–NF)[16] [commercially available] and the Japanese pharmacopoeia.

2.1.1. Pharmaceuticals for repeated use

Safety studies which are intended to obtain data on the properties of a test object and on its safety for humans and the environment and whose results must be submitted to an authority as part of a registration or approval procedure are compiled in Table 1.

[The so-called LD50 test (lethal dose for 50 % of animals) after a single administration is no longer required, and acute toxicity can also be determined in the context of other toxicity studies, e.g. as part of dose-finding studies.]

The application must provide exact details of the purpose for which the experiment is to be conducted and the guideline that is to be applied.

Such studies may (but in certain cases do not necessarily have to) be carried out according to the principles of Good Laboratory Practice (GLP)[17].

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8 ICH Safety Guidelines under “S (=Safety)”: test guidelines that are valid for the three regions of Europe, Japan and the USA

9 ICH Safety Guidelines under “M (=Multidisciplinary)”- Joint Safety/Efficacy, Topic M3”: studies in the context of drug development

10 http://www.fda.gov/, http://www.fda.gov/cder/index.html (CDER = Center for Drug Evaluation and Research; Einzelheiten: “Guidance, Compliance & Regulatory Information”

11 FDA Redbook (details on additives for foods and colorants in foodstuffs)

12 EMA Non-clinical Guidelines Human Medicines

13 EMA Veterinary Medicines Toxicology: guidelines for toxicity studies for veterinary medicines under “Toxicology”

14 http://ec.europa.eu/health/documents/eudralex/index_en.htm: legislation for testing medicines under “guidelines” in association with “human medicines”

15 http://www.edqm.eu/en/European-Pharmacopoeia-1401.html: European Pharmcopoeia

16 http://www.usp.org/USPNF/: US Pharmacopeia

17 Ordinance on Good Laboratory Practice (GLPV): of 18 May 2005

Informative *pilot studies* or *dose-finding studies* are often also necessary and recommended before the definitive animal experiment for approval purposes is started (e.g. in rabbits with regard to embryo-fetal studies or in rats before regulatory acute toxicity studies). These pilot studies serve as a means of determining the dose for subsequent regulatory studies and may play a role in assessing risks to humans. A distinction is essentially drawn between two design variants: ascending ascending-dose and fixed-dose studies. Separate applications are needed for pilot studies. The applicant should give exact details of the study.

Table 1: Animal experiments required by the regulatory authorities for pharmaceuticals (see also Appendix 1: Study types and corresponding guidelines. The first column of the table is used to denote the corresponding studies in the Appendix).

8	Short-term toxicity studies in rodents (2-/4-week), including toxicokinetics (may be performed as Extended single-dose toxicity study	**ICH** [18]
9	Short-term toxicity studies in non-rodents (2-/4-week), including toxicokinetics (may be performed as Extended single-dose toxicity study)	[18]
10	Subchronic toxicity studies in rodents (13-week), including toxicokinetics	
11	Subchronic toxicity studies in non-rodents (13-week), including toxicokinetics	
13	Chronic toxicity studies in rodents (6 month) , including toxicokinetics	[19]
13	Chronic toxicity studies in non-rodents (9-12 month), including toxicokinetics	[19]
17	*In vivo* Genotoxicity test (e.g. Micronucleus test in rats / mice)	[20]
16	Fertility study in rodents	[21]
15	Embryo-fetal development study in rodents and non-rodents	[22]
	Peri-/postnatal developmental studies in rodents	[22]
	Studies in juvenile animals (case-by case approach, normally in rodents only)[23, 24]	
12	Carcinogenicity study in rats	[25]
	Carcinogenicity study in mice or 6-month study in transgenic animals[42]	[26]
	Safety Pharmacology Studies (‚core battery' in rodents (CNS, Respiratory) and non-rodent species (Cardiovascular)	[27]
7	Skin sensitization	

