Animal Welfare Report 2018

Association of research-based pharmaceutical companies

interpharma iph

Content

1 Foreword
2 Digitization in Animal Welfare
8 3Rs Competence Centre Switzerland
12 10-point Animal Welfare Charter
14 3Rs competitions and events
20 Working groups and projects
28 Recommended websites

Dr Joachim Coenen
Chief Animal Welfare Officer with Merck and Chairman of the Interpharma Animal Welfare Working Group

It is already eight years since the Animal Welfare Charter was established by the research-based pharmaceutical industry in Switzerland. In this charter, the member companies of Interpharma commit, among other things, to promote high ethical and legal standards and strive to make improvements in animal experiments worldwide in their research and development activities. The chief rationale behind the charter is the principle of the 3Rs: to refine animal experiments so that they are as meaningful as possible and at the same time sparing of the animals, to reduce their number to the necessary minimum and, whenever possible, to replace them with alternative methods.

The last few years have seen the steady advance of digitization. This has led to changes in the requirements of drug development and also in laboratory animal husbandry and care, as well as the emergence of new possibilities. Today, for example, active pharmaceutical ingredients can to some extent be tested in artificially simulated miniature organs on a chip. Besides making for better extrapolation of results to humans, the organs on a chip also promote the 3Rs and benefit the wellbeing of laboratory animals. The potential of these innovative technologies, however, is far from exhausted, and further development and refinement is of utmost interest for the research-based pharmaceutical industry.

Foreword

Dr Kathy Riklin
Member of the National Council

For some time now, the public and societal debate about animal experiments has been shaped by the conflicting priorities between what is beneficial and what requires protection. The compatibility of animal experiments and biomedical research begs a number of ethical questions. It is almost impossible to find a consensus between the diverging interests, which makes it all the more important to create space for dialogue and to establish mutual trust.

Back in 1987, the 3R Research Foundation Switzerland already succeeded in bringing together various interest groups with differing ideas around a table. This down-to-earth, constructive dialogue was an important key to success: the Foundation has been sponsoring research on improved methods or alternatives to animal experiments now for more than three decades. In 2018, this development in Switzerland is set to be taken a step further and intensified with the new national competence centre 3RCC. I am convinced that the new competence centre 3RCC will bring further impetus to 3Rs research in Switzerland and will serve to promote the 3Rs at national level even more in the future.

Digitization in Animal Welfare

Digitization is advancing in all fields. Thanks to new and innovative technologies, it is also possible to substantially improve, amongst other things, quality standards in the husbandry and care of laboratory animals.

Human organs in miniature format: a new technology for drug development.

Miniature organs on a chip
It is only about as large as a USB stick or a smartphone, but can nevertheless offer a reflection of the human organism: the organ chip. One or more organs can be placed on small plates – so-called chips – in order to model the inner workings of the human body. These mini-chips are an innovative technology with which drug candidates can be tested for efficacy and toxicity at an early stage. This means not only that drug candidates can be made safer for clinical trials in humans, but also that it may allow animal experiments to be reduced in future.

Development and manufacture
Research into organ chips began around a decade ago at the Wyss Institute at Harvard University in the US, with the support of Swiss pharmaceutical companies among others. Ten years ago, the human genome had already been decoded, while stem cell research and microsystem technology had been sufficiently developed to enable the first mini-organs to be produced. Today, up to five organ models can be combined on a chip, although researchers are already working on a chip with ten or more mini-organs.

The production of organs on a chip requires biomedical expertise and is based on a variety of other technologies, including 3D cell cultivation, bioprinting, microfluidics and induction of pluripotent stem cells. Live human cells are used for the development of miniature organs in order to simulate the organs as realistically as possible. In order for several organs, such as the liver, heart and kidney, to be combined on a single chip, researchers have to create conditions similar to those in the human body. Besides the site of the artificial organs relative to each other, the temperature and movement of the organs also play a role. For example, a lung must be able to breathe and a heart must be able to beat. The various mini-organs have to be connected to each other through an artificial circulation. Cells are supplied with nutrients and the organs exchange information by means of a fluid in the circulation.

“Thanks to the use and selective promotion of innovative methods involving the 3Rs, the last few years have seen animal experiments in the pharmaceutical industry permanently reduced, replaced or refined.”

Dr Tobias Schnitzer
Global Head of Comparative Medicine at F.Hoffmann-La Roche AG

A factor of
100 000

With organ and tissue parts miniaturized by a factor of 100 000, it is possible to simulate the human organism on a chip.

Promotion of the 3Rs
In many cases, simple cell cultures are only of limited use for testing drug candidates, because they do not enable the complexity of the human organism and disease processes in patients to be satisfactorily reproduced. Until now, the only possibility for reproducing the complex interplay between different human organs has been to use laboratory animals such as mice and rats, whose bodies and metabolisms are comparable with our own. But even with animal models, the results of studies cannot always be extrapolated to humans. Three-dimensional organ chips, on the other hand, provide for the kind of conditions found in the human organ. Aside from the better extrapolation of results to humans, there is another reason why miniature organs on the chip are of interest for the research-based pharmaceutical industry. The idea of the 3Rs is that animal experiments should be reduced, replaced or refined wherever possible. For this reason, the further development and refinement of organs-on-a-chip technology has priority for numerous pharmaceutical companies.

