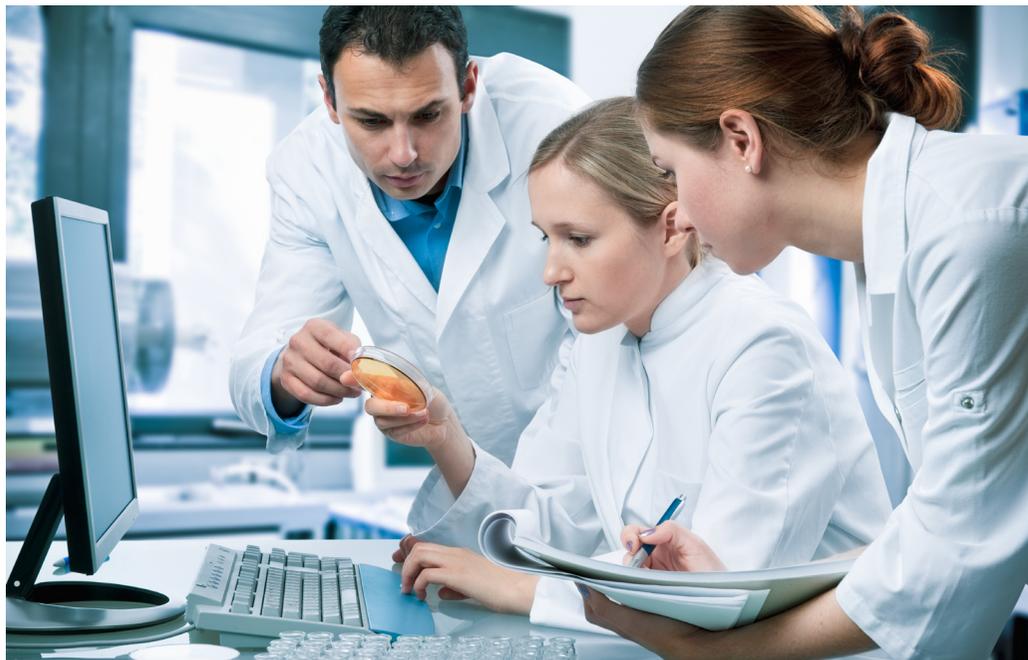
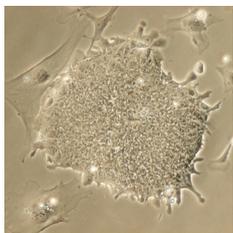
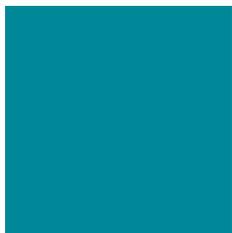


Putting animal welfare principles and 3Rs into action

European Pharmaceutical Industry Report 2016 Update





European Federation of Pharmaceutical
Industries and Associations

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This has been produced as an interactive PDF which can be used just like any normal PDF, and it is therefore easy to print and read like a brochure; however if you are using it online or on a tablet, you can use the interactive features just like a website to navigate through each section:

- * Click on the header buttons (Beyond Compliance; Leading by Example; Open Communications) allows you to jump to a new section
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The pharmaceutical industry is committed fully to the key principles of the 3Rs (Reducing the number of animals used, Refining experiments to minimise the impact on animals, and Replacing animal experiments wherever possible with alternatives), and through them, to ensuring high standards of animal welfare in the research process.

This concept of the 3Rs was developed some 50 years ago, and continues to be taken up and implemented within the pharmaceutical sector where the ongoing aim is to improve the quality of life for people by developing new products and services for the diagnosis and treatment of diseases, while ensuring high welfare to the animals involved. Furthermore, the pharmaceutical industry strongly supports the Directive 2010/63/EU on the protection of animals used for scientific purposes which has enhanced animal welfare standards and mandated the application of reduction, refinement and replacement ('3Rs') across the EU.

The use of animals in research remains a highly sensitive issue. While it is desirable to replace the use of animals in research & development, research involving animals continues to be necessary to protect human and animal, and environmental health; maintain the ability to respond to regulatory demands, and; understand the causes of diseases and functioning of complex biological systems in the body. Furthermore, Europe must remain a world leader in medical research and innovation to address the unmet medical needs of its citizens and to preserve its capacity to shape its health strategies.

The pharmaceutical industry along with all stakeholders have responsibilities to play in the development, uptake and dissemination of work on 3Rs and those taken by industry are visibly highlighted in this report. We strive to go beyond what is legally required and work to implement 3Rs to ensure high animal welfare and high quality science and ultimately improve

the lives of the people and animals that stand to benefit from the research.

Here we introduce you to our 4th report which gives an overview of EFPIA and its member's activities in putting into action animal welfare principles and the 3Rs of reduction, refinement and replacement. We give an extensive overview of the work taking place in the industry. With this in mind, the examples included in this report highlight the activities going beyond compliance, and examples where we are leading on 3Rs and transparency through open communication.

The previous reports "Putting Animal Welfare Principles and 3Rs into Action" are available [here](#).