[18] ICH M3 (R2) of 11 June 2009: Table 3 Footnote: c

[19] ICH S4 as of 2 September 1998

[20] ICH S2(R1) Draft of 6 March 2008

[21] ICH Guideline S5(R2) of November 2005 including Part II: Toxicity to Male Fertility

[22] ICH Guideline S5(R2) of November 2005

[23] FDA Guidance on Nonclinical Safety Evaluation of Pediatric Drug Products: February 2006

[24] EMA - CHMP Guideline on ...Non-clinical Testing in Juvenile Animals ...: 24 January 2008

[25] ICH Guidelines - S1A, S1C(R2)

[26] ICH Guideline S1B

[27] ICH Guidelines - S7A and S7B

	Phototoxicity study (only under certain conditions and in case of a positive *in vitro* test)	[28]
	ADME (Adsorption, Distrubution, Metabolism, Excretion) Studies	[29]
	Local tolerance studies for parenteral formulations	
	Ecotoxicologial studies (Tiered approach; for potential studies see Appendix 1)	

2.1.2. Biopharmaceuticals

In the case of biopharmaceuticals (e.g. therapeutic peptides/proteins and monoclonal antibodies) for regulatory purposes there are differences from the studies named in chapter **Fehler! Verweisquelle konnte nicht gefunden werden.**[30]:

In view of their high biological specificity and relevance for humans, studies in *non-human primates (monkeys)* are usually necessary. Endpoints for *local tolerability, safety pharmacology and fertility* may be incorporated into general toxicity studies in monkeys. The duration of studies is the same as for other pharmaceuticals and is based on the indication and duration of use in clinical studies.

If a second animal species (rodent) is biologically relevant, a study with repeated dosing must be carried out before the first use in humans. If the findings in the rodent and the monkey are comparable, the study programme may be continued with one animal species.

Genotoxicity studies are not normally necessary.

Carcinogenicity studies in rodent species are necessary if these substances are biologically active in rodents. The reasons for performing the studies must be explained.

Studies on *embryo-fetal and pre-/postnatal development in primates* are usually carried out in one study as an ‘Enhanced pre- and postnatal development’ (ePPND) study.

Further animal studies may be necessary for biopharmaceuticals, e.g.

- following a change in the manufacturing process that leads to analytical and functional differences in the molecule between two processes,
- following a change in the parenteral route of administration (e.g. from intravenous to subcutaneous),
- following chemical modification (so-called non-classical biopharmaceuticals, e.g. conjugates, fusion proteins).

2.1.3. Early safety tests in drug development

Toxicological studies are increasingly being carried out not only for development and product registration purposes, but also in the early phase for the selection of suitable substances. Especially in the context of drug development *different substances* can be toxicologically tested and compared in the sense of an early *'screening' or 'ranking'* in order to identify suitable candidates or to eliminate unsuitable ones from development, so safety studies are focused on substances that offer real potential for the patient.

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[28] ICH Guidelines S10 (in preparation)

[29] ICH Guidelines - S3A and S3B

[30] ICH Guideline - S6(R1): Addendum of 12 June 2011 to the Guideline of 16 July 1997

These early studies are carried out in close collaboration with research (pharmacology and biology), with the inclusion of defined endpoints (variables). In these studies it may make sense or even be necessary to include a registered or known product ("reference substance") in order to compare how the substances in differ in their toxicity profiles.

Usually, the duration of these studies is limited to a few days or weeks. Several dose levels per substance may be tested, but the numbers of animals are kept small. Apart from any special parameters that tend to be of a pharmacological character, studies (variables) are carried out in a manner similar or identical to experiments required by the regulatory authorities.

These studies are usually not carried out for regulatory approval purposes. There are no defined guidelines for this. [They are only to be carried out under GLP conditions if data is being gathered that is intended for assessing safety in humans / patients in initial clinical studies.]