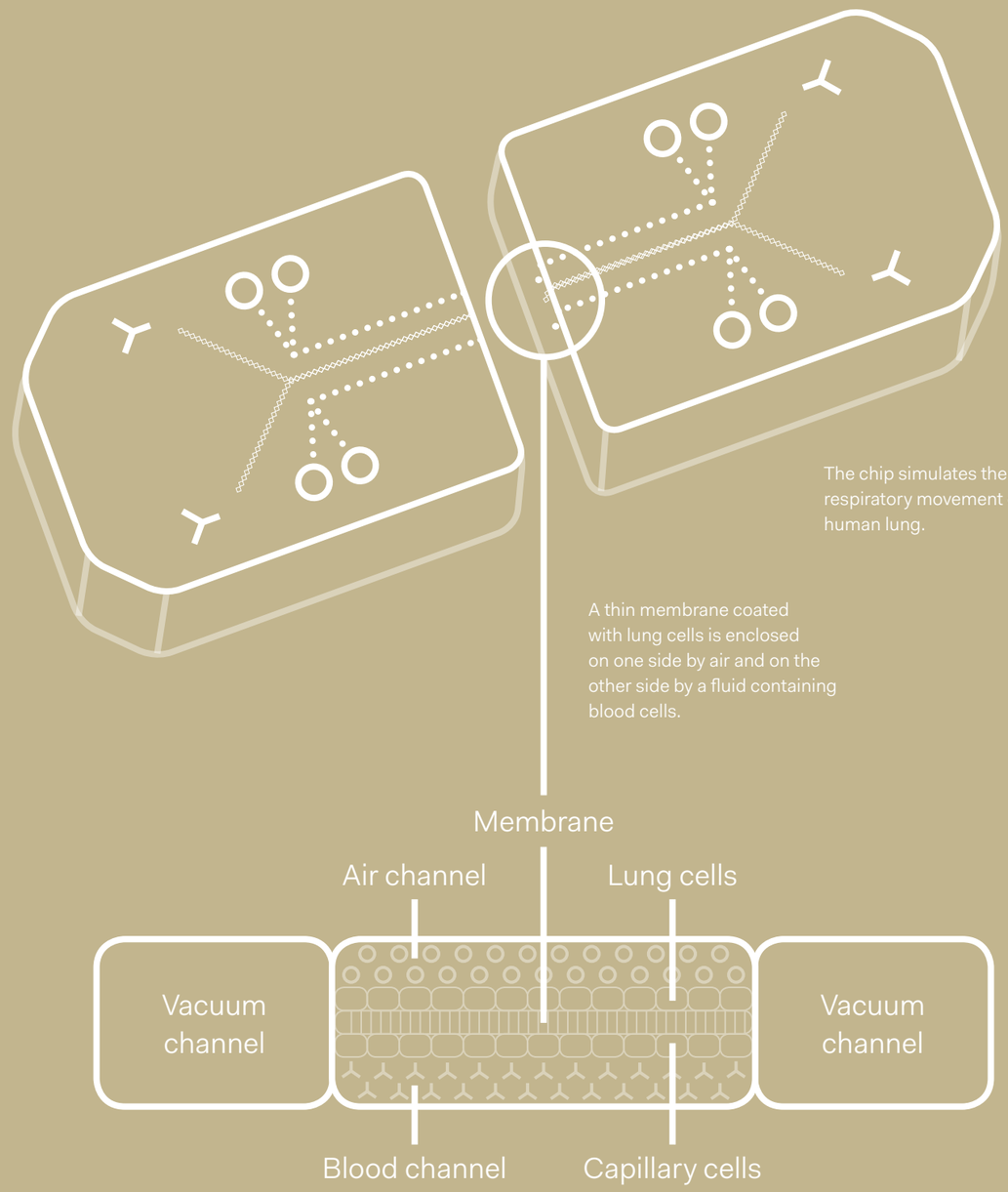
First step on a long journey
Although the development of organs on a chip sounds promising, it must be said that this technology is still in its infancy. At present, the chips can still not sufficiently reproduce the complexity of human organs. The human lung, for example, shows around 40 different cell types of lung tissue, blood vessels and immune system. The lung on the chip, however, can only reproduce one or two of these cell types. In addition, it is particularly difficult to combine several organs on a chip, because there is as yet no fluid in which all the different cell types can be cultivated. Today, therefore, only four or five organ models can be combined on the chip – a fraction of the entire human organism. For this reason, the pharmaceutical industry will also in the future be dependent on conducting animal experiments according to the principles of the 3Rs, because patient safety has top priority.

The breathing chip

The textbook example of organs-on-a-chip technology is the lung chip, which was developed by the Wyss Institute at Harvard University. On the silicon-coated chip, human lung tissues grow on a thin, elastic membrane. On one side, the tissue is enclosed with a layer of blood vessel-forming cells, while the other side is covered with lung cells. Vacuum pumps are used to pump air and a blood substitute through the chip, thereby simulating a respiratory movement, which plays an important role in various physiological processes, such as inflammation of the lungs.

Lung on a chip

With the organs-on-a-chip technology substances can be tested on artificial mini-organs.



The chip simulates the respiratory movement of a human lung.

A thin membrane coated with lung cells is enclosed on one side by air and on the other side by a fluid containing blood cells.

New digital technologies enable animal experiments to be replaced, the number of laboratory animals to be reduced and experiments to be refined so as to reduce any stress on the animals.

Great interest on the part of academic research
The new digital technologies, especially organs on a chip, are also meeting with a lot of interest among scientists working in academic research. Aside from the prestigious Wyss Institute at Harvard University, which unveiled the world's first breathing lung chip in 2010, Swiss academic institutions also have high expectations of the innovative technology. For example, a lung chip that offers an alternative to animal experiments in lung research has also been developed by researchers at the University of Bern under Professor Olivier Guenat, Center for Biomedical Engineering Research (ARTORG), in collaboration with the University Clinic for Pneumology at the Inselspital. This chip should be used above all for research on the rare, but aggressive disease of pulmonary fibrosis. A subproject, which is developing a model for acute pneumonia on the basis of the lung chip from Bern, is supported by the 3R Research Foundation Switzerland.

Testing new medicines
Besides the University of Bern, the School for Life Sciences at the University of Applied Sciences and Arts Northwestern Switzerland (FHNW) is also working with organs-on-a-chip technology in collaboration with Dutch partners. With the use of a miniature kidney on a chip, the aim is to test new medicines for nephrotoxicity. The focus of research interest here is on the testing of active pharmaceutical ingredients rather than modelling healthy and diseased tissue. This kidney on a chip could not only reduce the number of animal experiments but also lower the cost of drug development. This project is being sponsored by the UK National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) and by a number of pharmaceutical companies. The potential of organs-on-a-chip technology has also been recognized by other Swiss universities, which are currently engaged in research on promising organ chips.

Project name:	Organs-on-a-chip technology
Charter articles:	1, 2

Diversity and potential

The projects in the field of digitization are diverse and their potential is still far from exhausted. A great many practical applications are however only in the developmental stage. Digital technologies still have some way to go before they can be used as alternatives to animal models in future drug development.

Other activities of Interpharma member companies in the field of digitization
Research involving *in vivo* studies could be substantially enhanced by the introduction of innovative technologies in the field of animal housing. Pilot projects are underway to assess innovative digital animal housing systems, which deliver more comprehensive and more meaningful data for researchers and at the same time provide for improved well-being of the animals. Each housing unit (smart caging system) is equipped with smart sensors and high-resolution cameras. They monitor important parameters for disease development and treatment success, which are relevant for later implementation in clinical research. These include e.g. the movement, behaviour, breathing and body weight of the animals. The platform also records the ambient conditions in each housing unit (ventilation, humidity, temperature and control of lighting) and provides a continuous video recording of all laboratory animals. These novel technologies in animal housing can substantially enhance the validity of animal studies in preclinical research. Until recently, the gathering of data in animal studies was a manual process that was liable to subjective variations and carried the risk of human error. In addition, the animals were disturbed by manual data gathering, which could lead to a distortion of the results. The new technologies permit a more objective assessment of disease stages with quantitative parameters and provide for greater safety, ongoing knowledge gain from all animal studies and improved reliability and reproducibility.

New possibilities
Smart housing systems open up the possibility of extending animal studies to cover further criteria, such as the movement, behaviour, breathing and weight of the animals. This allows larger quantities of data to be recorded in real time. The result of this is that scientists can assess disease modes and the therapeutic potential of active substances more quickly and more precisely. But smart housing systems cannot only improve clinical research. They are also of benefit to animal welfare. On the one hand, smart systems reduce the daily disturbances caused by human intervention. On the other, the automatic reminder to animal attendants to replenish the food and water supplies also helps to ensure that the animals promptly receive the attention they need. The new systems can accordingly also detect early on when animals fall sick, so that immediate veterinary medical care can be initiated.
The new technologies enable Interpharma member companies to further raise the standards for the welfare of animals and hence promote the 3Rs.

