Animal Welfare Report 2015

Swiss research-based pharmaceutical industry
The research-based pharmaceutical industry is committed to finding new treatments and medicines for patients. In Interpharma (the association of research-based pharmaceutical companies in Switzerland) the industry has joined together to represent its shared interests.

Interpharma works closely with all parties involved in the healthcare system and the lobby groups of the pharmaceutical industry in Switzerland and abroad. We provide information on the concerns that are of relevance to the industry, on the pharmaceuticals market of Switzerland, the healthcare system and biomedical research.
Preface

The Animal Welfare Charter of Interpharma was adopted five years ago. With this charter we, the research-based pharmaceutical companies that are largely based in Switzerland, underline our commitment to meet our ethical obligations in animal experiments. We commit to further improving conditions in animal experiments and the protection of laboratory animals, replacing as many animal experiments as possible, keeping the number of laboratory animals as low as possible and reducing the stress on animals.

We support the improvement of the quality of life for humans and animals by developing more effective medicines and more accurate diagnostic methods. In doing so, we are mindful of the need for high quality and use the most advanced technologies and methods.

Research in animals is indispensable to the development and testing of new treatments. The appropriate use of laboratory animals provides important insights into the pathogenesis and mechanisms of serious diseases and makes sure medicines are safe, effective and well tolerated. Without this important foundation of research and development most medicines and treatments that society and patients benefit from today would not exist.

We are aware that the use of animals in research requires us by law and also ethically to apply the highest standards, and we live up to our responsibilities. We not only support projects in our member companies that specifically improve animal welfare above and beyond what is legally required. We also engage in an ongoing exchange of views and information with representatives from academia, politics, regulatory authorities and animal welfare organizations and contribute to the dialogue with the general public. This annual report is the fifth since the signing of the charter. It documents the diverse and ongoing efforts of the pharmaceutical industry to ensure that animals in research are handled responsibly.

* In 2015 Novartis celebrates the 10th anniversary of its global Animal Welfare Policy. This policy defines animal welfare standards and ethically responsible principles for handling laboratory animals that are observed worldwide in Novartis. The 3Rs concept (Reduction, Refinement and Replacement), well-trained personnel and compliance with legal directives form the basis of the policy. The Novartis Animal Welfare Organization, which has more than 20 Animal Welfare Officers, implements the Novartis guidelines at national and international level and monitors their implementation both within the company and with external business partners.
The long path to a new medicine

The long path to new products for the benefit of patients also inevitably involves studies in and with animals in many cases.* Even the most state-of-the-art technology cannot yet provide adequate means for modelling live organisms in their entirety or showing the interplay between organs and organ systems. At present, research in animals is still essential in order to understand disease mechanisms and develop and test new treatments.

In drug development, the animal experiment is always the last step taken by a drug candidate. Before this, there is a long path of animal-free experiments. Only drug candidates that produce particularly good results in these experiments will then be tested in animals for efficacy and safety as required by law. The overview shows the long pathway to the discovery of a new medicine and the targeted use of animals in research in the various (pre)clinical phases of development.

* With regard to the approval of medicines and the review of chemical risks, animal studies are frequently required for the assessment of possible health risks to humans and animals in the framework of standardized international test requirements (see ICH Guidelines; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). These guidelines apply not only to Switzerland, but also to Europe, the US and Japan.
**Preclinical phase**

**Chemical and biological research**
- Active-substance synthesis
- Targeted evidence of efficacy in biochemical experiments and in cell systems
- Proof of efficacy of positively tested medicines in the animal model
- Study of pharmacology (science of the interaction between substances and live organisms) and pharmacokinetics (entirety of all processes to which a medicine is subject in the body, such as absorption, distribution, metabolism and excretion) in the animal.

**Preclinical development**
- Tolerability study in animals
- Teratology (exclusion of malformations in the animal foetus)
- Production of active ingredient
- Development of suitable dosage forms

**Clinical Phase I**
- Safety and tolerability in humans
- Pharmacology and pharmacokinetics in humans (effects of substance)
- Effect in healthy volunteers
- Production of active ingredient in large quantities

**Clinical Phase II**
- Pharmacology and pharmacokinetics in patients (chemical alteration of active substance in the body)
- Effect in a relatively small number of selected patients
- Fertility (effect on reproduction in animals)
- Tolerability over 6, 12 and more months in animals

**Clinical Phase III**
- Effect in a relatively large number of patients under practical conditions
- Exclusion of a carcinogenic effect after prolonged use in animals
- Market launch parameters
- Development of final dosage forms
- Production of active ingredient for launch

**Clinical Phase IV**
- After launch of the medicine: further targeted clinical trials where necessary
- Monitoring of the medicine in medical practice
- Reporting and evaluation of side effects
Projects and programmes in support of the 3Rs

**3R Research Foundation Switzerland** has supported research for better methods or alternatives to animal experiments since 1987 and has been financed from the outset by the federal government and Interpharma. It is headed by an independent Board of Trustees. In the last 28 years, out of around 450 applications received for contributions the Foundation has supported around 138 research projects with a sum amounting to a total of about 18 million francs. These projects are assessed and monitored by a committee of highly qualified experts. An important indicator of how successful the work of the Foundation is – and the extent to which awareness of the research on alternative methods has increased at the same time – is the fact that the number of high-quality projects submitted annually has risen steadily in the last few years. The website of the Foundation lists all the sponsored projects and describes them in detail.