The applicant should give precise details concerning the framework of the application or applications, and also detailed information, where meaningful, concerning his or her specific needs. Depending on the pharmacological effect or the general subject of the investigation, these studies are carried out in rodents (primarily rat or mouse), or also in non-rodents. Separate applications are to be submitted with the corresponding explanations as to why and when which animal species is to be used.

2.1.4. Pharmacokinetic and mechanistic studies

Pharmacokinetic and mechanistic studies are not subject to GLP conditions.

Mechanistic studies are carried out when a specific aspect (a finding or a toxicity), whether based on animal studies carried out or data in humans, has to be investigated in detail. This may be an essential requirement demanded by an authority or basically serve as risk assessment for a specific or possible exposure to a substance in humans or animals (i.e. containing a scientific and ethical component).

For studies of this kind, it makes sense to submit a framework application.

2.2. Agrochemicals

As the name indicates, these are substances and products that are used in agriculture (crop growing).

Two sets of data are required for approval, one for the *active substance* and another one for every *commercial product*. Only *in vivo* studies are listed here.

The application must contain precise details on the purpose for which testing is to be carried out.

The tests are to be carried out according to the guidelines listed in the following tables and in compliance with international regulations: OECD[31], US EPA[32, 33], and EU[34].

These studies are usually performed according to the principles of Good Laboratory Practice (GLP).

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31 OECD Test Guidelines and OECD Draft Guidelines

32 http://www.epa.gov/

33 EPA Test Guidelines Series 870 Health Effects OPPTS Test Guidelines (Office of Prevention, Pesticides and Toxic Substances) OPPTS-TestGuidelines_MasterList-2010

34 http://www.ec.europa.eu/enterprise/sectors/chemicals/files/reach/volume4_en.pdf

2.2.1. Active substance

The requirements regarding the data for the active substance are to a large extent harmonised worldwide and include at least the studies listed in Table 2 for human and ecotoxicology (consumers, users etc. and environmental risk assessment):

Table 2: Studies for active substance and underlying guidelines (see also Appendix 1: Study types and corresponding guidelines. The first column of the table refers to the corresponding studies in the Appendix.)

1	Toxicokinetics
2	Acute oral toxicity
3	Acute dermal toxicity
4	Acute inhalation toxicity
5	Acute dermal irritation / corrosion
6	Acute eye irritation / corrosion
7	Skin sensitization
8	(Repeated dose 28-day oral toxicity study in rodents)*
9	Repeated dose 90-day oral toxicity study in rodents
10	Repeated dose 90-day oral toxicity study in non-rodents
11	Repeated dose dermal toxicity: 21/28-day study
12	Carcinogenicity studies
13	(Chronic toxicity studies)
14	Combined chronic toxicity/ Carcingenicity studies
15	Prenatal developmental toxicity study (rat & rabbit)
16	Two-generation reproduction toxicity study
17	In vivo Genotoxicity tests
18	Neurotoxicity study in rodents
19	Developmental neurotoxicity study
20	Acute avian oral toxicity
21	Avian dietary toxicity
22	Subchronic and reproductive toxicity to birds
23	Acute toxicity to fish
24	Fish, early-life stage toxicity
25	Fish, life cycle test
26	Bioconcentration: flow-through fish test

(* not a formal request but regularly performed as a dose range-finding study)

Furthermore, *mechanistic studies* may be required (see: chapter 2.1.4).

2.2.2. Commercial products

The requirements regarding the data for commercial products are largely harmonised and usually include the studies listed in Table 3 for human toxicology (users and people exposed on use):

Table 3: Studies for the commercial product and underlying guidelines (see also Appendix 1: Study types and relevant guidelines. The first column of the table shows the relevant studies in the Appendix.)

2	Acute oral toxicity
3	Acute dermal toxicity
4	Acute inhalation toxicity
7	Skin sensitization
	Skin absorption: in vivo method *
5	Acute dermal irritation / corrosion
6	Acute Eye irritation / corrosion

(* Alternatively, an *in vitro* method as shown in Appendix 2 may be used or a 'bridging' study considered.)

