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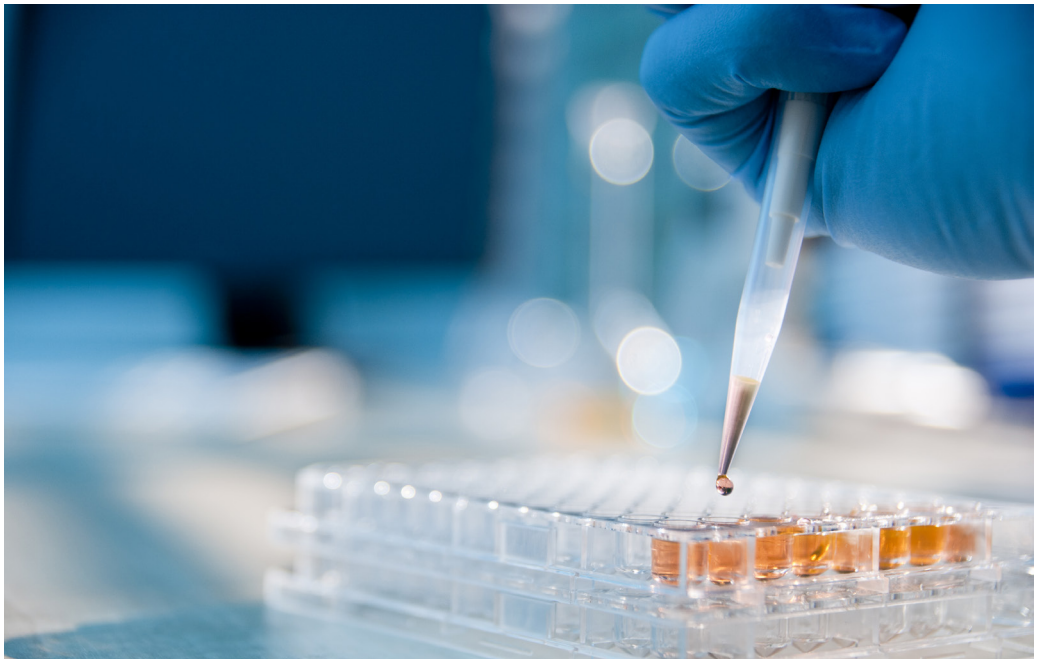
Putting animal welfare principles and 3Rs into action

European Pharmaceutical Industry Report 2019 Update



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Connecting healthcare across the industry and stakeholders to implement the 3Rs

The pharmaceutical industry is fully committed to the key principles of 3Rs (Reducing the number of animals used, Refining experiments to minimise the impact on animals, and Replacing animal experiments wherever possible with alternatives). 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.

The pharmaceutical industry continues to support the objectives of 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 while ensuring Europe remains a world leader in biomedical research. The use of animals in research and testing can be a controversial subject and therefore it is important to support an open dialogue and collaboration on the use of animals for scientific purposes, including a high degree of transparency and openness. We support:

- Dialogue - A stand out need is effective collaboration. It is essential in connecting healthcare to ensure innovation, value and transformation, which has a beneficial impact on animals and 3Rs development.
- Transparency - Telling what we do and how we do it, is crucial to explain and justify why the use of live animals is still an indispensable requirement to develop drugs for serious diseases or chronic illness. While at the same time, numerous activities are underway to move away from the reliance on animals and therefore it is important also to inform on the abundance of work and commitment of companies to move towards refining animal models and the development and implementation of alternative approaches to reduce the sectors reliance on animals.
- Collaborative Research - 2018 saw IMI, the Innovative Medicines Initiative – the largest health public private partnership - celebrate 10 years. Over the 10 years, over 100 projects have been established to accelerate the medicines development process. Many have impacted strongly on eliminating poorly predictive animal models, developing new improved models, replacing animals with better in vitro and in silico models and establishing a number of alternative tools.

Since the adoption of the EU legislation governing animal use, EFPIA and its members have been publishing reports to visibly highlight our actions on putting animal welfare principles and the 3Rs into action. Here we introduce you to our 5th report, Enjoy!

The previous reports "Putting Animal Welfare Principles and 3Rs into Action" are available **here**.