**NC3Rs CRACK IT**

NC3Rs (National Centre for the Replacement, Refinement & Reduction of Animals in Research) is an independent organization that is entirely funded by the government of the United Kingdom and is aimed at promoting scientific activities concerning the 3Rs. Under the CRACK IT programme, the organization addresses scientific challenges. On the NC3Rs homepage, researchers from industry publish an appeal e.g. for a new alternative method. Then academic groups that address this scientific question can apply for research funding from the NC3Rs.

One of the projects, which is supported by Interpharma member companies, is concerned with the discovery and investigation of renal toxicity using cell models. The model focuses on replication of the cellular architecture of the renal tubule, because this is an important site of potential drug-induced renal toxicity. This allows toxic effects to be identified early on in drug development.

**IMI – Innovative Medicines Initiative**

This initiative represents the world’s largest public-private partnership in the life sciences. It is pursuing the goal of developing the next generation of vaccines, medicines and treatments. Together with companies, universities, public-sector laboratories, innovative small to medium-sized enterprises (SMEs), patient groups and regulatory authorities, the aim is to find new treatments and to secure the future of the European pharmaceutical industry’s international competitiveness. IMI 1 was set up with a budget of EUR 2 billion for the period of 2008 to 2017. IMI 2, which runs from 2014 to 2024, is being given an even bigger budget of EUR 3.276 billion. The EU will contribute EUR 1.638 billion out of the EU framework programme for research and innovation Horizon 2020. The European Federation of Pharmaceutical Industries and Associations (EFPIA) has committed EUR 1.425 billion in the form of non-pecuniary benefits.

In the selection of topics for the IMI working programmes, planning has been informed by aspects relating to the 3Rs. One example here is the eToX project. In this project, innovative methods and strategies as well as novel software tools are being developed with a view to improving predictions of the potential toxicity of new drug candidates. This would mean that animal experiments would only have to be carried out in optimized substances, which would reduce the overall number of laboratory animals needed in preclinical studies. The project was endowed with a total budget of EUR 18.7 million and is set to run until 2017.

Another example is the StemBANCC project. The aim of the project is to obtain and characterize 1500 high-quality human induced pluripotent stem cell lines (iPS cells) from 500 patients as a research tool for drug discovery. The iPS cells are used to develop human disease models *in vitro* and to drive drug development in the early phase. Liver, heart, nerve and kidney cells can also be created for toxicological tests. The cell lines help to improve and speed up the process of drug development and to reduce toxicity studies in animals. To date, 50 pa-

**Article 1** “We commit to apply and actively promote the 3Rs* (Reduction, Refinement and Replacement of animal studies), especially with regard to the research, development and implementation of methods and techniques which allow further replacement of animal studies, a reduction in the number of animals used or alleviation of the pain and stress of laboratory animals.”

[The image contains a quote from Article 1: “We commit to apply and actively promote the 3Rs* (Reduction, Refinement and Replacement of animal studies), especially with regard to the research, development and implementation of methods and techniques which allow further replacement of animal studies, a reduction in the number of animals used or alleviation of the pain and stress of laboratory animals.”]
tients each have been recruited for patient cohorts in diseases such as Alzheimer’s, neuropathy, diabetes, Parkinson’s, migraine and bipolar disorder. The project has a budget amounting to EUR 55.6 million and is set to run until 2017.

**Dogs Rehoming Programme**

One of the member companies introduced a dog rehoming programme in 2015. This programme allows dogs above a certain age to lead a life embedded in a family after their services with the company. Prerequisites for rehoming of animals include the careful selection of animals with regard to their health and behavioural attitudes as well as careful selection of the new owners.

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**3Rs awards and working groups**

**In-house awards**

In some member companies, national and international in-house prizes are regularly awarded for work relating to the 3Rs. Researchers from the various departments have the opportunity to submit their work and developments for appraisal. The last few years have seen a steady increase in interest in participating in the 3Rs awards. One member company, for example, has reported a 30 per cent increase in the projects submitted.

Besides the regular 3Rs awards that take place in member companies, there has also been an overarching working group in place for some years in one member company, as well as a local cross-departmental 3Rs working group to promote the principles of the 3Rs.
Examples of in-house 3R awards

**Refinement:**

**A new dog model for non-invasive bile collection**

*In vivo* models for metabolite identification play an important role because they give an integrated picture of the total metabolic fate and provide information on the extent of direct elimination of unchanged drug. In this context, a non-invasive dog model for collection of bile was established in order to obtain metabolism data for potential drug candidates at an early stage of drug development. The procedure used so far for bile collection from dogs includes surgical bile duct cannulation with a risk of infection and a prolonged recovery period of 5 weeks. The new model operates with a commercially available device that is applied in humans for non-invasive sampling of upper gastrointestinal content. With this model the laparotomy could be replaced by a non-invasive procedure involving no pain and no recovery times.