Project name:	Digital animal housing systems
Charter articles:	1, 2

"The application of the 3Rs principles reduces not only the number of animals used, but also the variability of the data and thus enhances the quality of animal-based research."

Dr Birgit Ledermann
Novartis 3Rs Leader, Novartis Institutes for BioMedical Research

3Rs Competence Centre Switzerland

A new national competence centre should serve to promote the principles of the 3Rs even more in the future and ensure that they are put into practice in everyday research.

Interview with Dr Chantra Eskes, Director of the 3Rs Competence Centre

“The 3RCC provides all those involved with access to the latest information in the 3Rs and alternatives to animal experiments.”

What are the tasks and objectives of the new national 3Rs competence centre?
The 3Rs Competence Centre (3RCC) was founded on 27 March 2018 to promote the principles of the 3Rs in Switzerland: Refinement (minimizing the stress on animals); Reduction (reducing the number of animals used); and Replacement (finding alternatives to animal experiments). While the last decade has seen good progress in the implementation of the 3Rs at regulatory level, the newly established centre aims to further the promotion of the 3Rs also in research and education. To achieve this, scientific, ethical and regulatory aspects must be taken into account. The new centre has a higher budget for this than the 3R Research Foundation Switzerland. The aims of the 3RCC are to promote high-quality 3Rs research projects, to develop a strategy for training and continuing education on the 3Rs and to build a professional communications strategy. The 3RCC provides access to the latest information on the 3Rs and alternatives to animal experimentation for all those involved and it offers its services to authorities, teaching bodies and any other interested parties. Furthermore, the centre will monitor the progress made in these areas in Switzerland.

Are there already any specific projects that are supported by the 3RCC?
A first call for projects will be launched by the end of 2018. The aim is to subsidize research projects not covered by the currently existing funding schemes. For this purpose, a survey initiated by the 3RCC network is underway to establish the current challenges and opportunities in the implementation of the 3Rs in Switzerland.

The 3RCC brings together a range of different stakeholders. How will you satisfy all the different demands?
The 3RCC brings together academia, industry, authorities and animal protection organizations. The 3RCC addresses the shared goals of these different stakeholders: namely, the promotion of animal welfare and scientific excellence, for example by supporting relevant and reproducible approaches, and the distribution of pertinent information on the insights obtained in the implementation of the 3Rs. The 3RCC strives to foster a constructive exchange of ideas and open communication between the actors involved and stakeholders.

“I hope the 3RCC will succeed in motivating researchers, industry and authorities to develop and implement a new and improved set of instruments for the 3Rs. This can serve to improve the quality of research and to reduce the number of animal experiments to a minimum.”

Dr Chantra Eskes
Director 3Rs Competence Centre

Interview continued on page 10 ›››

-60%

The total number of animals used in Switzerland has been reduced from almost two million in 1983 to 614 581 in 2017. This is a decrease of more than 60%.

How is the 3RCC structured?
Based at the University of Bern, the Swiss 3Rs Competence Centre is an association that includes among its members 11 Swiss universities (EPFL, ETHZ, FHNW, UniBas, UniBe, UniFr, UniL, UniGe, UniZH, USI and ZHAW), the association of research-based pharmaceutical companies in Switzerland (Interpharma), the Swiss Federal Food Safety and Veterinary Office (FSVO), and Swiss Animal Protection (SAP). Since the 3RCC is a scientific centre of national importance according to Article 15 of the Federal Act on the Promotion of Research and Innovation, it also benefits from the support of Switzerland's State Secretariat for Education, Research and Innovation (SERI). All members of the association contribute financially or with in-kind contributions to the implementation of 3Rs in Switzerland. The various bodies provide for a wide-ranging network and foster the exchange of ideas between and within the various stakeholders involved. In particular, the presence on the Executive Board of 11 coordinators from the universities involved and the mapping of precisely defined research groups allow communication to be optimized and the exchange of information on the principles of the 3Rs for research purposes (see organization chart on page 11).

Where do you see the 3RCC in three years?
The 3RCC should become a focal point for networking and communication for all parties interested and involved in the implementation of the 3Rs and alternatives to animal experimentation in Switzerland. In addition, the 3RCC will contribute not only to the development of methods consistent with the 3Rs, including new alternative methods, but also to the concrete application of these new tools, be it at the level of research, industry or regulatory approval. Finally, through dedicated educational programmes, the 3RCC should bring about a change of mindset among future researchers regarding the necessity of applying the principles of the 3Rs for the benefit of laboratory animals and our society.

Project name:	3Rs Competence Centre
Charter articles:	1, 3, 9

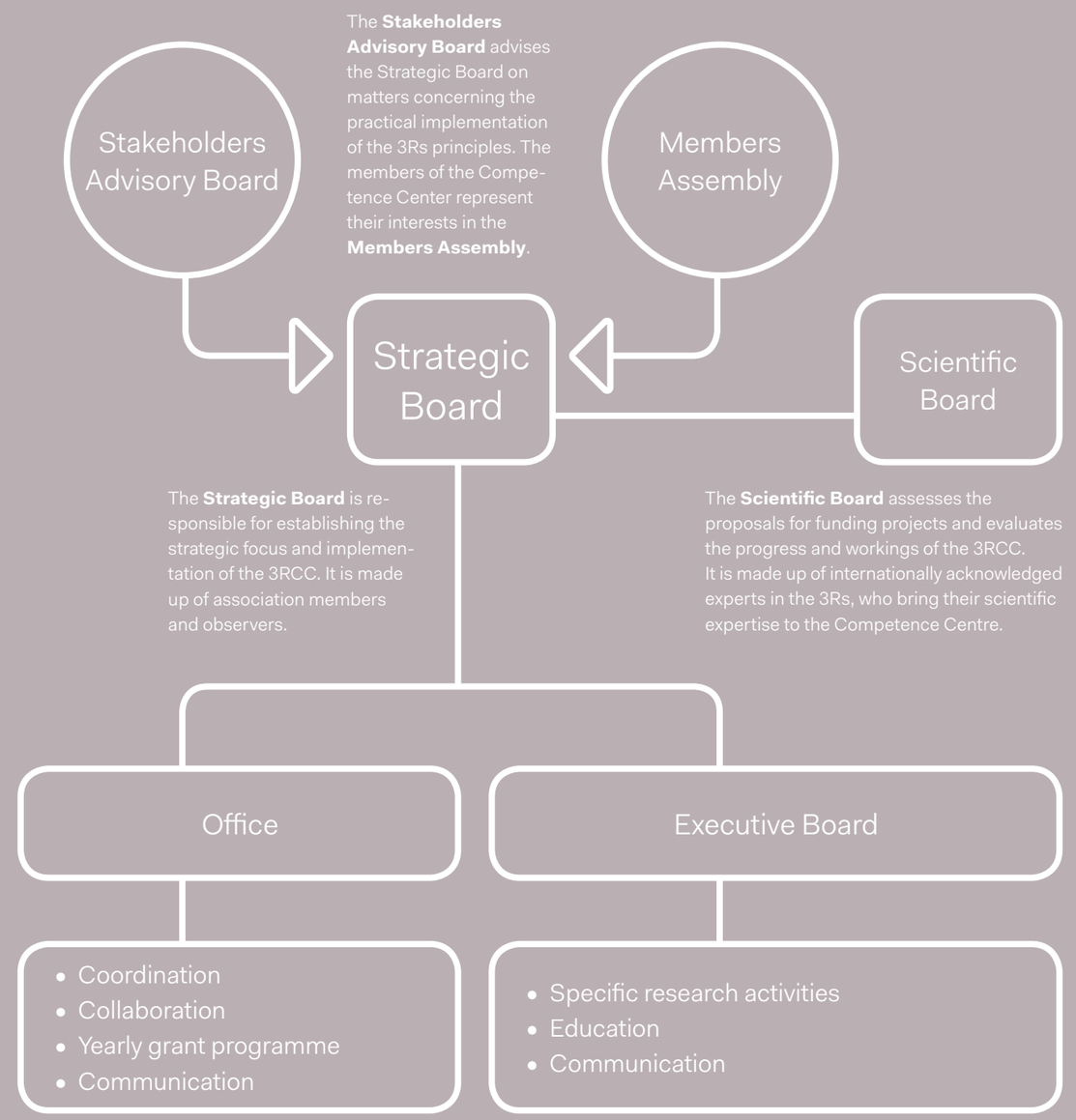
Achievements of the 3R Research Foundation Switzerland