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- * 3Rs and welfare in everyday practice
- * Science and technology drive 3Rs and welfare - We invest continuously in changing research paradigms
- * Staff training is an essential element of good science and good welfare

Leading by Example

Sharing Enforcing

Leading by Example

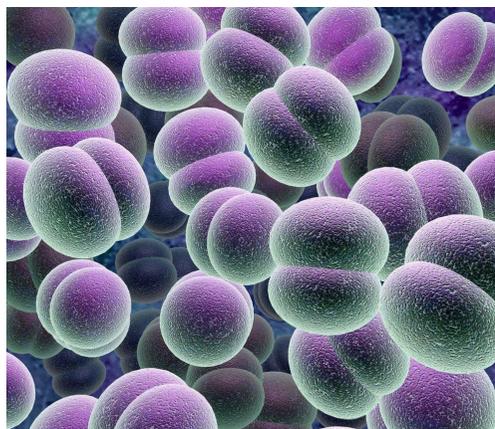
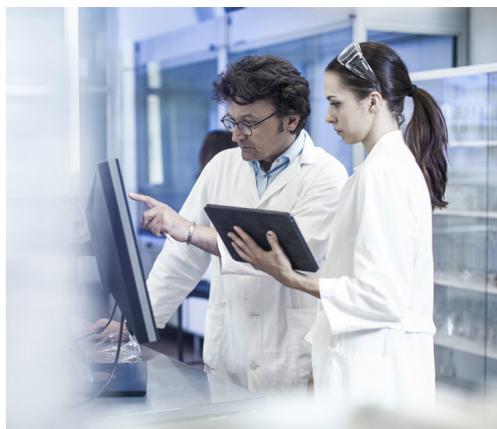
- * Dissemination beyond own department and own establishment drives improvement in welfare and general quality of science
- * In a global world, we exchange with and learn from international partners to drive convergence
- * Full and correct implementation of Directive 2010/63/EC on the protection of animals used for scientific purposes is the responsibility and endeavor of the whole scientific community

Open Communications

Dialogue Reporting

Open Communication

- * We tell what we do and engage in open dialogue with interested parties
- * Communicating progress made in animal welfare activities



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3Rs and welfare in everyday practice: Researchers go beyond the regulatory requirements to develop systems leading to improved 3Rs and animal welfare in every day practice

Refinement model to evaluate the non-specific side effects of anti-body drug conjugates moving away from use of non-human primates (Reduction and Refinement)

Antibody Drug Conjugates (ADCs) are targeted antibodies that are connected to a very potent chemotherapeutic drug that can be used in treating certain cancers. The ADC allows the treatment to be delivered directly to the site where the tumour is.

ADCs are challenging to develop as they have complex structures and are one of the leading causes of failure in their development are unexpected, non-specific side effects. These occur when the antibody used in the ADC binds to healthy tissue also.

To overcome this challenge, a model in rats was developed to evaluate the non-specific side effects. Normally, the complexity and specificity of ADCs necessitate the use of non-human primates where these specific

interactions occur in humans. An innovative study was conducted to show that there was no need to use an animal with the same specific interactions as in humans. Using rats rather than NHP is a significant refinement and substantial contribution to reducing the number of NHP used in research

In vitro gastrointestinal in vitro models to mimic processes in humans (Replacement)

When developing human medicines, there is a need for methods to rank different formulations for the medicines to be delivered in clinical trials. Mostly this is done using simple test-tube assays such as dissolution rates. These results occasionally need to be verified by assessing the kinetics in a live animal. However, species differences in the gastrointestinal tract are well known (e.g. differing pH, gastric emptying times), which may introduce difficulties in interpreting results for human relevance.



TNO have developed in vitro gastrointestinal models which are multi-compartmental dynamic non-animal systems that simulate the successive dynamic processes in the stomach, small and large intestine. This in vitro system allows the testing of formulations being developed for human use, in a system that mimics the human gastrointestinal tract instead of doing in vivo pharmacokinetic studies.

Implanted cannula for serial collection of cerebrospinal fluid reducing animal use (Reduction)

The development of a serial collection of cerebrospinal fluid (CSF) and plasma samples via implanted cannula in freely moving laboratory rats has led to a decrease in animal numbers.

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The CSF sample is a useful tool for translational analysis of biological efficacy markers and pharmacokinetic drug exposure. It shows how the drug candidate that is developed for treating brain diseases produces desired effects in the brain, such as elevation of dopamine in Parkinson's disease. Up to six samples of CSF at different time points can be collected from the same animal, which reduces significantly the number of animals needed, as compared with terminal CSF sampling, which requires an animal per time point. This new technique improves the quality of data because baseline and treated CSF samples are collected in the same animal and can be compared with the corresponding plasma levels.

Decrease in number of toxicokinetic sampling through micro-sampling (Reduction and Refinement)

Generally, blood samples are taken from animals during general toxicology, reproductive toxicology and safety pharmacology studies to demonstrate that

the compound is present in the groups of animals being tested and to understand how the degree of systemic exposure may be linked to any toxicological effects observed. The blood (plasma or serum) concentration data generated from each sample is used to derive toxicokinetic (TK) data and regulatory guidance dictates generally how and when these data are needed during compound development.

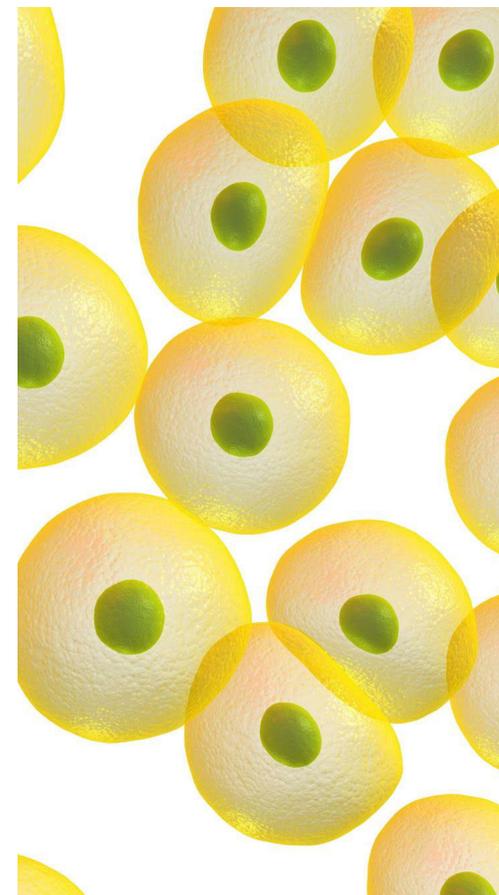
The information is used to establish safety margins for human clinical trials. The largest influence on animal numbers used in safety assessment, particularly rodents, is the collection of samples for TK analysis. However, advances in bio-analytical techniques have opened up the potential to use smaller sample volumes to assess drug exposure in blood, plasma or serum. The use of micro-samples holds exciting promise from business, scientific and animal welfare perspectives.