2.3. Industrial chemicals

These substances include household products (substances and products that are predominantly used in private households or are intended for such use).

The requirements regarding industrial chemicals are regulated in Europe by the EU regulation known by the acronym REACH[35]. Although this regulation has no legal force in Switzerland, its use is recommended.

The studies required depend on the quantity of manufactured / imported substance. The following distinctions are drawn:

- Quantities of 1 – 10 tonnes[36].
- Quantities of 10 – 100 tonnes[37]
- Quantities of 100 – 1000 tonnes[38]
- Quantities of 1000 tonnes or more[39].

Precise details must be given in the application to indicate the quantitative range in which the testing will be carried out and the guidelines that will be applied.

With regard to the various quantitative ranges of the studies to be carried out, reference is made to Annexes VII – X of REACH. All *in vivo* study types that may be required are listed in Appendix 1.

The listed studies are only to be carried out if relevant data already generated before by other producers are either not available or cannot be procured.

In cases of doubt, evidence must be provided to show that the relevant studies are required by the authorities (e.g. ECHA).

35 European Parliament and Council Regulation (EC) No 1907/2006 - REACH: Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals of 1st June 2007

36 REACH - ANNEX VII (page 103 et seq.)

37 REACH - ANNEX VIII (page 107 et seq.)

38 REACH - ANNEX IX (page 111 et seq.)

39 REACH - ANNEX X (page 116 et seq.)

2.4. Food (additives)

This group includes substances that are used as additives in food or are intended for such use. Also classified here are safety tests associated with new methods of manufacture for foods or novel foods.

The studies are to be based on both national and international requirements: US FDA[40] and the European Union (EU)[41].

All toxicity studies should be carried out according to the current OECD or similar guidelines and the principles of Good Laboratory Practice (GLP).

In principle, studies are to be carried out using oral administration, and the dosage form should resemble human exposure as closely as possible. Administration in feed or drinking water approximates uptake with food more closely than administration by gavage (bolus effect).

Mutagenicity / genotoxicity is initially tested in *in vitro* test systems using bacteria and mammalian cells. Only if the *in vitro* tests are positive are *in vivo* studies also carried out, e.g. *in vivo* micronucleus test. (The latter in turn may also be replaced, if necessary, by the *in vitro* micronucleus test (see Appendix 2).)

An analogous step-by-step procedure (*in vivo* tests only in the event of positive *in vitro* tests) is applied when testing for endocrine activity (see: chapter 2.4.2).

2.4.1. Additives

The following compulsory tests are listed in Table 4.

Table 4: Safety tests required where applicable for food additives (see also Appendix 1: Study types and relevant guidelines. The first column of the table shows the relevant studies in the Appendix.)

8	Two / four-week toxicity studies in rats (dose-range finding)
9	Repeated dose 90-day oral toxicity study in rats
13	Chronic toxicity study in rats
12	Carcinogenicity studies (2 year in rats or 1 year in Mice)
	Carcinogenicity study in transgenic animal models (6-month) accepted as alternative[42]
16	Mammalian erythrocyte micronucleus test in vivo (for restrictions see text above)
17	Two-generation reproduction toxicity study in rats

2.4.2. Novel foods

It is not possible to draw up a standard list of toxicity tests that are to be carried out in all cases. Novel foods differ widely in their chemical composition; they are often not pure molecules but complex mixtures (e.g. extracts or whole foods, for example a “new” fruit such as kiwi). Since they are food components, the exposure of the consumer is often several orders of magnitude greater than with other chemical substances, such as pesticides, medicines and additives.

40 FDA Redbook (detailed information on additives for foods and colorants in foods)

41 http://eur-ex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:050:0044:0059:en:PDF

42 EMA - SWP: Use of genetically modified animal models for carcinogenicity assessment

The classical toxicity studies can often not be used in such situations. With novel foods, toxicity studies are never the only basis for investigating food safety. It is just as important to know the chemical composition, chemical methods involved in processing them to the end-product, experience of comparable previous use (history of use), their anticipated application and exposure[43].