Establishing the 3R Research Foundation Switzerland in 1987 was a landmark achievement. The Foundation supported research into better methods or alternatives to animal experiments and was financed equally by the federal government and Interpharma from the outset. In the past 30 years, the Foundation has sponsored 146 research projects from 482 applications for support at a total cost of CHF 18.8 million. These projects were assessed and followed by a committee of experts.

Support of the 3RCC

With the establishment of a national competence centre, an important milestone was laid for 3Rs research in Switzerland. The centre, which opened in March, is still in its infancy, however, and the way it is put into practice and further developed will only become apparent over the course of time. To guarantee future support and successful collaboration, it is especially important for Interpharma and its member companies that decisions take into account both the interests and the existing expertise of the pharmaceutical industry.

Organization chart of 3RCC



The **Stakeholders Advisory Board** advises the Strategic Board on matters concerning the practical implementation of the 3Rs principles. The members of the Competence Center represent their interests in the **Members Assembly**.

The **Strategic Board** is responsible for establishing the strategic focus and implementation of the 3RCC. It is made up of association members and observers.

The **Scientific Board** assesses the proposals for funding projects and evaluates the progress and workings of the 3RCC. It is made up of internationally acknowledged experts in the 3Rs, who bring their scientific expertise to the Competence Centre.

The **Office** is responsible for the centralized coordination and implementation of activities of the 3RCC. It is made up of the Executive Director of the 3RCC and its scientific and administrative staff.

The **Executive Board** is responsible for implementing the strategy of the Competence Centre. It is made up of 11 Coordinators, the Executive Director of the 3RCC and representatives of the Swiss Animal Facilities Network, the network of Animal Welfare Officers, the Institute for Laboratory Animal Science and other laboratory facilities.

In the 10-point Animal Welfare Charter, we commit to:

1 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.

2 ensure high-quality and state-of-the-art housing and care conditions for our laboratory animals and strive to continuously improve these conditions.

3 develop and foster education and training for all our employees and associates who work with animals.

4 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.

5 apply vigorous internal auditing systems, which ensure compliance with the animal welfare standards agreed upon.

6 joint efforts in auditing our external partners on animal welfare standards and compliance on a global level.

7 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.

8 promote the validation and regulatory acceptance of methods which are suited to the replacement, reduction or refinement of animal studies.

The Animal Welfare Charter was launched in 2010 by Interpharma member companies. The aim of the charter is to continuously improve the protection and welfare of laboratory animals during breeding, housing and the experiments required.

9 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.

10 report annually on the progress made with regard to this Charter.

3Rs competitions and events

Competitions and events in the field of the 3Rs contribute to the steady, open and constructive dialogue and promote animal welfare.

Conferring national and international 3Rs awards promotes engagement for the protection of laboratory animals.

Internal awards are popular

Some Interpharma member companies regularly acknowledge their researchers with internal national and international 3Rs awards. Researchers from different departments are given the opportunity to submit their work and developments for consideration. The last few years have seen a steadily growing interest in 3Rs competitions. In the case of one Interpharma member company, the number of projects submitted since 2008 has more than tripled.

Category Refinement
Telemetry technology allows large quantities of quality data to be obtained without compromising the welfare of the animals. In collaboration with the respective producer, an improvement in the Weston telemetry model was tested in which a device implanted by minimally invasive means allows not only ECGs to be recorded, but also blood pressure and body temperature, thereby increasing the screening potential. The abdominal cavity no longer has to be opened to measure core temperature. A more conservative surgical procedure allows the implant to be placed between the internal and external transverse muscles of the abdominal wall. As a result of this improved design, data on respiration can also be derived from the blood pressure curve obtained. In addition, the animals were also tattooed during anaesthesia in order to mark the optimum location for the placement of ECG electrodes. The tattoo ensures that the electrode placement is always exactly the same for each subsequent data gathering procedure, which improves signal quality and reproducibility. This optimized analysis also means the results become available more quickly. The life of the battery in the implant is about 200 days when in constant use. The animals can therefore be used for up to ten studies a year.

Project name:	Improvement in Weston telemetry model in preclinical safety
Charter article:	1

Category Replacement
In the development of biotherapeutic agents, antibodies of human origin are the gold standard. Although methods for the efficient isolation of human antibodies have been used in recent times, limited capacity resulted in compromises in the performance of experiments. This also includes obtaining hybridoma cell lines from immunized rodents which were already humanized with regard to their antibody genes or which had to be subsequently humanized *in vitro*. Now scientists have optimized a technique (single B-cell expansion *in vitro*, or ScExp) for the multiplex screening of B-cell subgroups in single-cell analysis. ScExp has a modular design to ensure maximum flexibility and provides for the calculation of monoantigen and polyantigen-specific B-cell receptor frequencies (“functional repertoire”), followed by downstream molecular biological procedures for the validation, sequence analysis (“genetic repertoire”) and production of recombinant antibodies ready for use. These procedures allow experimenters to work directly with human donor material, so that immunization protocols for a large number of laboratory animals can be replaced.

Project name:	Efficient antibody detection in human material through the use of expansion techniques in single-cell analysis
Charter article:	1

Global 3Rs award programme

AAALAC initiated a global 3Rs award programme in collaboration with the IQ Consortium. The programme is aimed at researchers from academia and industry.

Category Reduction
Genetically modified laboratory animals are very often used for *in vivo* pharmacological studies in the field of oncology. However, the use of these animals is fraught with problems. It was to overcome these problems that the transformation of tissue-specific, genetically modified organoids into cancer precursor cells was developed using 3D cultivation. These genetically modified cancer precursor cells produced *in vitro* can form tumours with a short latency period when they are injected into immunocompetent mouse hosts *in vivo*. This method renders the production and housing of genetically modified rodents redundant and could therefore substantially reduce the number of laboratory animals needed.