**Replacement:**

**Human skin models for vaccines research**

Human skin equivalents and explants represent a valid alternative to animal models for studying skin infections and mode of action of vaccine formulations in the dermis. While skin equivalents are amenable to extensive manipulation, explants provide a closer representation of the human skin. Skin equivalents have been developed using primary or immortalized human keratinocytes, grown at an air-liquid interface on collagen type I, which was seeded with fibroblasts. Histology and immunofluorescence staining for the markers of skin differentiation showed that after several days of growth the keratinocytes fully differentiated. The characteristics appeared comparable to the ones observed analyzing human skin explants obtained from subjects undergoing surgical procedures, suggesting that the skin equivalent closely resembles human skin characteristics. The two models could be successfully used to study host-pathogen interaction of *Staphylococcus aureus*.  

![Image of a pig and a yellow ball]
Werner Scheuer was awarded the 2014 research prize of Rhineland-Palatinate in Germany for his development of alternatives to animal experiments. The cancer researcher and biochemist from healthcare company Roche succeeded in developing a method in which tumour growth can be measured at different times using luminescent agents in conjunction with 3D imaging studies.

You were awarded the 2014 Rhineland-Palatinate research prize for the development of alternatives to animal experiments. What is the approach that you are pursuing in your research?

The aim of our research was to measure simultaneously over time firstly the distribution of an active substance in the live animal (biodistribution), secondly the concentration of an active substance in the tumour and thirdly the antitumour efficacy. For this we use a combination of various methods and techniques.

What are these methods and what do they do in detail?

The antitumour efficacy is measured by using tumour cells that have been labelled with the enzyme luciferase. These cells luminesce in the animal only when they are alive and divide, so that the growth of the tumour and the metastatic spread to other organs can be monitored precisely by measuring the bioluminescence. By modifying the luciferase it is possible to describe the effect on the tumour cells in more detail. For example, we can now determine whether the substances to be studied induce cell death (apoptosis) or block the activity of kinases. The therapeutic active substances can be labelled quite easily using a fluorescent dye. After administration, the distribution of the substance in the live animal and its concentration in the tumour can now be determined by measuring the fluorescence, and the efficacy of the substance can be determined by measuring bioluminescence at the same time. In addition, the blood concentrations of the fluorescence-labelled active substance can be determined by measuring fluorescence in the eye of the mouse at any time, so no blood sampling is necessary anymore. This simultaneous measurement of the pharmacokinetics, biodistribution and pharmacodynamics in the live animal over the period of the study now allows us to determine the optimum dose of active substance for an antitumour effect.

“In the technique of three-dimensional fluorescence histology ensures that the effect of new active substances with regard to vascular supply in a tumour can be described in detail.”

In addition, we have developed a method that allows the vascular structure in a tumour to be described in exact detail. In contrast to classical immunohistochemistry, where labour-intensive and time-consuming manual slicing of the tumours is necessary, the new method allows optical cross sections of the tumour to be obtained without the need for slicing. For this the method makes use of a special illumination technique that highlights an individual ultra-thin plane of the tumour from the side using two very thin laser light sheets arranged opposite each other. The fluorescent light radiated here by the tumour tissue, dye-labelled blood vessels, cell types and active substances is detected by a special camera. In this way, the entire tumour is illuminated with laser light, layer by layer, and the fluorescence signals generated in the various planes are recorded. The scanning of a 5 mm tumour takes much less than half an hour – an extreme advantage when it is a question of filtering out the best anti-angiogenic substance from a series of drug candidates. The optical cross sections prepared in this way (500 to 1000 individual cross sections) can be automatically...
Stefan Weigt was awarded the 2014 animal welfare research prize of Hessen (Germany). The toxicologist from the Darmstadt pharmaceutical, chemical and life sciences company Merck has developed an in vitro alternative method with fish eggs that meets all the key criteria for developmental toxicity testing for the first time.

You were awarded the Hessen animal welfare research prize in 2014. What are you working on in your research?

In my research on the zebrafish embryo, I have devoted myself to a test that can be used to establish whether a substance has the potential to damage a developing embryo and to cause malformations (developmental toxicity). The main focus of my work was on the aspect of metabolic activation. There are substances that have only a minimal, if any, potential for developmental toxicity themselves, but whose metabolites damage the embryo.

These substances which only show their embryotoxic effect following modification or metabolism – this is referred to as metabolic activation – are described as proteratogens. Until a few years ago, it was assumed that such proteratogens could only be successfully activated and tested in the zebrafish embryo test when isolated extracts of rat liver, so-called microsomes, are included in the test-tube. But I was eventually able to show in my research that zebrafish embryos are capable of metabolic activation and that substances which only induce embryotoxic effects after metabolism or activation can be successfully tested in the zebrafish embryo.

What are the advantages of the new method and what impact will it have on animal numbers?

The combination of bioluminescence (measurement of tumour growth, metastasis and the efficacy of the therapeutic agent) and fluorescence (demonstration of the distribution of a therapeutic substance in the animal and its concentration in the blood) allows important features of an active substance (pharmacokinetics and pharmacodynamics) to be measured non-invasively at the same time over the whole period of the experiment. The technique of three-dimensional fluorescence histology ensures that the effect of new active substances with regard to vascular supply in a tumour can be described in detail.