The need for and suitability of toxicity studies must be established on a case-by-case basis. Their objective must be to obtain answers to questions that have not been settled and cannot be answered by any other means. In principle, studies are to be carried out using oral administration, and the dosage form should as similar as possible to human exposure. Administration in feed or drinking water approximates uptake with food more closely than administration by gavage (bolus effect). Toxicity studies with one rodent species (generally the rat) are sufficient.

The tests listed in Table 5 are considered suitable.

Table 5: Safety tests required where applicable for novel foods (see also Appendix 1: Study types and relevant guidelines. The first column of the table shows the relevant studies in the Appendix.)

8	Two / four-week toxicity studies in rats (dose-range finding)
9	Repeated dose 90-day oral toxicity study in rats (depending on potential use as juvenile toxicity study[44, 45])
17	Mammalian erythrocyte micronucleus test in vivo (for restrictions see text above)
	Special studies, depending on the indication
1	Toxicokinetics in rats
	Immunotoxicity[52]
18	Neurotoxicity study in rodents
30	Oestrogenic activity in vivo[46]
16	Two-generation reproduction toxicity study in rats
	Nutritional studies

2.5. Other special fields of application and risk

- Environmental contaminants (includes the field of ecotoxicology, i.e. the investigation of potential hazards of environmental contaminants, including radiation)
- Veterinary medicines for use in animals intended for food production. Here both tolerability studies in the target species and studies on residue behaviour are required.
- Medical devices [ISO guidelines]
- Nanotoxicology[47]
- Use of biomarkers and new technologies (e.g. imaging, '-omics')
- others.

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43 Howlett J., Edwards D.G., Cockburn A., Hepburn P. et al (2003) The safety assessment of novel foods and concepts to determine their safety in use. International Journal of Food Sciences and Nutrition 54 (supplement September 2003):1-32

44 Guideline on the Need for Non-Clinical Testing in Juvenile Animals of Pharmaceuticals for Paediatric Indications: EMEA

45 Nonclinical Safety Evaluation of Pediatric Drug Products: FDA

46 http://www.oecd.org/dataoecd/38/15/37773938.pdf - “Rat uterotropic test”

47 Regulatory Aspects of Nanomaterials: REACH

The underlying development strategy, the experimental design and the guidelines of any studies where applicable must be given in detail, described and explained. However, the studies relevant to safety must be carried out within the general framework of national and international guidelines (e.g. ordinance on medicines, OECD, ICH).

3. Replacement, reduction and refinement of animal experiments - the 3Rs

('Replace, reduce, refine' – the 3Rs.)

Validated *methods that are recognised by the regulatory authorities as alternatives to animal experiments* must be used instead of animal experiments. If this is not done, detailed and plausible reason must be explained to the approving authorities. Appendix 2 lists the relevant alternative methods.

Methods not recognised by the regulatory authorities as alternatives to animal experiments may be useful in an initial phase before preclinical studies as screening methods to stop further investigations with unsuitable substances at an early stage, to research mechanisms of action or to select particularly promising substances for further investigation. There are not yet any standardised guidelines for these test methods. But some are recommended by expert committees[48, 49, 50].

With a view to *reducing and refining animal experiments* it is increasingly being recommended that specific toxic endpoints be integrated into the classical standard studies (subacute, subchronic and chronic) whenever this is possible and scientifically acceptable, e.g.:

- *In vivo* micronucleus test in 4-week toxicity study[51].
- Juvenile toxicity in subacute or subchronic toxicity study.
- Chronic toxicity study and carcinogenicity study combined.
- Immunotoxicity[52], neurotoxicity and reproduction toxicity (e.g. sperm analysis) parameters in a subchronic study.