Project name:	Use of *in vitro* CRISPR-corrected organoids as an alternative to genetically modified mouse tumour models
Charter article:	1

Repeated use of laboratory animals
The last few years have seen a sharp increase in the number of biotherapeutic agents (biologics) to be tested. The high target and species-specificity of biologics means that only non-human primates (NHPs) are suitable for testing in view of their closeness to humans. These biotherapeutic agents stimulate an immunological response or anti-drug-antibody (ADA) formation following repeated exposure to the active ingredient. This indirectly rules out the repeated deployment of the NHPs used from the outset, which poses an ethical dilemma. To overcome this problem, a qualitative antibody-based ADA assay method (ELISA) was developed for the repeated use of laboratory animals. This enables a distinction to be drawn between ADA-positive and ADA-negative plasma samples. In a second screening procedure, animals that tested negative must undergo substance-specific ADA screening before they can be used for these studies. Animals that tested positive can no longer be used for studies of biologics and are available for experiments with low-molecular substances. This advance screening allows more than 80% of animals to be made available for renewed use in further studies.

Project name:	Development and use of an anti-drug antibody (ADA) screening procedure
Charter article:	1

"With the Animal Welfare Charter, the research-based pharmaceutical companies in Switzerland assume social responsibility with respect to the area of tension between biomedical research and animal welfare."

Dr René Buholzer
General Secretary Interpharma

Outstanding commitment
Christian Schnell, Senior Scientist Oncology at Novartis Basel, received this year's 3Rs award for his many years of achievement in the field of the 3Rs. (From left to right: Christian Schnell, Birgit Ledermann, Kurt Lingenhöhl and Jennifer Lofgren)

3Rs exemplary achievement award
In addition to its annual 3Rs award, a member company of Interpharma invited submissions in 2017 for a 3Rs exemplary achievement award to acknowledge employees who strive tirelessly with particular dedication to the implementation of the 3Rs in their own company. The winner of the 3Rs exemplary achievement award started with the implementation of the 3Rs more than 30 years ago and was the first who, aside from many other 3Rs projects in his company, used telemetry in 1989 for the development of two approved medicines. Telemetry technology allowed data to be gathered without interventions in the animal, thus enabling the stress on the animals to be reduced. The winner of this year's award has also repeatedly submitted other 3Rs projects for the annual 3Rs award since its introduction in 2007.

Project name:	3Rs exemplary achievement award
Charter article:	1

Other 3Rs awards
Interest in the 3Rs awards has enjoyed a sharp increase not only within individual companies, but also throughout the industry. Interpharma member Merck conferred an award for outstanding achievements in the field of animal welfare for the first time in 2018. Johnson & Johnson also offered an in-house 3Rs award and, for more than 10 years, has sponsored postdoc positions in support of the 3Rs in the areas of pharma, medical devices and consumer products. In addition, Janssen Laboratory Animal Science & Welfare Group offers an annual 3Rs award to encourage all employees involved in animal experiments to develop alternatives. The most recent examples are guidelines for reducing aggression in male mice, non-invasive and minimally invasive methods for the assessment of local drug delivery systems in the gastrointestinal tract of dogs and non-invasive monitoring of virus replication by means of bioluminescence imaging (IVIS® 200).

Project name:	Various 3Rs awards in Interpharma member companies
Charter article:	1

Science and You(th) – science belongs to young people
The Swiss Academies of Arts and Sciences held a participatory workshop in June 2018 as part of the project "Science and You(th) – science belongs to young people". This event was attended by 66 secondary school students aged 14 from the city of Bern and the surrounding region. The project was all about scientists listening to the students and then addressing questions together in groups. One of these questions was: "Scientific guidelines and animal experiments – are animal experiments acceptable?". Dr. Birgit Ledermann, Novartis 3Rs Leader (Novartis Institutes for BioMedical Research) took part in this workshop as an expert in the field of animal experiments. The event was organized by Science et Cité, the competence centre for dialogue, which is associated with the Swiss Academies of Arts and Sciences.

Project name:	Science and You(th)
Charter article:	9

11th conference of Swiss Animal Protection (SAP) on animal experiments: better research with fewer animal experiments?

Promotion of the 3Rs in Switzerland
At the 11th conference of Swiss Animal Protection (SAP) on animal experiments, the focus was on the new 3Rs Competence Centre and the search for alternatives to animal experiments. Chantra Eskes, director of the new competence centre 3RCC, explained the role of the centre. She pointed out that the primary focus is to establish an international network in order to reinforce a 3Rs mentality among researchers. A further important goal for the director is to promote all the 3Rs. Kaspar Jörger, veterinarian and head of Animal Welfare with the Federal Food Safety and Veterinary Office (FSVO), emphasized in his presentation the high expectations that the FSVO has of the competence centre, especially with regard to the key elements of training, communications and 3Rs research.

Development in Germany
Prof Stefan Hippenstiel, Medical Clinic of the Charité University Hospital Berlin, very much welcomed the establishment of the national Competence Centre 3RCC, especially since a similar development is currently underway in Germany. In 2014, the research platform BB3R was founded at the Free University of Berlin with the aim of pooling and fostering 3Rs-related expertise in the Berlin-Brandenburg region. Last year also saw the opening of the Charité 3Rs Centre, which should make the engagement in animal welfare in research and teaching even more visible.