The pharmaceutical industry has addressed the concerns of barriers to using micro sampling by conducting a number of

bespoke studies that have illustrated that micro-sampling has no or negligible impact on the parameters assessed across many study types. Many of these have been published enabling a broader uptake of the technique and the pharmaceutical industry has contributed to a regulatory question and answer document to encourage the use of micro-sampling where possible.

Change in housing conditions to allow urine samples to be taken in own cages reducing stress (Refinement)

In many studies, e.g. safety studies, urine is collected so that urine concentration of specific parameters can be measured, which may indicate alterations, e.g. kidney function change. Traditionally, rodents have been housed singly in glass metabolism cages with no food, to allow the collection of uncontaminated urine samples. Some companies have trialed the use of hydrophobic sand as an alternative to housing in metabolism cages for urine collection from mice. As a result of this work mice can be housed in their



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home cage with sand substrate for urine collection thus reducing the stress for the animals of being moved. Data have shown that samples collected are of high quality.

Numerous replacement methods developed for skin and eye irritation and corrosion testing, and skin sensitisation

Pharmaceutical companies have implemented and perform regularly a number of in vitro alternative assays that were put in place as prescreens for in vivo testing of skin corrosion/skin irritation and ocular corrosion/irritation. Implementation of these tests have led to an end of extensive rabbit use for these methods. The Skin Corrosion test can be either a colourmetric test which changes colour if the test sample is corrosive or a 3D in vitro skin model in which if the test article kills the cells within a defined time period it is considered corrosive. The Skin Irritation test uses different commercially- available 3D in vitro skin tissue models, however they are

unable to determine the potency of that irritancy response.

The Ocular Corrosion/Severe Irritant Test uses ex-vivo tissue (cow's eyes) where the cornea is used as a biological barrier between the test article and a nutrient medium. If the test article is corrosive or a severe irritant, it will damage visibly the cornea and maybe even penetrate it. For Skin Sensitisation testing, 3 methods have been accepted internationally as in vitro alternatives for determining skin sensitisation.

Welfare assessment framework for dogs to produce reliable results (Refinement)

Stress can cause a variety of different responses in different animals, increasing variation in results between animals and reducing confidence in the data produced. Ensuring animals are fit and well, and making sure all their behavioural needs are met reduces stress, reduces variation and produces better quality data from fewer



animals. One organisation has supported a PhD project developing a welfare assessment framework for dogs, which has been used to measure refinements. Some of these resources have been made available in an NC3Rs resource on dog housing and husbandry.

Read also:

- * [New methods for monitoring and improving the welfare of laboratory dogs](#)
- * [The National Centre for the Replacement, Refinement, and Reduction of Animals in Research](#)

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Non-invasive dog model for bile collection (Refinement)

A new dog model for non-invasive bile collection has been developed. 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 the unchanged drug. In this context, a non-invasive dog model for the 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 until now for bile collection from dogs includes surgical bile duct cannulation with a risk of infection and a prolonged recovery period. 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.

Understanding behavioural needs of pigs and dogs to improve welfare and produce better quality results (Refinement)

Companies continue to apply refinements to their animal care and welfare programmes, in the development of non- or less- invasive techniques and also in considering the fate of animals at the completion of their experimental life.

Companies also collaborate and share good practice to further enhance animal care Programmes Collaboration with consultant behaviourists helps enhance the use of positive reinforcement training to refine handling, restraint and technical procedures in both dogs and pigs to better understand the behaviour of the animals and build an enhanced and specific training regime for animals prior to studies. This consistent approach to training has refined greatly procedures and has had a positive impact on animal welfare:

- * Enhance dog well-being by organising periods of play with volunteer employees who do not work routinely with dogs.

- * Introduction of a new toy consisting of small rubber tires for newly-weaned minipigs. The tyre can hang from above or simply be placed on the floor. The inside of the tyre can be filled with food pellets making it even more interesting.

- * Older minipigs tend to show less interest in rubber toys, for them large ice cubes layered with ice, straw and chow diet keep them highly interested for several hours.

- * Development of a LABgility programme, for dogs and minipigs which is a modified form of agility training. Like agility, animals negotiate different obstacles to enhance their intelligence and agility". Enrichment plays a vital role in reducing animal boredom and enhancing their well-being in what is inevitably a restricted environment. LABgility was developed and is tailored to meet the special needs of laboratory