The methods of in vivo and ex vivo imaging described allow new active substances to be tested in detail for their effect with regard to growth of the primary tumour, metastasis and tumour vascularization. In addition to reducing the number of laboratory animals, this approach also allows more accurate results to be generated and avoidable repeat tests to be reduced.
With the new method, you can test the effect of substances on development \textit{in vitro} using fish embryos. How does this work?

Immediately after fertilization, the substance to be tested is added to the fertilized eggs. A special buffer is used here as a medium in order to guarantee a physiological pH value. This is important, because the stability of reactive metabolites may be dependent on the pH value. The embryos are then exposed over the whole embryo development period of 3 days and are tested daily under the microscope for survival and a wide variety of malformations. The rat liver tissue used in the previous test brought with it certain problems: the tissue and thus also the test substance had to be removed from the reaction vessel again after only one hour, because otherwise embryo damage would occur even without the addition of a test substance. It is a fact that most malformations are very heavily dependent on the duration and/or time of exposure. With this further development of the test without rat liver tissue, it is now possible to cover the entire development of the embryo.

“The zebrafish embryo test is an \textit{in vitro} or alternative method that for the first time meets all the key criteria for developmental toxicity testing.”

What are the advantages of the method and what influence does it have on the number of animals?

Testing active substances for possible malformations in embryos is required by the regulatory authorities for the approval of medicines and in some cases also chemicals. Until now, developmental toxicity has been tested in pregnant rats and rabbits, where 80-100 mother animals per species and up to 600 (rabbit) and 1400 (rat) foetuses have to be used for testing one substance. The zebrafish embryo test is an \textit{in vitro} or alternative method that for the first time meets all the key criteria for developmental toxicity testing: it covers the entire period of embryo development – from the fertilized egg cell to the fully developed embryo. Potential damage caused by metabolites is also taken into account without having to use mammalian tissue for this. There is thus also no indirect need for animals resulting from organ removal experiments. A further major strength is that both the nature of the effects and the concentrations at which they are induced are very similar to the situation in humans.

Since the method has not yet been validated, its main field of use at present is in the screening of candidates for drug development, which can also be used to reduce animal experiments.
International guidelines and standards

**EU Directive**
In the EFPIA working group for animal welfare, Interpharma representatives collaborate with representatives from member companies to include suggestions for high animal welfare standards throughout Europe. Since 2010 this European group has been headed by a representative from an Interpharma member company. One of the main tasks of the group consists in actively collaborating on the realization and implementation of EU Directive 2010/63 on the protection of animals used for scientific purposes in the 28 Member States of the European Union.

The group also champions open exchange and good cooperation with other organizations committed to research in the field of the 3Rs. The EFPIA working group is made not only up of experts in toxicology, pharmacology, ethics, the law, public affairs and animal welfare, but also of observers from universities and regulatory authorities.

**ICH**
*(The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).*

This project brings together regulatory authorities from Europe, Japan and the US and experts from the pharmaceutical industry to discuss the scientific and technical aspects of pharmaceutical product registration. The purpose of the ICH is to harmonize the tests that are used during the research and development of new medicines and the technical directives and requirements for product registration. The aim of this standardization is to bring about a more economical use of human, animal and material resources and to eliminate unnecessary delays in the global development and availability of new medicines. At the same time it should serve as a guarantee for quality, safety and efficacy.

The harmonization process is complex and can take several years. It touches on quality, safety (which is where animal experiments come in), efficacy and multidisciplinary areas. The ICH Steering Committee meets every two years for one week; 10–15 working groups involving 200–300 experts take part. The European umbrella organization of the pharmaceutical industry (EFPIA) is represented on the Steering Committee. EFPIA is a very active partner in the field of safety tests and the use of alternatives to animal experiments.

**Ethical standards**
A representative of an Interpharma member company also has a seat on the ethics group of ICLAS, the International Committee for Laboratory Animal Science. The aim of ICLAS with its international network of researchers, universities and institutes is to improve standards in laboratory animal science worldwide through ethical guidelines.

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**Article 2** “We commit to ensure high-quality and state-of-the-art housing and care conditions for our laboratory animals and we strive to continuously improve these conditions.”

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**The ICH Steering Committee**

**WHO**

**EU**

**EFPIA**

**MHLW**

**JPMA**

**FDA**

**Swissmedic**

**IFPMA**

**PhRMA**

**Health Canada**
IQ Consortium – 3Rs Leadership Group
Various Interpharma member companies are also members of the IQ Consortium (International Consortium for Innovation and Quality) and participate in the 3Rs Leadership Group. The group was established to promote the exchange and realization of high-quality scientific practices and thus to promote the principles of the 3Rs in animal research aimed at the discovery and development of new medicines, vaccines, medical devices and health products for use in humans and animals.

There are official contacts with Interpharma through the European Liaison Working Group of the IQ Consortium’s 3Rs Leadership Group. This sub-group promotes the exchange of 3Rs expertise and mutual willingness to share not only know-how of relevance to the 3Rs but also the firm belief – based on mutual interest – that similar objectives are being pursued both in the US and in Europe. The 3Rs Leadership Group seeks collaboration in anticipation of a shared added value.