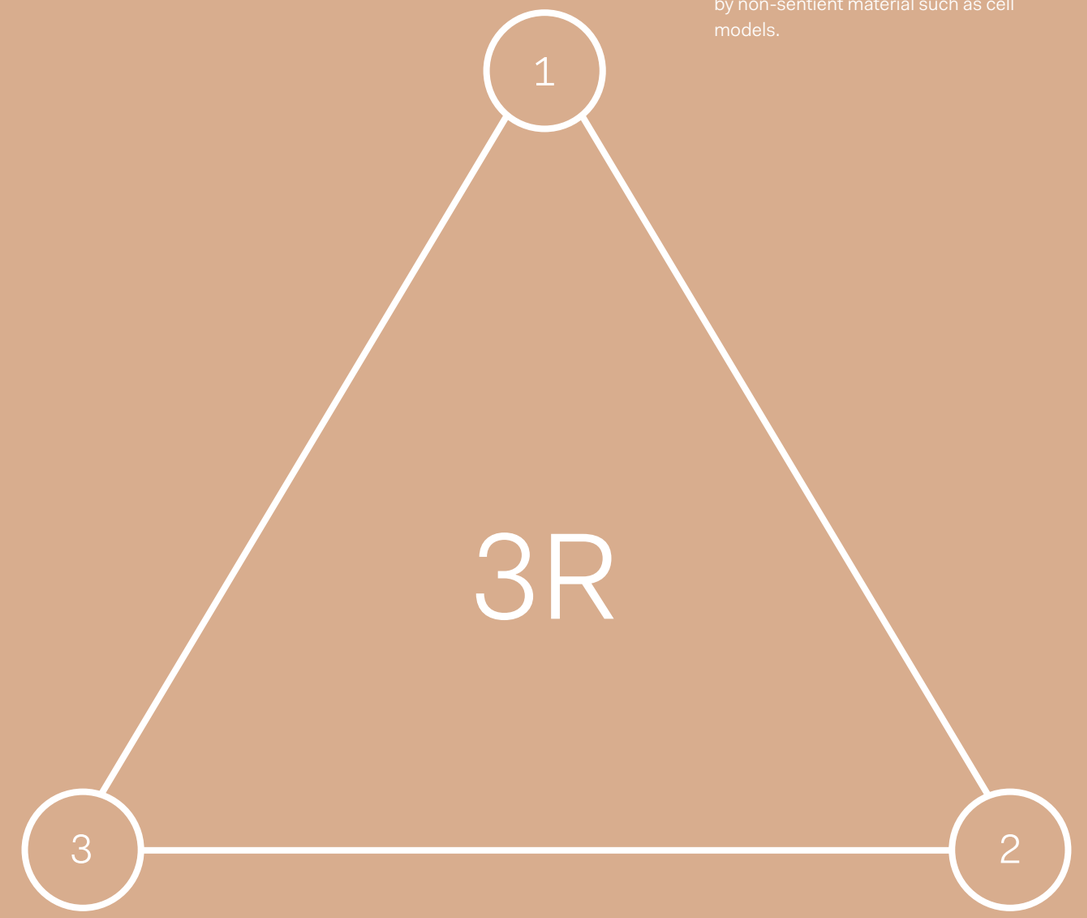
Important progress
The process of completely replacing animal experiments in biomedical research is a long and complicated one. But researchers have managed to celebrate some successes in the 3Rs over the last few years. For example, a chemical serum can now be used as an alternative to foetal calf serum, and antibodies can also be produced without the use of animals. A crucial contribution to progress in this field is also being made by organs-on-a-chip technology (see page 2). This technology is now being used in the development of new drugs and is especially important in toxicology. Prof Michael Raghunath, Head of Cell Biology and Tissue Engineering at Zurich University of Applied Sciences (ZHAW), also pointed out that animal models are not suitable for all studies and that *in vitro* models deliver better results when it comes to specific questions.
In the subsequent panel discussion, the speakers were agreed that continued investment in alternative methods and especially in the promotion, implementation and practical application of the 3Rs is essential. For despite the numerous alternative methods and huge engagement in this field, it is not possible to manage without animal experiments at present.

Project name:	SAP animal experiment conference
Charter article:	9

"From the SAP perspective, the establishment of the 3Rs Competence Centre is a positive development. But the animal protection association also expects this to lead to better-quality research with fewer animal experiments."

Dr med. vet./MLaw Julika Fitzi-Rathgen
Head of Animal Experiments, Gene Technology and Dogs, Swiss Animal Protection (SAP)

Published for the first time in 1959, the principles of the 3Rs today are enshrined in both national and international law on animal welfare.



Live and sentient laboratory animals should be replaced as far as possible by non-sentient material such as cell models.

The laboratory animals used are treated as gently as possible. This relates to the entire life of the animal: breeding, transport, housing, experiment and, where applicable, also euthanasia.

The objective of the experiment should be achieved with as few animals as possible.

Working groups and projects

Numerous working groups and projects have been in place for many years. They promote national and international cooperation on the 3Rs for the benefit of laboratory animals.

AAALAC International
(Association for Assessment and Accreditation of Laboratory Animal Care)
The private-sector, non-state organization promotes the humane treatment of animals in science with the aid of voluntary evaluation and accreditation programmes. To date, almost 1000 organizations, institutions and companies in 46 countries have been accredited by the AAALAC. Several sites of Interpharma member companies are also AAALAC-certified. Since 2013, Interpharma has had a seat in the delegation of member organizations and can thus exert a direct influence in order to advance the promotion of independent animal welfare certification programmes. To bring research assignments in line with animal welfare, the AAALAC has more than 360 ad hoc consultants, who accompany committee members during on-site visits and make recommendations. The consultants – who also come from Interpharma member companies – can offer experience that extends beyond the field of conventional laboratory animal species and in some cases provide additional expertise in fields such as applied neuroscience, behavioural science, toxicology, pharmacology or physiology.

Project name:	AAALAC International
Charter articles:	2, 7
Link:	www.aaalac.org

AALAS
(American Association for Laboratory Animal Science)
AALAS is an association of experts from government agencies, science and the private sector who are committed to the welfare of laboratory animals and the quality of research involving animal experiments. The association provides researchers and animal welfare officers with teaching materials, administers certification programmes, publishes scientific journals, supports biomedical research and serves as a forum for the exchange of information and expertise in the husbandry and care of laboratory animals.

Project name:	AALAS
Charter articles:	1, 2, 9
Link:	www.aalas.org

IQ Consortium
(International Consortium for Innovation and Quality)
Various member companies of Interpharma are also engaged in the IQ Consortium and participate in the 3Rs Leadership Group of this consortium. The group was established to promote the exchange and realization of high-quality scientific practices and thus to advance 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. The subgroup European Liaison Working Group, with which Interpharma maintains official contacts, promotes the exchange of 3Rs expertise and the mutual interest in similar objectives being pursued both in the US and in Europe. In addition to a global 3Rs award, the group also offers 3Rs training and continuing education courses.

Project name:	IQ Consortium
Charter articles:	1, 3, 9
Link:	www.iqconsortium.org

Promoting the validation and acceptance of alternative methods is important for advancing research.

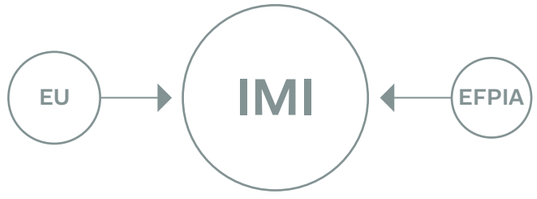
CAAT
(Center for Alternatives to Animal Testing)
Some member companies of Interpharma are represented on the European advisory board of CAAT. This organization promotes the development and validation of alternative methods in research and drug safety, as well as in education. CAAT Europe organizes 2-4 workshops and think tanks each year with 10-20 experts in each case. The experts are leading representatives from academia, regulatory authorities, and the pharmaceuticals, chemicals, cosmetics and food industries, as well as animal welfare organizations. The results of the workshops are usually published in the ALTEX journal. The CAAT Academy brings together specialists from Europe and the US to combine theory with practice in the field of alternative methods and toxicology. The courses are designed both for beginner students and for laboratory and department heads. Eleven courses were held in 2017. The two-day sessions are held throughout Europe and consist of 20% lectures and 80% hands-on training in the laboratory.

Project name:	CAAT
Charter articles:	1, 3, 8
Link:	caat.jhsph.edu

EPAA
(European Partnership for Alternative Approaches to Animal Testing)
The EPAA platform, a partnership between the European Commission and various industrial sectors that sets great store by the exchange of know-how and resources to improve the development, validation and acceptance of animal-free methods of research. In the past two decades, the EPAA has organized 40 workshops and brought out numerous publications. The EU Commission and 35 companies from seven industrial sectors (chemicals, pharmaceuticals, cosmetics, perfume, soap and detergent industries, as well as animal health) agreed in 2016 to a further 5-year collaboration up to 2020. The focus is on cooperation with international supervisory bodies and national regulatory agencies. The EPAA aims to continue its intensive support for the international harmonization of regulatory safety requirements, whenever appropriate and possible.