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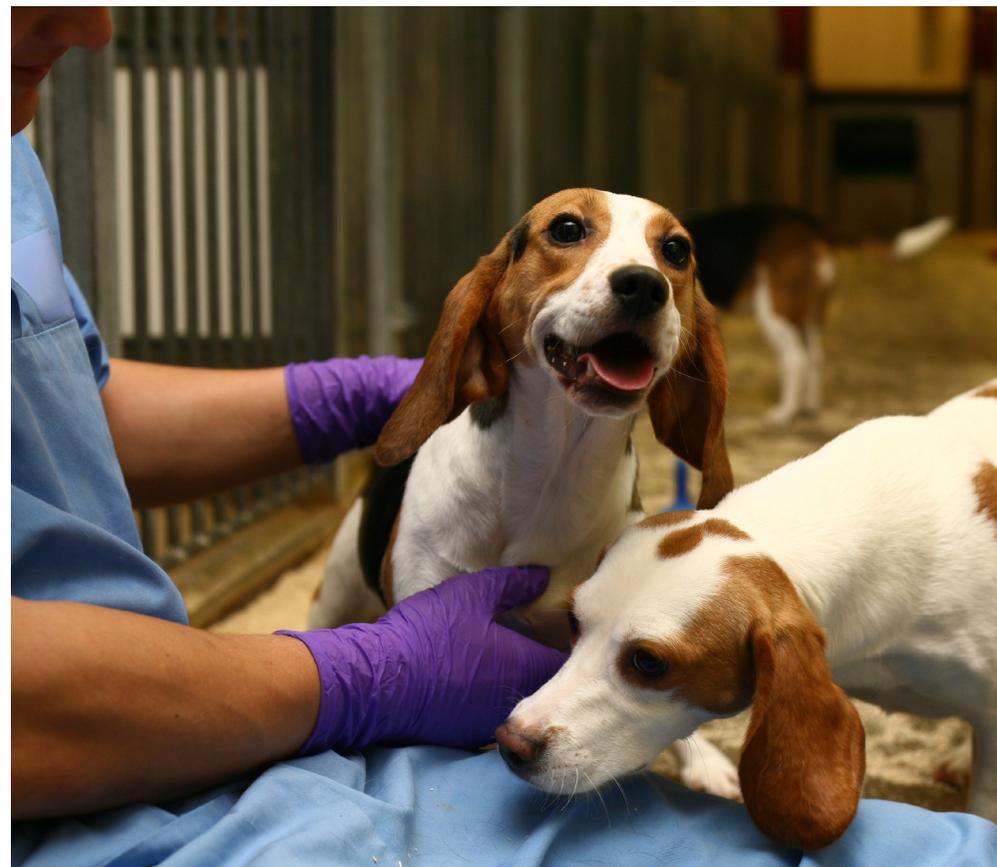
animals, with a focus on body awareness, coordination and flexibility with the aim of providing physical and mental stimulation, promoting the animal-human relationship, where the level of excitement is controlled. This ensures that animals do not over stimulate and the training of basic behaviours is maintained, such as sit, walking on the leash etc., to refine animal husbandry, handling and experimental protocols.

* Introduction of a dog rehoming programme, which allows dogs above a certain age to lead a life embedded in a family. Prerequisites for rehoming of animals include the careful selection of animals with regard to their health and behavioural attitudes as well as the careful selection of the new owners.

and ultimately to improvements in animal welfare. Whilst recognising the individuality of each facility, the participating CROs valued, for example, the opportunity to discuss the welfare needs of primates within a laboratory setting or to benchmark their procedures with similar laboratories. By respecting each other's positions, the group was able to identify ways in which they could further refine animal and technician welfare at their respective facilities, for example, positive reward training or sharing details of protective clothing used during procedures. By developing a peer-to-peer expert network the group demonstrated the commitment and passion for animal welfare within the contract research industry.

Open dialogue amongst CROs leads to improved animal welfare (Refinement)

Open dialogue and a strong commitment to animal welfare amongst several CROs led to sharing knowledge and expertise



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Science and technology drive 3Rs and welfare
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Impact of science and technology

Replacing animal tests in persistent, bioaccumulation and toxicity studies of chemicals (Replacement)

In collaboration with academic scientists, better test methods were found to assess Persistence, Bioaccumulation and Toxicity (PBT) studies required for the environmental registration of all chemical products. Advanced in vitro or other tests not using vertebrate animals allow for a more realistic assessment of chemical properties and propensity to degrade, meaning less compounds progress through reliance on animal tests, sparing thousands of fish from the high severity tests. Through scientific publications, communications and training workshops these new tests are available

widely and have now been adopted within European regulations for PBT assessments.

Introduction of a fully automated system to perform behavioural tests decreasing stress on animals and making results more reliable (Refinement)

Behavioural analyses in animal disease models are a major challenge for the development of new drugs. Besides being time consuming and labour intensive, first and foremost behavioural tests are heavily observer- and environment-dependent, and frequently stressful for the animals making results from behavioural analyses often inconclusive, due to high variability, lack of reproducibility, and limited validity towards the investigated behavioural phenotype.



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The OptiMan (Operator-independent Motor analysis) System has been designed to overcome these issues by means of a fully-automated behavioural testing system for rats. It combines three manually-operated behavioural tests into the fully automated platform. Thus addressing key shortcomings of conventional behavioural readouts in animal research and contributing to improving animal welfare by reducing stress and animal use by limiting variability.

Advancements in use of non-invasive imaging technologies (Refinement and Reduction)

During the last decade, some companies have fostered the implementation of non-invasive imaging technologies like MRI, US, CT, SPECT, PET and optical imaging into animal studies covering a broad range of applications. Non-invasive imaging offers the unique opportunity to observe and measure anatomical, pathological and metabolic changes within the same animal over time. This helps to refine animal experiments by getting a better understanding of the human pathology and

backward translation of these findings, to improve animal models. Furthermore, the non-invasive nature of imaging leads to a major reduction in the number of animals used. An example is a recent in-house-established

model for inflammatory bowel disease led to a reduction of animals in drug research. Here, imaging helped to reduce the number of animals by two-thirds, including colonoscopy and MRI exams. The findings in

the study showed a high correlation between colonoscopy as a gold standard in clinics and MRI.

Human skin models as replacements to animals for understanding skin infections and mode of action of vaccines (Replacement)

Human skin equivalents and skin explants from clinical samples represent a valid alternative to animal models for studying skin infections and the mode of action of vaccine formulations. Generally, skin equivalents are amenable to extensive manipulation, whilst explants provide a closer representation of the human skin. Both models have been characterised extensively and data generated suggest that the skin equivalent closely resembles human skin characteristics. The two models have been used successfully to study host-pathogen interaction of *Staphylococcus aureus*.