4. Content of applications

A separate application must be submitted for every study type and field of use.

Separate applications must be submitted for rodents and non-rodents.

Besides the usual information, the individual applications must contain the following details:

- Field of use or likely field of use (as described in chapter 2 of this information) of the test substances, also for ecotoxicity studies.
- All study guidelines used and, where applicable, registration requirements must be indicated and the standard protocols attached, where applicable.
- Number of doses and controls, animal species and strain (including, where applicable, an indication as to whether transgenic animals are to be used), number of animals per dose and total number of animals to be used per study.

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48 EU-EFSA: In silico methods (these are performed without any biological material)

49 US-FDA: use of 'Toxicogenomics'

50 http://www.oecd.org/document/62/0,2340,en_2649_34377_2348606_1_1_1_1,00.html and http://www.efsa.europa.eu/en/efsajournal/pub/1932.htm. Endocrine activity *in vitro*

51 http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129117.pdf and http://www.jstage.jst.go.jp/article/jemsge/32/2/37/_pdf

52 US-FDA: Redbook - Immunotoxicity Studies

- Study procedure and planned monitoring of animals. It is important here to describe clearly what will happen with the animals.
- Expected severity of constraint and criteria for discontinuing the study.
- Modes of administration of the test substances and study parameters (clinical study, nature and number of blood samples, urine and faecal samples etc.) in the animal.
- Quantity of substance: mg or ml per kg bodyweight, site and mode of administration.
- Blood samples: ml/kg body weight, sampling site and frequency.
- Total number of animals requested for use in the application.
- Variations regarding the number of animals, additional groups etc., including details of the conditions under which they are used.
- Detailed explanation of the need for the animal experiment and plausible information showing that there are no alternatives to the animal experiment. A ethical review must be held in which not only the benefits of the experiment for research and humans are discussed, but also the suffering of the laboratory animal.

5. Principles of approval

Experiments that expose animals to constraints are not permitted if they are intended to test products (end-products) / articles of daily use and the information sought can be obtained by analysis of the data on their components or the hazard potential is sufficiently known[53].

Applications for testing *cosmetic agents* (products, end-products) only require approval if the Federal Office of Public Health confirms that this is necessary.

[Experiments are admissible in the testing of possible allergenic effects of end-products. Before any approval is granted, the various interests must be considered, in which the needs of the consumer and the manufacturer for the cosmetic product in question should weighed against the constraints to be expected on the laboratory animals (pain, suffering, harm, fear, substantial impairment of wellbeing).

Applicants should established early on with the relevant foreign health authorities or their employers what other methods may be accepted without the use of animals.]

Applications for the testing of *tobacco and tobacco products* or *alcohol, recreational drugs and similar products* will not be approved. The hazard potential of these products is regarded as sufficiently well known today or can be researched without the use of animals. Applications concerning scientific questions on chemically defined ingredients of tobacco and tobacco products may be permitted.

Animal experiments for the *registration of substances and products in another country* may be approved if the registration requirements conform to international regulations[54].

Testing of generics: in certain cases, generics are not manufactured / formulated in the same way as the reference substance, and Swissmedic will demand re-testing, if necessary.

The *ecotoxicity of medicines* must be established on submission for approval of a new active substance. If a theoretically calculated value is exceeded here, experimental studies in organisms are required by the authorities.

Applications for *tests in fish for the monitoring of wastewater pipes* from companies will usually be rejected. Exceptions may be justified if, in the case of toxicity occurring in fish, the wastewater can be

53 Animal Welfare Ordinance (TSchV) of 23 April 2008: Art. 138 Para. 1 b

54 Animal Welfare Ordinance (TSchV) of 23 April 2008: Art. 138 Para. 1 a

withheld from direct discharge and the applicant can adequately explain that methods of analytical chemistry or other methods that do not involve the use of animals cannot offer sufficient reliability.