Project name:	EPAA
Charter articles:	1, 8
Link:	ec.europa.eu/growth/sectors/chemicals/epaa

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. The aim is to discover new therapies and secure the future of the international competitiveness of the European pharmaceutical industry together with companies, universities, public-sector laboratories, innovative small to medium-sized enterprises (SMEs), patient groups and regulatory authorities. IMI 1 was set up with a budget of 2 bn euros for the period of 2008 to 2013. IMI 2, which runs until 2024, was given an even bigger budget of 3.276 bn euros. The EU is contributing an additional 1.638 bn euros out of Horizon 2020, the EU framework programme for research and innovation. The European Federation of Pharmaceutical Industries and Associations (EFPIA) has committed 1.425 bn euros in the form of in-kind contributions. At present, there are almost 100 projects underway, some of which also involve Interpharma members.



Project name:	IMI
Charter articles:	1, 8, 9
Link:	www.imi.europa.eu

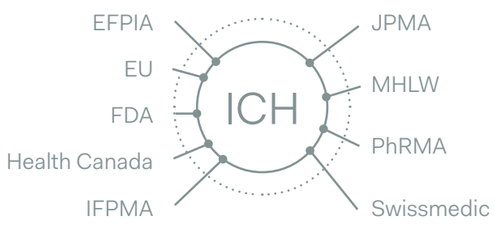
3.3 billion

The EU and EFPIA are investing 3.3 bn euros in IMI 2 (2014–2024) to develop the next generation of vaccines, medicines and antibiotics. The principles of the 3Rs also feed into the selection of projects.

TEDD
(Tissue Engineering – Drug Development)
Organ-like human tissue and cell models are of major importance for drug development and for the assessment of compounds. The National Competence Centre TEDD pools and transfers knowledge and technology to promote the further development and application of *in vitro* cell and tissue culture. New technologies that offer a physiologically more relevant representation of the function and structure of healthy and diseased tissues and organs are gaining ground. However, they are still in an early phase of development and are only of limited suitability for routine use. To exploit their full potential, there is a need for new methods of analysis to be developed, along with the further development of controlled and standardized production of tissues, preservation, automation, routine application and quality control. Concrete research projects in a network of partners from various stakeholders – including several member companies of Interpharma – have resulted in a platform that is actively helping to shape the development and application of alternative test methods for routine use in industry.

Project name:	TEDD
Charter articles:	1, 8
Link:	www.zhaw.ch/en/lsfm/research/chemistry-and-biotechnology/competence-centre-tedd

ICH
(The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use)
ICH brings together regulatory authorities from Europe, Japan and the US with the pharmaceutical industry to discuss scientific and technical aspects of pharmaceutical product registration. The purpose of the ICH is to harmonize the tests used during the research and development of new medicines and the technical standards and requirements for product registration. This standardization is intended to ensure a more cost-effective deployment of resources and to eliminate unnecessary delays in the global development and availability of new medicines. The harmonization process is complex and can take several years. It refers to the areas of quality, safety (which is where animal experiments come in), efficacy and multidisciplinary fields. ICH members meet every two years for a week; 10–15 working groups with 200–300 experts take part.



Project name:	ICH
Charter articles:	1, 8
Link:	www.ich.org

EFPIA working group for animal welfare
In the EFPIA working group for animal welfare, Interpharma member companies contribute ideas for high animal welfare standards throughout Europe. A primary function of the group is to collaborate actively in the implementation of EU Directive 2010/63 on animal experiments in EU member states. The implementation of this Directive was reviewed by the European Commission last winter and declared to be a sound regulatory basis for the protection of animals used for scientific purposes. The group also champions an open exchange of ideas and close collaboration with other organizations engaged in research in the field of the 3Rs. The group is made up of experts in toxicology, pharmacology, ethics, law, public affairs and animal welfare, as well as observers from universities and regulatory authorities. The EFPIA also publishes an annual online 3Rs report.

Project name:	EFPIA working group for animal welfare
Charter articles:	1, 2, 8, 9
Link:	www.efpia.eu/about-medicines/development-of-medicines/animal-use-and-welfare

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. With this representation, Interpharma aims to ensure that the debates taking place in Switzerland and Europe are also heard in the US.

Project name:	ILAR Guide
Charter articles:	1, 2, 8, 9
Link:	www.dels.nas.edu/ilar

Internal continuing education
One member company of Interpharma offers various 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 continuing education 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. In addition, the company has set up a Training Services group for continuing education in-house. The group offers not only training for new employees in the field of animal experiments to ensure that standards are consistent, but also specific events for experienced members of staff.

Project name:	Internal continuing education
Charter articles:	1, 3, 9

Medicine and animal experiments at the University of Basel
In May 2018, the module on Medicine and Animal Experiments for second-year medical students was offered for the tenth time already by a member company of Interpharma in collaboration with the Faculty of Medicine at the University of Basel and the vice-president of the cantonal commission on animal experiments. The students focused in depth on the various aspects of animal experiments in medicine: legal framework, theory and practice of animal experiments, ethical aspects around the treatment of animals by humans, scientific gains from animal experiments and drug safety. After visiting the animal housing facilities of the Interpharma member company, the students also spent a day in a research laboratory. The students this year again gave a positive assessment of this module. They praised the open and transparent information policy and the opportunity to gain an objective impression of the way laboratory animals are treated (housing and use in experiments).

Project name:	Medicine and animal experiments
Charter articles:	1, 3, 9

Basel Declaration
The objective of the Basel Declaration Society is to reinforce public trust in biomedical research involving the use of animal experiments and to promote open and transparent communication between researchers and the public. It aims to help get ethical principles such as the 3Rs applied worldwide in animal-based research. To date, more than 4500 researchers worldwide have signed the declaration. The activities of the Basel Declaration Society include participation in meetings and events concerning animal experiments, regular publication of the magazine Mice Times and the organization of an international congress every two years. This year, the fifth international congress was held in San Francisco (USA). Over the course of two days, more than 100 researchers, animal welfare officers and other stakeholders discussed how transparency in animal-based research can be improved and public understanding of this field increased. In addition, the Basel Declaration Society offers an annual award with the aim of promoting the harmonization of quality standards in the handling of laboratory animals. Interpharma and two of its member companies have provided the Basel Declaration Society with financial support for many years.

Project name:	Basel Declaration
Charter articles:	1, 9
Link:	www.basel-declaration.org

With an international engagement across companies, joint audits of external partners are carried out to check their animal welfare standards and compliance.

Dialogue with Swiss Animal Protection and Animalfree Research
Interpharma has been in dialogue with Swiss Animal Protection (STS) for more than seven years. Meanwhile, Animalfree Research and the Zurich animal protection group Zürcher Tierschutz have also joined the dialogue. The regular meetings serve to foster mutual understanding, to elucidate questions of animal protection and to address technical questions on animal experiments and the protection of laboratory animals.