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Supporting R&D for better science and more welfare – examples of national and European initiatives supported and/or funded by industry

Collaborations funding work on 3Rs in pharmaceutical safety testing

The British pharmaceutical industry trade association (ABPI) has an ongoing collaboration with the UK National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), which is now in its 11th year. The collaboration, funded by ABPI members, supports a programme manager working on disease models, efficacy and safety assessment. The collaboration has been extended to support an additional programme manager post for a two-year period, working on

3Rs in pharmaceutical safety testing. The extension of this highly-productive collaboration demonstrates the ongoing commitment of the UK industry to work collaboratively to address challenges and bottlenecks in the application of the 3Rs to the development of new medicines.

Read more [here](#).

Berlin prize for 3R research

The German pharmaceutical industry trade association (VFA) and some of its member companies, in collaboration with the local animal welfare consortium, are funding the Berlin prize for 3R research. The prize focusses on 3R methods/projects developed/located in Berlin and Brandenburg (academia and industry). The winner project receives a monetary award for further work to lead to a reduction in animal numbers. The award for 2015 was for the development of cell-based assays to measure botulinum neurotoxin activity.



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Innovative Medicines Initiative - world's largest public-private partnership in the life sciences driving animal welfare and 3Rs

The Innovative Medicines Initiative (IMI) is a public-private partnership between the European Union and EFPIA. IMI is pursuing the goal of developing the next generation of vaccines, medicines and treatments by improving research practice; getting new healthcare solutions to patients faster; and improving health outcomes thanks to new tools, methodologies, research infrastructure and big data.

Established in 2009, and further expanded in 2014, the IMI consortia (involving industry, academia, SMEs, patients, regulators, etc.) have a direct or indirect impact on the use of animals and IMI projects are contributing enormously to the 3Rs.

IMI successes have brought results in 3Rs or new research paradigms (different ways of addressing scientific challenges) or more predictive testing tools that do not require – or require fewer – animals by removing from pipelines harmful molecules before animal studies are conducted. IMI funded projects

are contributing to a better understanding of the challenges faced in using animal models and what impact their results are having on the use of laboratory animals in research and development. Through the unique approach and collaborative platform of IMI, the 3Rs are addressed on multiple different levels such that the selection of models to be tested, protocols to be followed and the interpretation of results generated are being optimised, reducing the use of animals overall. Examples of such projects from the 100 project IMI portfolio include:

- ◇ **ABIRISK** - Anti-Biopharmaceutical Immunisation - Prediction and Analysis of Clinical Relevance to Minimise the Risk: develops tools for determining patient response directly, i.e. without the use of animals
- ◇ **COMPACT** - Collaboration on the optimisation of macromolecular pharmaceutical access to cellular targets: sets up sophisticated in vitro models of biological barriers and appropriate animal models to identify and exploit novel cell pathways for effective delivery of biopharmaceuticals
- ◇ **DDMoRe** - Drug Disease Model

Resources: A drug and disease model library will be developed, as well as modelling and simulation solutions for better prediction and the reduction of animals used

- ◇ **EBiSC** - European Bank for induced pluripotent Stem Cells: iPS cells help to reduce the use of animals in research.
- ◇ **EMTRAIN** - European Medicines Research Training Network: pan-European platform for education and training. In this framework SafeSciMET - European Modular Education and Training Programme in Safety Sciences for Medicines: implements training for a new generation of safety specialists
- ◇ **eTOX** - Integrating bioinformatics and chemoinformatics for the development of Expert systems allowing the in silico prediction of toxicities: combination of this knowledge will enable them to create more reliable computer models
- ◇ **EU-AIMS** - European Autism Interventions - a Multicentre Study for Developing New Medications: construct for the first time cellular models of ASD with construct validity
- ◇ **EUROPAIN** - Understanding chronic pain and improving its treatment: elucidate the mechanisms of pain, using novel

experimental models, human volunteers and clinical data of pain

- ◇ **IMIDIA** - Improving beta-cell function and identification of diagnostic biomarkers For treatment monitoring in diabetes: pancreatic β -cell line for drug efficacy testing in diabetes R&D as well as for a preclinical model for cell replacement therapy
- ◇ **iPIE** - Intelligent Assessment of Pharmaceuticals in the Environment: based on existing data help identify which 'legacy' APIs are most likely to pose a risk to the environment and so should be prioritised for testing – reduction of overall number of animals used
- ◇ **MIP-DILI** - Mechanism-Based Integrated Systems for the Prediction of Drug-Induced Liver Injury: develop new tests that will help researchers detect potential liver toxicity, including combinations of non animal models
- ◇ **NEWMEDS** - Novel methods leading to new medications in depression and schizophrenia: develop improved experimental models that mimic schizophrenia or depression in humans
- ◇ **Pharma-Cog** - Prediction of cognitive properties of new drug candidates for

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neurodegenerative diseases in early clinical development: development of experimental human models for the study of drugs ameliorating cognitive impairment

◆ **Prelect** - New models for preclinical evaluation of drug efficacy in common solid tumours: focus on complex but transferable next generation in vitro and in vivo models

◆ **PreDiCT-TB** - Model-based preclinical development of anti-tuberculosis drug combinations: in silico modelling for the prediction of efficacy of novel drug regimens for tuberculosis

◆ **SAFE-T** - Safer and Faster Evidence-based Translation: focus on measuring sets of safety biomarkers across a variety of patient populations

◆ **STEMBANCC** - Stem cells for biological assays of novel drugs and predictive toxicology: supply of cells that mimic more accurately what happens in the human body

◆ **U-BIOPRED** - Unbiased biomarkers for the prediction of respiratory disease outcomes: will be linked to results of preclinical models, in order to facilitate future drug development

VAC2VAC – Vaccine batch to vaccine batch comparison by consistency testing: aims

to develop and validate quality testing approaches for both human and veterinary vaccines using non-animal methods

In 2015, IMI launched several new calls for proposals with new topics with 3Rs impact, such as translational imaging methods in safety assessment or quantitative systems technology. In 2016 additional topics with direct 3Rs impact were launched such as on data quality and reproducibility in Central Nervous System research or on preclinical data sharing.