Examples of current activities
- JAALAS special edition: with the cooperation of the 3Rs Leadership Group a special edition of the Journal of the American Association for Laboratory Animal Science (JAALAS) was published on the subject of the 3Rs (title: “Global 3Rs Efforts: Making Progress and Gaining Momentum”; March 2015).

- Global 3Rs Awards Programme: in collaboration with the AAALAC International (Association for Assessment and Accreditation of Laboratory Animal Care International) a global 3Rs awards programme has been initiated. The programme is aimed at researchers from academia and industry. The projects may include changes to existing research techniques or innovative research approaches, such as improvements over whole-animal models, tissue-based models (cell lines, tissue cultures), molecular techniques, analytical and computational models, study design or technical refinements (sampling techniques, improved test methods) and translational medicine applications.

- 3Rs Webinar Series: joint organization of webinars on the 3Rs together with the NJABR (New Jersey Association of Biomedical Research). The 3Rs Webinar Series comprises nine sections covering the basic principles of the 3Rs and shows their importance in drug research and the development of medicines involving animal studies.

Continuing internal and external education
- One member company offers 1 to 2 officially accredited days of continuing education in Switzerland every year, allowing people who work on animal experiments to complete the further training required of them by law. Part of this event covers topics relating to the 3Rs, such as the presentation of contributions that have been submitted for the 3Rs award. The presenters also include representatives of the cantonal veterinary office, which makes sure employees are kept informed about the current status of legislation and about the concerns of the animal research commission.

- One of the member companies hosted the annual general meeting of the SVBT (Swiss Association for Animal Husbandry Training). Subsequent to the meeting the participants were invited to visit the animal facility of this company.

**Article 3** “We commit to develop and foster education and training for all our employees and associates who work with animals.”
Global audits of partner and subsidiary companies
Research institutions that carry out animal experiments on behalf of Interpharma companies, as well as partner and subsidiary companies, must commit to complying with stipulated technical requirements and ethical standards. The individual member companies of Interpharma carry out regular audits with external research partners throughout the world. These audits serve not only to ensure harmonization of standards and compliance with these standards, but also help to boost capacity and expertise in markets where the use of animals in research is insufficiently regulated in law, if at all.

Article 4 “We commit to contractually oblige external partners to comply with our high standards of animal welfare when they conduct animal studies for us or supply us with animals.”

What is an audit?
An audit is defined as the systematic and independent inspection of the data, statements, records, processes and activities of a company for a specified purpose. In an audit procedure, the auditor examines the material made available for inspection, verification and evaluation and, on this basis, arrives at an assessment that is reflected in an audit report. One member company has taken efforts to ensure compliance with animal welfare standards a step further by initiating regular visits to internal laboratory and animal housing facilities, as well as frequent informal meetings with people who have to do with animal experiments.
Audit/auditing in the context of the Charter on Animal Welfare encompasses procedures and/or (control) processes which have been established in order to ensure compliance with sets of conditions of housing, care and handling of animals which have been agreed on by the signatories of the charter. These sets of applicable conditions have as a minimum level the legal standards of animal welfare laid down in the US Animal Welfare Act (AW Act 1966/2007) – extended to all vertebrates (i.e. AW Act [9 USC §3] – and its regulations, and the US Guides for the [1] Care and Use of Laboratory Animals and [2] Agricultural Animals in Agricultural Research and Teaching. The guides are enforced by the USDA (United States Department of Agriculture), APHIS (Animal and Plant Health Inspection Service), and Animal Care agency. (http://www.nal.usda.gov/avic/legislat/usdaleg1.htm). Interpharma audits: In countries where the legal requirements are above this level the minimum standard is adapted accordingly.

**Article 5** “We commit to apply vigorous internal auditing systems*, which ensure compliance with the animal welfare standards agreed upon.”

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**Strict internal audits**
The member companies check compliance with defined quality standards in their own research institutions worldwide according to individual procedures. All criteria assessed by the companies are defined in writing and have global validity.

**Global internal exchange**
To obtain an in-depth insight into its sites in Asia and the USA, one Interpharma member company dispatched its Animal Welfare Officers from Switzerland on a 6-week stay abroad, during which they had the opportunity to gain an insight into the work procedures of colleagues and to familiarize themselves better with the legal requirements and processes. The sites concerned also benefit in turn from the know-how and expertise of the Animal Welfare Officers.
Joint audits of Interpharma member companies
The audit working group of Interpharma was set up in 2010 following the establishment of the Animal Welfare Charter. The basic idea of this audit working group is to undertake joint audits of breeding companies from which the Interpharma member companies obtain animals. These audits are designed to identify any deficits in animal welfare early on and to arrive at improvements in a spirit of partnership. The exchange is intended to ensure optimum compliance with the minimum legal requirements and to improve and simplify efforts that go beyond this basic minimum for observing the principles of the 3Rs. The relevant checklists, position papers and joint regulation took some time and were developed over the last few years across all companies. In 2014, the first audits were successfully conducted in other European countries.

Audits in 2015
In the year under review, a total of four joint audits were carried out. Two audits were conducted in other European countries and two additional ones at mutual breeders’ in the US. The audit results are used jointly within the member companies and treated in confidence.