#WeWontRest
in our efforts to ensuring
high standards
of animal welfare
in the research process

KIRSTY REID
DIRECTOR SCIENCE POLICY
EFPIA

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Sally Robinson
AstraZeneca
Chair of the EFPIA Research and Animal Welfare Group

Despite significant scientific and technological advances research using animals plays a small but essential role in the discovery and development programmes that bring new medicines to patients. The data generated provides critical information on the likely efficacy and potential safety risks of new candidate drugs that cannot be obtained by other means. Using animals in research is a privilege not a right and the pharmaceutical sector recognises the importance of upholding this privilege through responsible animal use.

The EFPIA Research and Animal Welfare (RAW) Group is another of many examples of the Pharmaceutical sector working together. The group's mandate is:

- Horizon scanning of animal research and political, legal and regulatory environments, to detect and address business threats and opportunities.
- To promote implementation and good practice sharing of 3Rs and Culture of Care to support Directive 2010/63 and Commission reports.
- To share information about our 3Rs activities

I have been part of the EFPIA Research and Animal Welfare Group for 6 years and chairing it for 4 of those years and I have seen through the years the passion and commitment of individuals and their companies to responsible animal use, with tangible outcomes leading to improved animal welfare and high-quality science as demonstrated with the examples in this brochure.
The strength of EFPIA research and animal welfare group lies in the breadth of the experience and the different roles and perspectives of its members and the willingness to consider and share ways of working across member states learning from each other. This brochure highlights a number of the sector's initiatives towards the 3Rs and others can be found in our individual company collaborations e.g. with UK NC3Rs, regulators, animal welfare groups and IMI.

Chris Petursson, DVM, DACLAM
Bristol-Myers Squibb
Chair of the EFPIA 3Rs focus group

As the chair of the EFPIA 3Rs focus group it is my pleasure to help introduce the 2019 Putting Animal Welfare Principles and 3Rs into Action brochure. In preparing this brochure our aim was to provide an overview of the activities of the EFPIA Research and Animal Welfare (RAW) and 3Rs Groups and showcase the status of some of the 3Rs initiatives and technologies currently in pharmaceutical research. This brochure gives an overview of new initiatives, continuing the series of information shared in previous brochures.

First a little bit about us. The 3Rs focus group is comprised of dedicated professionals from EFPIA member companies that work in the pharmaceutical industry or related associations with a global focus. Our team members include subject matter experts that work as global 3R leads in their organisations, veterinarians, toxicologists, pharmacologists, and scientists. Each of us is passionate about the 3Rs and represent organisations that have a strong commitment to animal welfare. Our companies strive to go beyond the regulations in our 3Rs efforts and understand that the way to accomplish this is to invest directly in the 3Rs and cooperate as an industry through associations like EFPIA. One way we do this is to share experiences and best practices between companies to learn from each other of how to improve animal conditions, techniques and implementation of 3Rs.
As a group we work together to leverage our passion, knowledge and resources to best advance the 3Rs as we drive to discover and develop new and innovative medicines and technologies to improve the health and quality of life of patients worldwide. We believe that the 3Rs are an integral component of good science and also help evolve the advancement of new methods and technologies in animal research.

I invite you to read our brochure and discover how EFPIA is contributing to the 3Rs in pharmaceutical research. We are optimistic that many of these exciting and promising developments will evolve in a way that will help us continue to advance on the 3Rs, improve animal welfare and deliver the highest quality science and medicines to the patients.

I trust that you will find the brochure valuable and informative.

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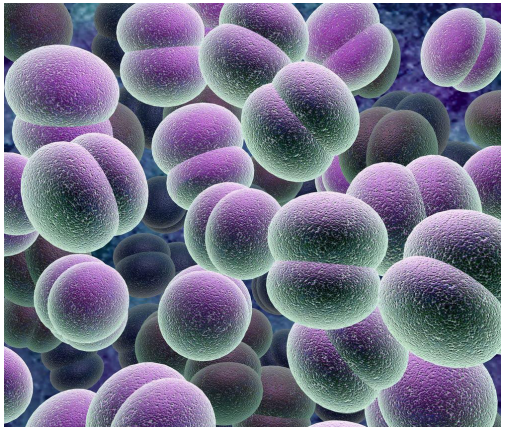
* 3Rs and welfare in everyday practice: Researchers go beyond the regulatory requirements to develop systems leading to improved 3Rs and animal welfare in every day practice
* Science and technology drive 3Rs and welfare – We invest continuously in changing research paradigms
* Staff training is an essential element of good science and good welfare