Project name:	Dialogue with SAP/Animalfree Research
Charter article:	9
Link:	www.animalfree-research.org www.animal-protection.net

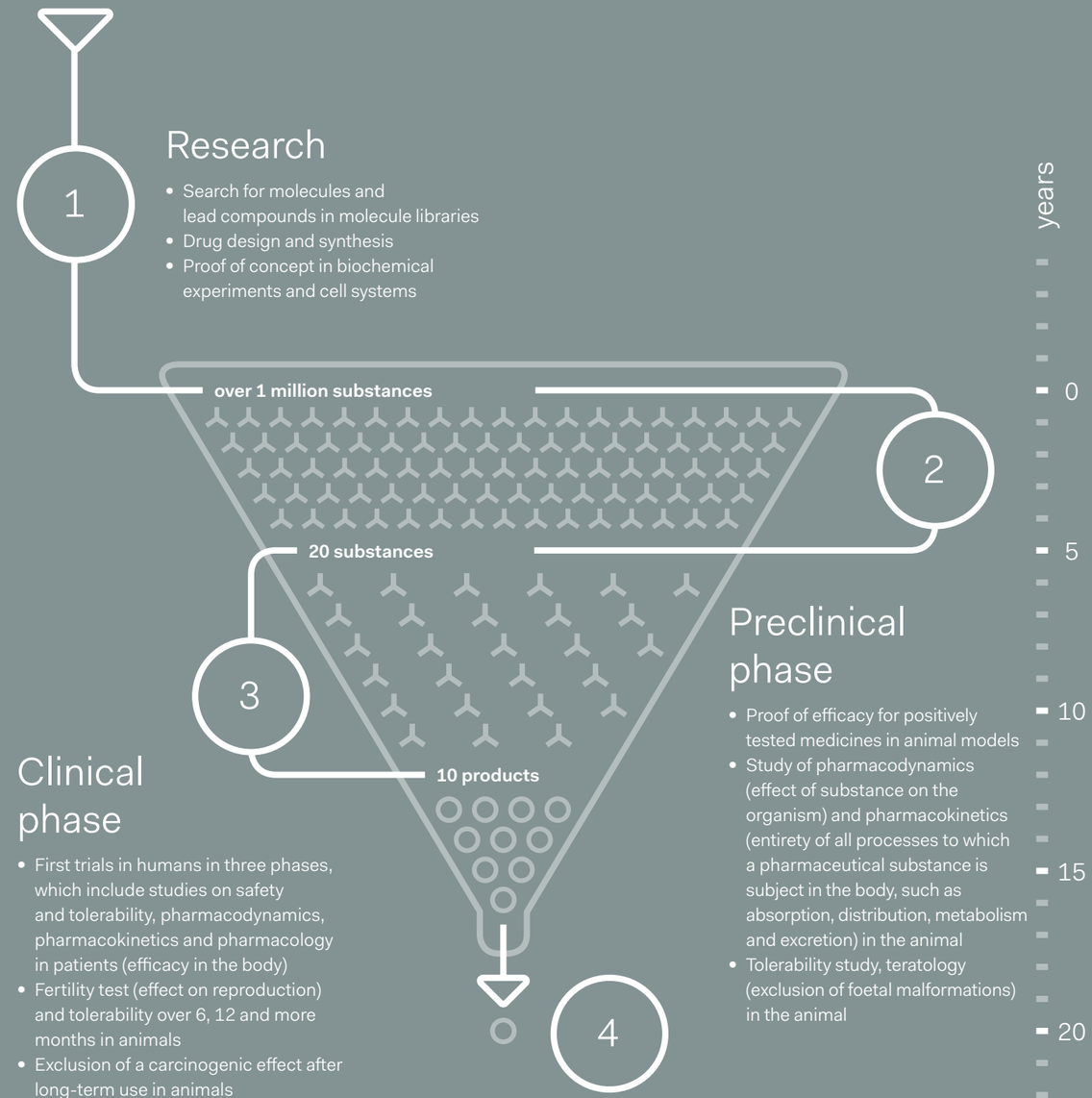
Joint audits
Research institutions and their partner and subsidiary companies which conduct animal experiments on behalf of Interpharma members must commit to comply with technical requirements and ethical standards in the husbandry and care of laboratory animals. Member companies of Interpharma regularly carry out joint audits at external research partners and breeders all over the world. These audits not only serve to ensure that standards are harmonized and laboratory animals protected, but also help to expand capacity and expertise in markets where research in animals is not adequately regulated by law, if at all. A total of twelve joint audits have been carried out since 2014. The audit results are jointly used and treated in confidence within the Interpharma member companies.

Project name:	Interpharma audits
Charter articles:	4–6

A years-long development process

On the long path to new medicines for the benefit of patients, studies in and with animals are still indispensable in many cases. At the start of drug development, however, a long path of animal-free experiments lies ahead. Only drug candidates that show particularly good results in these experiments are then tested for safety and efficacy in animals as required by law. This overview shows the years-long development process of a new medicine and the selective use of animals necessary in the various phases of development.

Pathway to a medicine



Recommended websites

Alternatives to Animal Experimentation – ALTEX
www.altex.ch

American Association for Laboratory Animal Science – AALAS
www.aalas.org

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 Centre TEDD
www.zhaw.ch/en/lsfm/research/chemistry-and-biotechnology/competence-centre-tedd

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 Consortium for Innovation and Quality – IQ
www.iqconsortium.org

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use – ICH
www.ich.org

International Council for Laboratory Animal Science
www.iclas.org

Johns Hopkins University Center for Alternatives to Animal Testing – CAAT
caat.jhsph.edu

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

New Jersey Association for Biomedical Research
www.njabr.com

Swiss Animal Protection – SAP
www.animal-protection.net

Swiss Laboratory Animal Science Association – SGV
www.naturalsciences.ch/organisations/sgv

Tierversuche verstehen – eine Informationsinitiative der Wissenschaft
www.tierversuche-verstehen.de

Understanding Animal Research
www.understandinganimalresearch.org.uk

vtk online
www.vtk-online.de

Zürcher Tierschutz
www.zuerchertierschutz.ch

Imprint
8th edition, published in 2018 by

Interpharma
Association of research-based
pharmaceutical companies
Petersgraben 35
P.O. Box
4009 Basel
Phone: +41 (0)61 264 34 00
Email: info@interpharma.ch

Editorial team Interpharma:
Sara Käch, Jessica Wüthrich

Design:
BERTA Kommunikation AG
www.berta.ag

Disponible en traduction française
Deutschsprachiges Original verfügbar

About Interpharma

The research-based pharmaceutical industry is committed to the discovery of new treatments and medicines for patients. In the association of research-based pharmaceutical companies, the industry has come together to represent its shared interests. Interpharma works closely with all stakeholders in the healthcare system and the lobby groups of the pharmaceutical sector both at home and abroad. We provide information on the concerns that are of importance to the industry, on the pharmaceutical market in Switzerland, the healthcare system and biomedical research.

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The ten articles of the Animal Welfare Charter

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.

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

3. We commit to develop and foster education and training for all our employees and associates who work with animals.

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.

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

6. We commit to joint efforts in auditing our external partners on animal welfare standards and compliance on a global level.

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.

8. We commit to promote the validation and regulatory acceptance of methods which are suited to the replacement, reduction or refinement of animal studies.

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.

10. We commit to report annually on the progress made with regard to this Charter.