Complex process and comprehensive checklist
An audit process is very complex and requires all parties to have a sound and detailed knowledge of the legal regulations and requirements specific to animal housing.

The documents required for the local audit procedure are sent out with the checklist to the breeder in the run-up to the actual audit. The breeder may already answer some of the questions in advance and prepare validation documents. During the actual on-site audit, which usually lasts two days, the Interpharma audit committee (usually representatives of two to three Interpharma member companies) inspects the individual animal housing facilities and meets the animal technicians on site, as well as the responsible veterinarians. The joint checklist covers around 200 questions on the following areas:

- Country-specific accreditation status by the respective veterinary office
- Qualification and training certification of the employees
- Nature and method of data gathering
- Details of animal breeding and animal housing
- Feed and water supplies
- Information on hygiene, pest control, cleaning of cages and waste management
- Guidelines on veterinary care, disease and quarantine measures
- Health and safety programmes for employees
- Emergency and crisis management plan
- Regulations on transportation and procurement of laboratory animals
- Species-specific requirements

Further procedure and conclusion
Following the actual audit on site, the audit committee compiles an audit report, provides a detailed list in the CAPA (corrective action, preventive action) plan of any possible objections for the various areas and determines the next steps. The breeder may then respond to the report and make possible amendments.

In a final conference call with Interpharma and the breeder concerned, items still pending are clarified and concluding measures are defined: time frame for corrective action, definition of contact persons, recommendations, further follow-up work and a possible revisit.

The whole process with preparation and follow-up usually takes about three months. The aim is to repeat the audits of the breeders concerned every two to three years.

Article 6 “We commit to join efforts in auditing our external partners on animal welfare standards and compliance on a global level.”
AAALAC International
The private non-government organization promotes the humane treatment of animals in science with the aid of voluntary evaluation and accreditation programmes. To date more than 900 organizers, institutions and companies in 37 countries have been accredited by AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care). Several sites of Interpharma member companies are also AAALAC certified and are represented on the Board of Trustees by a member of the European Federation of Pharmaceutical Industries and Associations (EFPIA). Interpharma has also held a seat on the Board of Trustees since 2013 and can thus exert a direct influence in order to promote independent animal welfare certification programmes of Interpharma. Yet not only our member companies, but in many cases also their partners are getting themselves inspected by AAALAC and endeavouring to meet the required standards. This in turn provides one of the basic principles for good cooperation between companies and for cross-company compliance with animal welfare standards.

AAALAC ad hoc consultants
In addition, our member companies campaign with professional ad hoc consultants to implement accreditations along the lines of AAALAC with other companies, institutions and organizations. AAALAC has more than 300 ad hoc consultants, who accompany committee members during on-site visits and make recommendations to the committee. Many of these consultants possess expertise that extends beyond conventional laboratory animal species. Others in turn have skills in a specialist field, e.g. in applied neurosciences, behavioural science, toxicology, pharmacology or physiology. These specialists lend a broader horizon to the team that carries out the on-site visit and understand the complexity when it comes to reconciling research with animal welfare.

CAAT
Some member companies of Interpharma are represented on the advisory boards of both the European and the US Center for Alternatives to Animal Testing (CAAT). Moreover, several experts from Interpharma member companies contribute their expert knowledge to the various projects of CAAT through their active participation. CAAT promotes the development and validation of alternative methods in research and drug safety, as well as in education.

CAAT Europe organizes 2–4 workshops and think tanks a year on various topics, each involving 10–20 experts. The experts are leading representatives of academia, regulatory authorities, the pharmaceutical, chemical, cosmetics and food industries, as well as animal welfare organizations. They meet for 2–3 days to discuss a certain topic, find solutions and come up with recommendations. The results of the workshops are generally published in the ALTEX journal.

CAAT Information Day this year was held in Berlin in June. An Interpharma member company was the main sponsor of the event on the subject of Biology-Inspired Microsystems, such as 3D cell cultures or organ chips intended to simulate human organ systems.

**Article 7** “We commit to promote, in addition to regular authority inspections, the development of external, independent assessment programmes of our animal welfare standards and facilities on a global level.”
EPAA

Interpharma members actively promote the EPAA (European Partnership for Alternative Approaches to Animal Testing), which as a partnership between the European Commission and various industrial sectors sets great store by the exchange of know-how and resources in order to improve the development and validation of animal-free methods of research.

The EU Commission and 35 companies from seven industrial sectors (chemical, pharmaceutical, cosmetics, perfume, soap and cleaning industries and animal health) have agreed on a further 5-year collaboration from 2016 to 2020. The focus will be increasingly on cooperation with international regulatory authorities and national regulatory agencies. The EPAA plans to maintain its intensive efforts to promote the international harmonization of regulatory safety requirements, wherever appropriate and possible.

The competence center TEDD (Tissue Engineering – Drug Development) is led by Prof. Dr. Ursula Graf-Hausner, Zurich University of Applied Sciences, Institute of Chemistry and Biological Chemistry, Wädenswil. TEDD pools and transfers know-how and technologies in order to drive the further development and application of in vitro cell and tissue culture. It is an integral part of the Tissue Engineering technology platform of the national research consortium Biotechnet Switzerland and belongs to the national thematic network (NTW) Swiss Bio-tech.