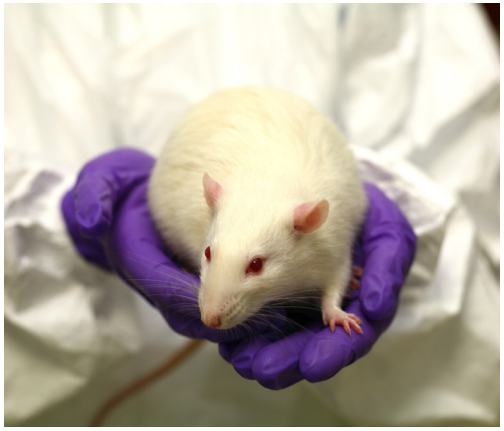
Leading by Example

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

* Communication, transparency and dialogue with the public





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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

Aiming for the removal of the Abnormal Toxicity Test as Regulatory Requirement

The Abnormal Toxicity Test (ATT) is a quality control (QC) test used for batch release testing; mainly by government laboratories in different countries; of biologicals, vaccines and other products. The objective is to determine whether each batch of drug product contains any unexpected contaminations. The species used are mice and guinea pigs. The ATT results in the unnecessary and unethical use of animals since there is no scientific rationale as to how that test would be able to fulfil its objective of detecting contaminations. The networks across the industry and regulators coordinated cooperation in order to remove requirements to use the ATT test. The European Partnership for Alternative Approaches to animal testing (EPAA) hosted an international workshop in September 2015 covering case studies including the ATT test with the aim for international convergence on the issue. Participating international regulators supported deletion of the ATT from all national / jurisdictional requirements & international guidance. Since then 49 individual monographs removed the requirement of the ATT from the European Pharmacopoeia which provides common quality standards throughout the industry to control the quality of medicines, and the substances used to manufacture them. This will result in a direct reduction of animal use and make use of the effect of the European Pharmacopoeia's influence on other countries (e.g. China and Russia) in favour of the ATT removal from other pharmacopoeias worldwide. At the meeting of the WHO Expert Committee on Biological Standardization held from 29 October to 2 November 2018, a decision was made on the immediate discontinuation of the inclusion of the ATT in all future WHO documents on vaccines and other biologicals published in the Technical Report Series (including WHO Recommendations, Guidelines and manuals).

Enhancing Welfare and Science by group housing when conducting Primate Metabolism Studies

The understanding of Absorption, Distribution, Metabolism and Excretion (ADME) for new pharmaceuticals is required in regulatory submissions. Currently, ADME studies are conducted with metabolism cages involving single housing of animals for up to 14 days, so that all excreta can be collected to meet the scientific objectives. Even though such metabolism cages have limitations for animal welfare, they have remained largely unchanged for years. A new cage was designed and built to fulfill requirements on enrichments and dimensions for group housing of primates. The scientific validity and positive welfare outcomes of conducting ADME studies with the new improved metabolism cage

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for group housing of Cynomolgus monkeys were demonstrated by comparison of the scientific results, by measuring stress hormones and through behavioural assessments of stress. These observations indicated that group housing had a positive benefit on the behaviour of the animals, compared to single housing, without compromising the scientific objectives of the study. This therefore supports the use of group-housed animals in these regulatory studies as the new benchmark for Contract Research Organisations and Pharmaceutical companies.

A novel approach to conducting dog metabolism studies allowing dogs to be pair housed