For some years, the so-called fish egg test has been used abroad as an alternative to the acute fish test in wastewater testing[55]. For this there is an OECD Draft Guideline on using the fish egg test (now called the "fish embryo test") for testing chemicals[56].

Applications for *investing the cause of fish deaths* will only be approved if the applicants can provide sufficient justification to show that methods of analytical chemistry or other methods that do not involve the use of animals cannot produce adequate results and that only a few animals per test are used.

Applications for testing *discharges from municipal sewage treatment plants* in animal experiments will only be approved if these are adequately justified in scientific terms or are required by the authorities.

6. Reporting on tests performed

A report must be compiled on the number of animals used in a calendar year by the end of February in the following year (Form C)[57].

The report must contain at least the following information:

- Total number of animals used, broken down by species and degrees of severity[58].
- Precise number of substances tested.
- Number of animals per substance tested, summarised according to number of substances for which the same number of animals were used; additionally, in the case of deviations from the standard, the number of doses and the number of animals per group. Deviations must be explained.
- Additionally, for approvals involving several protocols, itemisation of details for the various protocols.

Federal Veterinary Office

[55] Germany: DIN 38 415-6, ISO 15088 (2007)

[56] http://www.oecd.org/dataoecd/39/59/36817070.pdf

[57] Animal Welfare Ordinance (TSchV) of 23 April 2008: Art. 145

[58] FVO information: c nachlassification of animal experiments according to degrees of severity, 800.116-1.04 and 800.116-1.05

7. Appendix 1: Study types and corresponding guidelines

	Guideline	OECD[59]	OPPTS[60]	EU[61]
1	Toxicokinetics	417		B36
2	Acute Oral Toxicity – Fixed Dose Procedure Acute Oral Toxicity – Acute Toxic Class Method Acute Oral Toxicity – Up-and-Down Procedure	420, 423, 425	870.1100	B1bis B1 tris
3	Acute Dermal Toxicity	402	870.1200	B3
4	Acute Inhalation Toxicity	403	870.1300	B2
5	Acute Dermal Irritation/Corrosion	404	870.2400	B4
6	Acute Eye Irritation/Corrosion	405	870.2500	B5
7	Skin Sensitization	406	870.2600	B6
8	Repeated Dose 28-day Oral Toxicity Study in Rodents	407	-	B7
9	Repeated Dose 90-day Oral Toxicity Study in Rodents	408	870.3100	B26
10	Repeated Dose 90-day Oral Toxicity Study in Non-Rodents	409	870.3150	B27
11	Repeated Dose Dermal Toxicity: 21/28-day Study	410	870.3200	B9
12	Carcinogenicity Studies	451	870.4200	B32
13	Chronic Toxicity Studies	452	870.4100	B30
14	Combined Chronic Toxicity/ Carcingenicity Studies	453	870.4300	B33
15	Prenatal developmental Toxicity Study	414	870.3700	B31
16	Two-Generation Reproduction Toxicity	416	870.3800	B35
17	Mammalian Erythrocyte Micronulceus Test Mammalian Bone Marrow Chromosome Aberration	474, 475	870.5385, 870.5395	B11 B12
18	Neurotoxicity Study in Rodents	424	870.6200	-
19	Developmental Neurotoxicity Study	426	870.6300	-
20	Acute Avian Oral Toxicity	223	850.2100	(1)
21	Avian Dietary Toxicity	205	850.2200	205 (3)
22	Subchronic and Reproductive Toxicity to Birds	206	850.2300	206 (3)
23	Acute Toxicity to Fish	203	850.1075	(2)
24	Early-Life Stage Toxicity in Fish	210	850.1400	210 (3)
25	Life Cycle Test in Fish[62]		850.1500	
26	Bioconcentration: Flow-Through Fish Test	305	850.1730	305 (3)
27	Amphibian Metamorphosis (Frog)	231	890.1100	
28	Fish Short Term Reproduction	229	890.1350	
29	Hershberger Assay (Rat)	441	890.1400	
30	Uterotrophic Assay (Rat)	440	890.1600	

(1) SETAC — Procedures for assessing the environmental fate and ecotoxicity of pesticides
(2) 92/69/EEC, Method C
(3) OECD Guideline

[59] Full list of OECD guidelines

[60] OPPTS Harmonized Test Guidelines - Master List

[61] Test Methods Pursuant to Regulation (EC) No 1907/2006; Part B: Methods for the Determination of Toxicity and Other Health Effects, Page 143 ff.