Approaches to Animal Testing – from bench to industrial application

EFPIA and a number of its members are founding members of the EPAA (European Partnership for Alternative Approaches to Animal Testing) – a cross-sectoral and multidisciplinary partnership between five European Commission services and seven industry sectors. The mission of the EPAA is to promote 3Rs in regulatory testing, and facilitate the development and implementation/regulatory acceptance of alternative testing strategies.

After a first decade, during which the EPAA started to deliver tangible results (see 2015 activity report), the Commission and the industry decided to prolong the partnership for the new five-year term.

◆ In 2015 and 2016, the pharmaceutical sector led the industry delegation at the Steering Group.

◆ EFPIA and its members play important roles on the EPAA Project Platform focusing their work on skin sensitisation, vaccines and other biologicals as examples.

◆ A successful project identified differences in legal requirements for vaccines testing between different regions (Europe, US, China, Japan, Brazil, etc) and brought together regulators from these regions to align views on usefulness of alternatives to four safety tests and kick off actions to remove obsolete tests from national and international guidance. Two in vivo safety tests were recognised as obsolete by 12 regulators from 4 regions who committed (and started the relevant processes) to kick off deletion in European Pharmacopoeia, WHO and OIE guidelines, and national legislation as appropriate.



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Staff training is an essential element of good science and good welfare

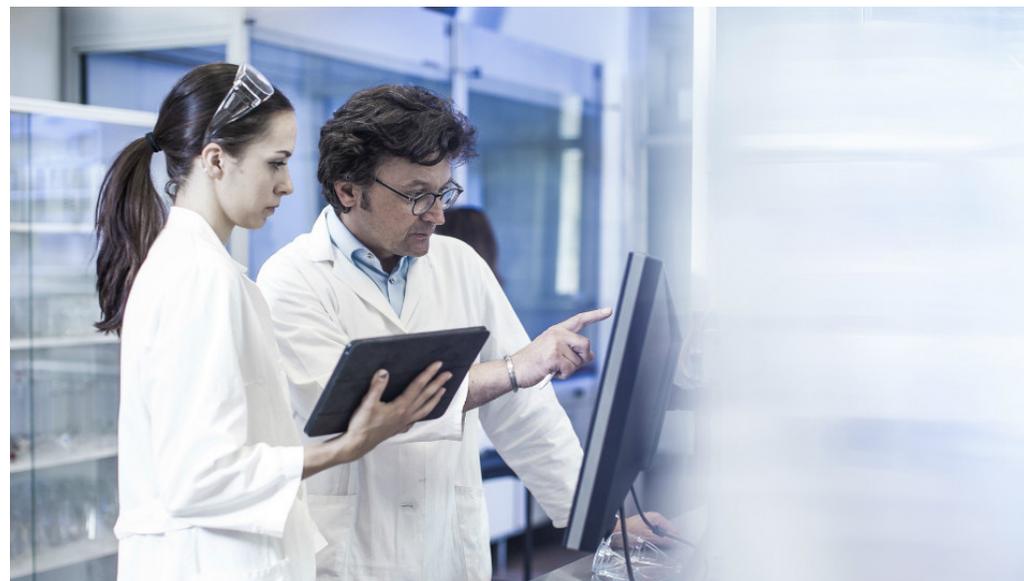
Training courses

To further strengthen the knowledge sharing and application of global standards, a global laboratory animal sciences course is provided at all sites and covers animal ethics, 3Rs considerations in research, as well as rules/regulations (company policies, local laws and the EU Directive), welfare and husbandry.

Workshops

In silico (or computational) toxicology is a sub-discipline of toxicology that uses data and mathematical/statistical modelling to generate knowledge. A workshop was held in one company, which included both internal and

external experts in this field. The goal was to assess technology and scientific strengths and weaknesses, as well as practical applications and future roadmaps within the field of in silico toxicology. Several examples were provided of how in silico modelling provided useful alternatives to in vivo testing and in some instances, impacted the design of future safety studies.



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Dissemination beyond own department and own establishment drives improvement in welfare and general quality of science.

Determining the most effective anaesthesia for fish (Refinement)

Fish are used to assess the potential impact of new medicines on the environment, but surprisingly little is known about appropriate anaesthesia in fish. For some studies, fish need to be anaesthetised to minimise pain and distress. This is done by flowing anaesthetic into the fish tank. However, some chemical substances in the water can be unpleasant for the fish. A study has shown that zebrafish detect and actively avoid seven of nine most commonly used anaesthetics, however Etomidate appears to be the most effective anaesthetic. Industry has shared this work through publication and is working with other laboratories and groups to broaden the use of Etomidate in work with adult zebrafish.

Sharing experiences to improve knowledge on compound administration in minipigs (Reduction)

Minipigs are increasingly being used in pre-clinical testing as an alternative to dogs. To administer compounds in fluid form, a vehicle (compound suspending agent) has to be identified. The vehicle needs to have a good safety profile, showing little or no side effects for the intended species. However, only few vehicles are cited on publically available databases for use in mini-pigs. A collaborative project was conducted with the purpose of summarising the experience of numerous laboratories in a review paper. The paper reports tolerability and compositions used in minipigs for dermal, oral, subcutaneous and intravenous routes of administration.