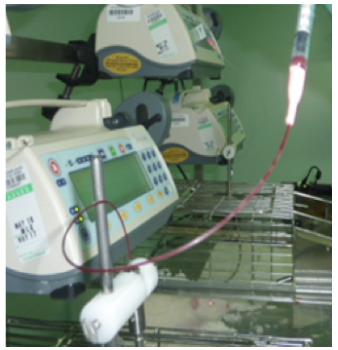
Standard metabolism cages for the purposes of conducting ADME studies that enable an 'excretion balance' scientific objective to be met, involve singly housing animals for up to 14 days. Such cages have limitations for normal social behaviours. A metabolism cage for dual housing was designed to improve the welfare of dogs involved in these studies. An excretion balance study was conducted to compare dual and single housing of dogs in metabolism cages, and therefore to demonstrate the suitability of conducting regulatory studies with a pair housing design without compromising the scientific integrity of the study (overall recovery of dosed radioactivity in excreta). Welfare assessment was evaluated using stress markers including cortisol and clinical scoring, when animals were either singly housed or dual housed.
Mean recoveries of radioactivity from three pairs of dual housed animals were comparable with recoveries from six singly housed animals. In addition, the pharmacokinetics of radioactivity in both singly housed and dual housed animals were consistent. Cortisol analysis was inconclusive. It is thought that the process of blood sampling from the animals introduced a bias in the data. However group housed animals were observed to be calmer and did not exhibit signs of stress. These data support the suitability of dual housing of dogs for future metabolism ADME studies, which is a major refinement measure for these regulatory studies and a significant welfare improvement.

Modifying the bile-duct cannulated Rat Model

Bile duct-cannulation of rats is an important research model that allows the investigation of the excretion and metabolism of xenobiotics.
Historically, catheters are placed in the bile-duct of the liver to collect bile, and in the duodenum to infuse replacement bile salts. They are exteriorised via a tail cuff and the animal is tethered and singly housed during both recovery and experimental periods.
In the modified model they are tail cuffed, using a pin-port adapter, which permits the animal's own bile to be re-routed back into the duodenum during the post-surgical recovery period. Animals can then be group housed whilst recovering from surgery and are not tethered or singly housed during this time. The experimental phase of the study remains unchanged. Vascular catheters can also be added during surgery for blood sampling and intravenous dosing. All catheters are exteriorised though a single tail cuff and are sealed during group housed surgical recoveries.

Detachable Tail Cuff System

Animals are group housed during recovery and washout phases



Blood samples are collected through the indwelling catheter

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Validation studies demonstrated improvements and comparability in surgical success rates, reductions in body weight losses, excretory output and bile flow. The modifications offer the potential to reduce the number of animals undergoing surgery, and shows welfare benefits by limiting the period of tethering and single housing.

Move to group house ferrets used for Flu vaccine commercial testing

It is a regulatory requirement for each batch of a flu vaccine to undergo a verification test. This requires several hundred ferrets to be used each year. Ferrets are used because they are susceptible to flu virus just as in humans. As a social animal, ferrets prefer to be housed in groups. However, the study relies on measuring changes in body temperature to indicate that the flu affects them, and group housing was previously thought likely to raise temperatures because of raised levels of activity. The team worked with a contract research facility to prove that group housing did not affect body temperature, and so improved the welfare of the ferrets by facilitating group housing during these essential regulatory studies.

Using in vitro mechanistic studies to de-risk a compound that induced vacuolation in rats

In order to replace rat and non-human primate studies that have a duration of 13 weeks, scientists have developed an in vitro strategy with a compound that is currently in clinical phase 2 development. This project was initiated as the health authorities wanted justifications as to why an observation of effects on the liver in a previously conducted 13-week rat study would not be considered adverse and why a combination toxicity study would not be needed. By using long-term cultures of liver cells, the molecular mechanism leading to the effect was demonstrated to be due to rat-sensitive modulation of a specific biochemical pathway. This mechanism was demonstrated to not occur in human liver cells, thereby de-risking its relevance to humans. Based on these results, the 13 week studies in rats and non-human primates for mechanistic investigations are now avoided.

Reduction and replacement: Evolution of strategies to improve preclinical cardiac safety testing

The early and efficient assessment of cardiac risks in preclinical testing is essential to safely administer new molecules into healthy volunteers or patients. Cardiac safety issues still represent an important reason of drug discontinuation or withdrawal from the market. Over the last few years, a new paradigm named CiPA (for Comprehensive in Vitro Proarrhythmia Assessment) has emerged, driven by both the pharma industry and the regulatory authorities. It proposes the use of human-based in silico and in vitro assays for an early detection of cardiotoxicity risk. It includes 3 components: an in vitro cellular

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assay evaluating electrophysiological activity (an ECG); an in silico tool which simulates the effects the compound will induce in 'virtual' human cardiac cells; and finally an in vitro model using real human stem cell-derived cardiac cells. These assays are indicating better predictivity and sensitivity than the original animal-based models. Various validation studies have been conducted by several pharma companies and service providers. Although some additional efforts are still needed to harmonise and standardise these assays, and despite the fact that this new paradigm is not yet a 'mandatory' guidance, many pharma companies have started to implement them in their drug safety strategies[1].