[62] OECD: Detailed Review Paper on Fish Life-Cycle Tests

8. Appendix 2: Alternatives to animal experiments and other methods

As part of the effort to replace, reduce an refine (3Rs) the last few decades have seen the development, validation and recognize the development, validation and recognition of numerous alternative methods (as at June 2011)[63, 64].

Animal experiment	OECD	Alternative or supplementary method	OECD
Fish, Acute Toxicity Test	203	Short Guidance on the Treshold Approach for Acute Fish Toxicity and OECD Draft Guideline on the Fish EmbryoToxicity Test *(currently undergoing round robin testing and validation)*	126
Skin Absorption: In Vivo Method	427	Skin Absorption: In Vitro Method	428
Skin Sensitisation	406	Skin Sensitisation	429
Phototoxizität in vivo	-	In Vitro 3T3 NRU Phototoxicity Test	432
Acute Dermal Irritation/Corrosion (since 2002 amended by Supplement on ‚weight-of-evidence analysis')	404	In Vitro Skin Irritation	439
		In Vitro Skin Corrosion: Transcutaneous Electrical Resistance Test (TER)	430
		In Vitro Skin Corrosion: Human Skin Model Test	431
		In Vitro Membrane Barrier Test Method for Skin Corrosion	435
Acute Eye Irritation/Corrosion	405	Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants	437
		Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants	438
In vitro Mammalian Chromosome Aberration Test (Micronucleus Test)	473	In Vitro Mammalian Cell Micronucleus Test	487
Two-Generation Reproduction Toxicity	415	Extended One-Generationen Test *(currently in an advanced stage of evaluation; Release expected in 2011)*	

63 OECD Section 4: Health Effects

64 European Centre for the Validation of Alternative Methods - ECVAM: European Commission – Joint Research Centre – Institute for Health and Consumer Protection

9. Appendix 3: Details on compilation of technical information

- This technical information was drawn up between April and June 2011.
- The working group was made up as follows:

Organisations / fields of use	**Represented by:**
Federal Veterinary Office	Dr. Ingrid Kohler
Coordination: Swiss Society of Toxicology	Prof. Dr. Friedlieb Pfannkuch
Approval authority for applications	Dr. Ignaz Bloch (cantonal veterinarian BL)
Agency for approval of medicines	Dr. Beat Schmid (for Swissmedic)
Pharmaceuticals (*)	Dr. Jacques-André Maring (CSL Behring)
	Dr. Rudolf Pfister (Novartis)
	Dr. Marianne Treher (Actelion)
Agrochemicals / industrial chemicals	Dr. Werner Kobel (for Syngenta)
	Dr. Helmut Schmid (Harlan Laboratories)
Food (additives)	Dr. Irène Perrin (Nestlé)
Ecotoxicology	Prof. Dr. Kirstin Schirmer (EAWAG)
Alternative methods – 3R	Dr. Stefanie Schindler (Animalfree Research Zürich)
University research	Prof. Dr. Hanns Ulrich Zeilhofer (Uni / ETH Zürich)

(*) Special contributions: general toxicology	Dr. Georg Schmitt (F. Hoffmann-La Roche)
Biopharmaceuticals	Dr. Sven Kronenberg (F. Hoffmann-La Roche)
Early safety studies	Dr. Berhard Schlaeppi

- The working group recommends having the references contained in this information updated / checked annually by a specialist.