What can three-dimensional (3D) tissue models achieve in the development of medicines?

Many scientific and medical questions on the research and treatment of human diseases cannot be addressed either with conventional cell cultures or with animal models. Both approaches offer limited scope for modelling the complex biological processes in the human body. Human three-dimensional (3D) tissue models have considerable potential for realistically simulating the situation in the live organism. They can be used for toxicity studies and for drug development. Drug effects can be identified early on and the development process decisively optimized. Since the models involve the use of human material, the conclusions are more relevant than the results obtained from animal experiments. As alternatives to animal experiments, they contribute to the concrete implementation of the 3Rs concept. Animal experiments, especially stressful and severely stressful experiments, can be markedly reduced.
Can you name some examples of their successful use? The skin models already established and in use for testing cosmetics provide an impressive example. However, no other tissue models have yet been validated by the regulatory authorities apart from the skin models. Nevertheless, tumour models for example are already providing a very good service in the study of disease and the development of treatments. With these models, the patient’s own cells can be used for the preparation of tissue models, thus allowing a personalized strategy. Convincing results are also being obtained already with liver models, in which the side effects of medicines are identified. Highly complex organ-like models and even the combination of several organ models in a multi-organ system are under development. But their biological function and validity have yet to be demonstrated to a large degree.

“Many models are already established on a laboratory scale, but their reproducible use for routine practice, including efficient analysis, has yet to be approved.”

Where do the limits of the technology lie at present? It is a huge challenge to simulate the high degree of complexity of our organs and their interplay in vitro. Innovative technological approaches from the fields of microsystems technology, bioprinting, automation, cell culture and a combination of these offer new opportunities for the creation of organ-like 3D tissue models. But the biological structure and functionality have to be unequivocally demonstrated before the methods can be considered for reliable use. Many models are already established on a laboratory scale, but their reproducible use for routine practice, including efficient analysis, has yet to be approved. This also requires adequate validation in order to meet the high standards required in terms of relevance and safety for the patient in the pharmaceutical industry and medicine. Resolving these challenging issues is only possible in interdisciplinary teams from the worlds of science, engineering, the clinical setting and industry.

What approach is being pursued by the researchers and industry representatives involved in TEDD? This is precisely the point where the TEDD competence centre comes into its own. The network brings together competent partners and competencies from the whole value chain. In network projects, new technologies produce 3D tissue models that are well thought out and deployable until they find routine use with the end user, e.g. the pharmaceutical industry. One example is an ongoing KTI project from 4 TEDD partners. Here, muscle/tendon tissue is bioprinted directly in specifically developed multiwell devices in which the influence of active substances can be analyzed in direct, medium-throughput screening (Chimia 2015, 69 no. 1/2). TEDD initiates network projects of this kind and provides for sufficient funds. □

In vitro 3D muscle model (myosin heavy-chain staining). Human muscle cells were positioned together by means of 3D bioprinting using BioInk™ and were differentiated for 7 days. The immunohistological staining shows differentiated muscle fibres.

Article 8 “We commit to promote the validation and regulatory acceptance of methods which are suited to replace, reduce or refine animal studies.”
Visits to animal housing facilities
To enhance the communication and transparency of the industry with policymakers from Switzerland and abroad, our member companies offer policymakers from Bern and Brussels the opportunity to visit their facilities in Basel. In 2015 several of these visits took place. Members of the European Parliament and their staff had the opportunity to see the housing of different species and learn about the multiple efforts of Swiss industry to enhance the 3Rs in daily practice.

Round-table meetings with the FSVO – Federal Council report on the 3Rs
Together with stakeholders from academia, animal welfare, industry and the authorities, Interpharma took part in the round-table meetings of the Federal Food Safety and Veterinary Office (FSVO). The purpose of the meetings was to discuss the future of the 3Rs Foundation and of research into alternative methods. Together with the federal authorities, Interpharma has supported the 3R Research Foundation Switzerland for almost three decades and welcomes the interest in the 3Rs.

In July 2015, the Federal Council published a report on the 3Rs, which includes concrete measures to reinforce the 3Rs. One of the key elements is a widening of the training and continuing education of researchers in the field of the 3Rs. Researchers who conduct animal experiments today already undergo several days of theoretical and practical training. Now the subject of the 3Rs is to be included in the curriculum of students in all natural sciences and medicine.

A further key measure to be considered is the establishment of a national competence centre for the 3Rs. The aim of such a centre is specifically to promote research and to ensure that the relevant results are put to sustainable use in collaboration with industry and the universities. The competence centre could provide services for the law enforcement authorities, industry and the universities in the field of training and continuing education on the 3Rs. It should also undertake a scientific analysis of data relevant to the 3Rs and make the data available to research groups, initiate research and validation of 3Rs methods and ensure that an international scientific networking system is in place. A clearly defined field of activity and stable funding must form the basis for this centre.

The report also comes to the conclusion that the 3R Research Foundation Switzerland can continue to make a valuable contribution to research on alternative methods.

At present the Federal Food Safety and Veterinary Office and the State Secretariat for Education, Research and Innovation are jointly seeking solutions for the implementation of these measures within the limits of the funds available.