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By sharing these data, testing of inadequate formulations and studies to qualify these vehicles in minipigs can be minimised or avoided, thereby contributing to reduced animal usage.

Driving 3Rs within pharmaceutical companies (Refinement, reduction and replacement)

Some companies have established 3Rs departments or introduced 3Rs leaders in order to take a more strategic approach to driving 3Rs innovation within their company. Many companies run an annual 3Rs award process often with external judges included. These awards not only recognise and reward innovative new science that has 3Rs benefit, as well as care and welfare, but also help promote the importance of the 3Rs in animal research within individual companies. These awards are often recognised at the most senior levels within companies.

Many companies enter into collaborations (e.g. with other stakeholders such as national 3Rs centres/ platforms) to share and gain

knowledge within the 3Rs. Some companies also help sponsor external 3Rs awards e.g. NC3Rs, IQ/AAALAC e.g. in the first year of the IQ/AAALAC awards, scientific papers from Switzerland, the United States and Brazil were chosen.

Rehoming Policies

Some companies have rehoming policies. 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. For example within the framework of the « live saving products » production the use of horses is required as plasma donors. At the end of their donor “career”, these horses cannot be re-used. As the horses are often healthy young and well socialized, rehoming is conceivable. To study the feasibility, a partnership with the GRAAL association (Group of Reflection and Actions for Animals: an animal protection association involved in rehoming program of animals used by the biomedical research) was set up. This project permits horse lovers to adopt young and healthy horses.

Exploring changes with using 3Rs in safety assessment over the past 30 years

A peer-reviewed study was published exploring how the use of in vitro alternatives in the safety assessment of new medicines has changed over the last 30 years, to determine patterns, drivers and challenges in uptake. The British Pharmaceutical Industry Trade Association conducted a survey looking at how many in vitro assays were used in different areas of safety assessment between 1980 and 2013. Responses were collected from four pharmaceutical companies and three contract research organisations. There was a large and steady increase in the use of in vitro tests by companies between 1980 and 2013; more than 20% of all in vitro tests reported were conducted in 2013, the last year of the survey period, and over 70% were conducted since 2010. In vitro assays were most widely used in genotoxicity, safety pharmacology, and drug metabolism studies. The survey highlighted periods of step change in the uptake of in vitro assays, which may have been linked to the adoption of relevant international guidelines or EU legislative decisions. These results are

encouraging and highlight the advances the pharmaceutical industry has made in this area. This also builds on a previous publication showing the pharmaceutical industry is increasingly working in collaboration on 3Rs research.

Read more:

- * [Development and use of in vitro alternatives to animal testing by the pharmaceutical industry 1980–2013](#)
- * [Quantifying the pharmaceutical industry's contribution to published 3Rs research 2002–2012](#)

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Full and correct implementation of Directive 2010/63/EC on the protection of animals used for scientific purposes is the responsibility and endeavor of the whole scientific community

Activities of EFPIA and its members

EFPIA and its members remain committed to full and correct implementation of Directive 2010/63/EU and enhance the cultures of care, challenge and openness for research involving animals. They have undertaken numerous activities on this regard recently:

- * **Supporting Directive 2010/63/EU:** EFPIA and its members signed the statement supporting European Directive 2010/63/EU (“Directive”) on the protection of animals used for scientific purposes following the European Citizen’s Initiative Stop Vivisection which was seeking to repeal the Directive and ban animal research. The Directive is vital to ensure that necessary research involving animals can continue whilst requiring enhanced animal welfare standards. (read more)
- * **Working with the User community:** EFPIA organizes annually “users workshops” to allow experts from industry, academia and research funding organisations to exchange

good practice and recommend a course of action to enable progress. The recent 2 workshops focused on ‘Enhancing 3Rs provisions’ and on ‘Culture of Care’. The first mentioned workshop led to the discussion evaluating opportunities to **enhance the implementation of selected welfare and 3Rs provisions of Directive 2010/63.**

- * **Culture of Care:** Establishing, promoting and maintaining a good ‘culture of care’ is a fundamental requirement if legal, ethical and animal welfare obligations, along with wider responsibilities towards employees and the public, are to be met. Defining culture of care across Europe remains diverse. In early 2016, the EFPIA Research and Animal Welfare Working Group started a reflection on the concept of culture of care (referred to as ‘climate of care in recital 31 of the Directive and covered in most of the guidance documents developed) and how it is understood and applied across research institutions/companies in Europe and conducted a survey that offered insights into good practice and areas for improvement within the user community. Following

this, a workshop was organised bringing together numerous people who had views on implementing a Culture of Care in a “thought-starter” workshop.

- * **Guidance and trainings:** To ensure proper implementation of the provisions laid out in the Directive, it is essential guidance is taken up, best practices are shared and trainings take place. EFPIA are recognized expert stakeholders by the EU institutions and have been involved in numerous expert working groups organized by the Commission. These working groups have led to the development of endorsed guidance documents which EFPIA and its members support and promote. Further to this they support trainings for example on understanding and implementing severity assessment of animal tests correctly.

- * **Joining forces:** EFPIA remains open to a constructive dialogue and engagement of all stakeholders who are committed to share experiences and expertise on the requirements laid out in the directive and disseminate these in best practices. Consortia have been formed with diverse stakeholders on focusing on areas to bring about positive change. EFPIA

also work closely with the EU institutions and have participated in the European Parliament’s Intergroup for the Welfare and Conservation of animals.