Medicine and animal experiments
The “Medicine and animal experiments” module for second-year medical students was held again in May this year at a member company in Switzerland in collaboration with the University of Basel’s Faculty of Medicine and the vice-chairman of the cantonal committee on animal experiments.

The students immersed themselves in the various aspects of animal experiments in medicine (legal framework, theory and practice of animal experiments, ethical aspects of the way humans treat animals, the scientific gain from animal experiments and drug safety). After visiting the animal housing facilities of a member company, they spent a day in a research laboratory. The feedback from the students this year was again positive. They appreciated the open information policy and the opportunity to form an objective impression through invaluable insights into the way laboratory animals are treated (housing and use in experiments).

Article 9 “We commit to contribute to a continuous, open and constructive dialogue on animal research and welfare with the public at large as well as with authorities, policy makers and other interested stakeholders.”
**Basel Declaration**
The aim of the Basel Declaration Society is to reinforce the public’s trust in biomedical research using animal experiments, to foster communication between researchers and the public and to increase acceptance of the Basel Declaration. Like the Declaration of Helsinki, in which the basic ethical principles of clinical research in humans are formulated, the Basel Declaration Society aims to help ensure that ethical principles such as the 3Rs are applied in research using animal experiments worldwide. Interpharma and two member companies have provided financial support for this project for years.

The Basel Declaration Society organizes an international congress every two years. This year it was held in Rome at the beginning of October. The venue was not a random choice, because the research community had recently had to battle with radical opponents of animal experiments who, amongst other things, had destroyed at a stroke many years of research on mental disorders. The main focus of the congress was therefore on the question of how the research community was to cope with such attacks and how the public can be better informed about the benefits of animal experiments both in basic research and in applied research. The discussions considered how to deal with misinformation on animal experiments, what strategy to adopt in the event of a crisis and how transparency can be improved on the subject of research with animals.

**Swiss Animal Protection**
Interpharma has been in dialogue with Swiss Animal Protection (SAP) for more than four years. The organizations AnimaLfree Research and Zurich Animal Protection have also joined in the dialogue. The regular meetings are intended to foster mutual understanding and to make questions on animal welfare more accessible and to discuss technical issues regarding animal experiments and the protection of laboratory animals.

At the 8th conference of Swiss Animal Protection on animal experiments, with representatives from politics, academia and both national and international regulatory authorities, an Interpharma member company presented a paper on Animal Welfare and the 3Rs – from the Perspective of the Pharmaceutical Industry. The speaker had the opportunity at this conference to describe, amongst other things, the company’s globally binding animal welfare policy, to explain the duties of the Animal Welfare Officer in an international company and to present ongoing internal and external initiatives related to the 3Rs. In the discussion that followed, the paper was praised and appreciation expressed for the insight that was provided into the activities.

**ILAR Guide**
A representative of an Interpharma member company has been a member of the ILAR Council (advisory body of the Institute for Laboratory Animal Research) of the National Academies in the US for some years. The Council meets twice a year. This body is responsible for the “ILAR Guide”, the American regulations for housing, husbandry and handling of laboratory animals. The aim of this representation for Interpharma is to make sure the debates taking place in Switzerland and Europe are also heard in the US.
Article 10  “We commit to report annually on the progress made with regard to this charter.”

Fifth annual report
The 2015 annual report is the fifth report to appear since the Animal Welfare Charter was adopted in 2010. The working group for animal welfare of the European association EFPIA has decided to follow this example and likewise produce a report on the present status of animal welfare standards at European level. ■

Orders and suggestions to info@interpharma.ch
Links to the institutions mentioned and other information on research with animals

**ALTEX – Alternatives to Animal Experimentation**
www.altex.ch

**Animalfree Research**
www.animalfree-research.org

**Association for Assessment and Accreditation of Laboratory Animal Care International – AAALAC**
www.aaalac.org

**Basel Declaration**
www.basel-declaration.org

**Competence Center TEDD**
www.project.zhaw.ch/en/science/tissue-engineering-for-drug-development.html

**European Federation of Pharmaceutical Industries and Associations – EFPIA**
www.efpia.eu

**European Partnership for Alternative Approaches to Animal Testing – EPAA**
www.ec.europa.eu/growth/sectors/chemicals/epaa

**Federation of European Laboratory Animal Science Associations**
www.felasa.eu

**Institute for Laboratory Animal Research**
www.dels.nas.edu/ilar

**International Committee for Laboratory Animal Science**
www.iclas.org

**International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – ICH**
www.ich.org

**International Consortium for Innovation and Quality**
www.iqconsortium.org

**Johns Hopkins University Center for Alternatives to Animal Testing – CAAT**
http://caat.jhsph.edu

**National Center of the Replacement, Refinement & Reduction of Animals in Research**
www.nc3rs.org.uk

**New Jersey Association for Biomedical Research**
www.njbr.com

**Swiss Animal Protection (SAP)**
www.animal-protection.net

**3R Research Foundation Switzerland**
www.forschung3r.ch

**Understanding Animal Research**
www.understandinganimalresearch.org.uk

**vtk online**
www.vtk-online.de

**Zurich Animal Protection Association**
www.zuerchertierschutz.ch/en/home.html