- * **Scientific input:** The European Commission will report in 2016 on the impact of Directive 2010/63/EU in advancing the 3Rs and welfare of animals and creating level playing field. The Directive is delivering benefits for animal science in Europe, which remains critical for the discovery and development of new medicines. Given the state of science, and importance of ensuing animal welfare, access to medicines, and retention of biomedical research and drug development in Europe, EFPIA do not recommend amendments to the directive at this stage. Attention should remain focused on properly implementing and enforcing the current Directive, advancing the 3Rs, and delivering on the concrete actions identified at the Commission’s recent scientific conference on ‘non-animal research – the way forward, which EFPIA and its members attended and provided expertise.

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Global collaborations

Directive 2010/63/EU sets a high scientific standard of good quality science, good animal welfare and implementation of the 3Rs as a bench mark for **global harmonization**. There are a number of challenges with regulatory requirements differing internationally, making global collaborations necessary to lead towards improved animal welfare and implementation of 3Rs:

Replacing batch testing of animals for quality control safety testing of vaccine

Currently, regulations worldwide require that acellular pertussis vaccines are tested in mice to ensure the safety of every batch, and especially the lack of residual toxin (HIST test). HIST tests have been employed for quality control safety testing of pertussis combination vaccines for many years. The level of distress of these tests are considered as severe, using large numbers of mice with a lethal endpoint. A lot of work was done on in vitro alternatives since the early 2000s in close collaboration with national control laboratories and regulators. The most challenging aspect

has been the global regulatory agreement for a suitable harmonized replacement test. An International Working Group for Alternatives to HIST was formed in 2010 involving regulators, control laboratories, industry, 3Rs groups (6 workshops, 2 collaborative studies). This finally culminated in consensus at a workshop in 2015 that a modified in vitro cell approach was an acceptable alternative. This method have been very recently optimized and validated. Worldwide laboratory animal population, this could prevent undue suffering and death to an estimated 84,000 mice every year.

Cell lines to replace animal use for Polio vaccine

The Polio Eradication plan engages all 145 countries that currently use OPV Oral Polio Vaccine in their routine immunization programs. It includes the introducing at least 1 dose of Inactivated Polio Vaccine IPV into the routine immunization schedule globally and ultimately stopping OPV use in 2019-2020. The kidney cells from monkeys were used to ensure the full inactivation of the vaccine doses. The goal of the project was to replace cells from monkeys by cells from a continuous cell



line L20B (full in vitro model) for the control IPV inactivation. The current IPV inactivation test is used since 1959, the beginning of the IPV manufacture. This test has been critical all along the history of the IPV since the Cutter incident in US (lack of reliability of the inactivation test & process causing 204 cases of polio and 11 deaths in 1955). This test is the

critical test for ensuring the safety of the IPV. This project initiated 15 years ago encountered many challenges: adherence to the new method worldwide except in US&CA who requested additional evidences of equivalence.

[Read more: Polio Global Eradication Initiative](#)

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We tell what we do and engage in open dialogue with interested parties.

Openness on animal research

Over 100 UK companies are signatories to the Concordat on Openness on Animal research. They have hosted open days for staff and family, community science fairs and visits around their facilities. In addition they have contributed to blogs externally on 3Rs award process and progress towards openness to ensure greater transparency and understanding of animals used in research.

Read more:

- * Great progress in openness on animal research
- * Recognising and rewarding 3Rs developments at AstraZeneca

Disseminating an encouraging openness on work using animals

The British Pharmaceutical Trade Association has undertaken a number of activities to be, and to support and encourage our members to be, increasingly open about their use of animals in research, to facilitate informed

public dialogue. This includes expanding their Animals in Research materials, explaining how and why animals are used in the development of new medicines, examples and descriptions of projects involving animals including the harms to the animals, and examples of how the 3Rs are applied. They also produced a Members' Guide to the Concordat on Openness on Animal Research, highlighting examples and advice to support our member companies in being more open on this topic.

Read more:

- * Members' guide to the Concordat on Openness on Animal Research in the UK

Visits to research facilities

To enhance the communication and transparency of the industry with policymakers from Switzerland and abroad, 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.

Transatlantic publications

EFPIA members contributed to a special edition of the Journal of the American Association for Laboratory Animal Science (JAALAS) focusing on the 3Rs.

The Basel Declaration Society

The aim of the Basel Declaration Society is to reinforce the public's trust in biomedical research when 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. In 2016 it was held in Rome at the beginning of October. The venue was specifically chosen 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 discussed 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.

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Communicating progress made in animal welfare activities

In addition to participating in international events and platforms, the pharmaceutical industry is communicating on the 3Rs through Corporate Social Responsibility (CSR) reports. Each pharmaceutical company has a website where CSR reports are available. A dedicated section on animal welfare and the 3Rs are included in these reports. A few examples can be found here:

- * AstraZeneca
- * GlaxoSmithKline
- * Interpharma
- * Novartis
- * Novo Nordisk
- * Merck
- * Sanofi
- * UCB

EFPIA have produced three previous reports on Putting animal welfare principles and 3R into action since 2011 (available on EFPIA's website). Furthermore, some of its member companies produce their own annual 3Rs report illustrating industry's commitment to applying the 3Rs principles in animal research and to enhancing scientific advances leading to the implementation of one of the 3Rs.



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Useful Links

Accreditation of Laboratory Animal Care International (AAALAC) - www.aaalac.org

Alternatives Approaches to Animal Testing (EPAA) - www.ec.europa.eu/growth/sectors/chemicals/epaa_en

European Centre for the Validation of Alternative Methods (ECVAM) – www.eurl-ecvam.jrc.ec.europa.eu

European Commission - www.ec.europa.eu/environment/chemicals/lab_animals/home_en.htm

Federation of Laboratory Animal Science Associations (FELASA) - www.felasa.eu

Innovative Medicines Initiative (IMI) - www.imi.europa.eu

Institute for Laboratory Animal Research (ILAR) - www.dels.nas.edu/ilar

National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) - www.nc3rs.org.uk

3R Foundation - www.forschung3r.ch

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