Combined General and Genetic Toxicology Studies Supports 3Rs Principles

For programs advancing through non-clinical development, in vivo studies involving general toxicology studies and genetic toxicology are often run separately. However, now where certain criteria have been met, the genetic toxicology studies can be integrated into repeat dose toxicity studies. For example, a 4-week oral gavage toxicity study in rats with an 8-week recovery period, where the general toxicology endpoints and genetic toxicology endpoint were collected in the same study. The implementation of this approach also set the precedent for future study plan generation and review for combined studies.

Using Application of the 3Rs to Gain Regulatory Support for the Development of Medicine

Studies to understand the safety of biologically active compounds are required in rodents and non-human primates. Using scientific justification and regulatory experience for a specific molecule, a nonclinical data package with in vitro (human tissue) and in vivo (rat only) studies was presented to European (EMA), US (FDA) and Japanese (PMDA) regulatory authorities who accepted the studies to support Phase I & II clinical trials. This spared more than 100 primates and saved several million dollars of costs whilst helping to progress an important potential medicine.

Progress towards the replacement of the rabbit blood sugar assay for quality control of insulins required by US Pharmacopeia by an in vitro test

The US Pharmacopeia requires, for insulins and insulin analogues marketed in the US, a bioassay in rabbits to evaluate the biological activity for the release of each batch of drug substance and for the characterization of drug product in development and after major changes during production. The number of animals used in these tests depends on the requirements to meet the respective acceptance criteria. The Pharmacopeias of Europe, Japan, India no longer require the animal method. In 2012 an in vitro cell-based test was developed and validated to replace the rabbit blood sugar assay for batch release of insulin glargine in a first step. This test in plate format determines the biological activity

[1] *Gintant et al., Evolution of strategies to improve preclinical cardiac safety testing, Nature Reviews Drug Discovery, 2016, doi:10.1038/nrd.2015.34*

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of insulin by its binding to the human insulin receptor over-expressed in Chinese hamster ovary cells. This cell-based test was validated to meet the requirements of the US Pharmacopeia and US Food and Drug Administration (FDA). A bridging study of in vivo and in vitro testing revealed superior precision and equivalent accuracy of the in vitro test compared to the animal assay. The validation data for batch release of insulin glargine drug substance were submitted to the US FDA and resulted in regulatory acceptance of the cell-based test as an alternative to the rabbit blood sugar assay in 2015. As of 1 January 2016 this animal experiment is no longer performed by many companies. Simultaneously the in vitro test was further validated for a wide a range of marketed insulins and analogs. These data, the test protocols and the cell line were made available to the USP (United States Pharmacopeia) with the final goal to modify the USP Chapter "Insulin Assays" to include the in vitro test as an alternative to the rabbit blood sugar test. This process is ongoing. See: Progress towards the replacement of the rabbit blood sugar bioidentity assay by an in vitro test for batch release of insulins in quality control[2].

Outreach and Rehoming programmes

Over the past few years companies have begun to look beyond merely providing the best care for their animals while in their care, but also to be concerned with what to do with animals no longer needed for research. For one company in particular, in an animal welfare and care spirit, by collaborating with colleagues at outside organizations, a robust, successful laboratory animal re-homing program has been developed. These include an internally-developed dog temperament testing paradigm that has helped to identify potentially risky adoptions. A questionnaire to help determine if the home of the potential adopter is appropriate and matched for a specific animal has also been developed. Additionally, "common sense" Terms and Conditions that satisfy Corporate Security and Legal concerns have been developed. Finally, regulators ensure that the program is compliant with all regulations and applicable guidelines. Recently a small group of non-human primates no longer suitable for research was placed at a retirement sanctuary. Accomplishing this goal of ensuring appropriate lifelong care for these animals required due diligence to help mitigate any risks as well as extensive fundraising.

[2] *ALTEX - Alternatives to animal experimentation. 34, 4 (Nov. 2017), 565-566. https://doi.org/10.14573/altex.1708091*

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Science and technology drive 3Rs and welfare
We invest continuously in changing research paradigms

Impact of science and technology

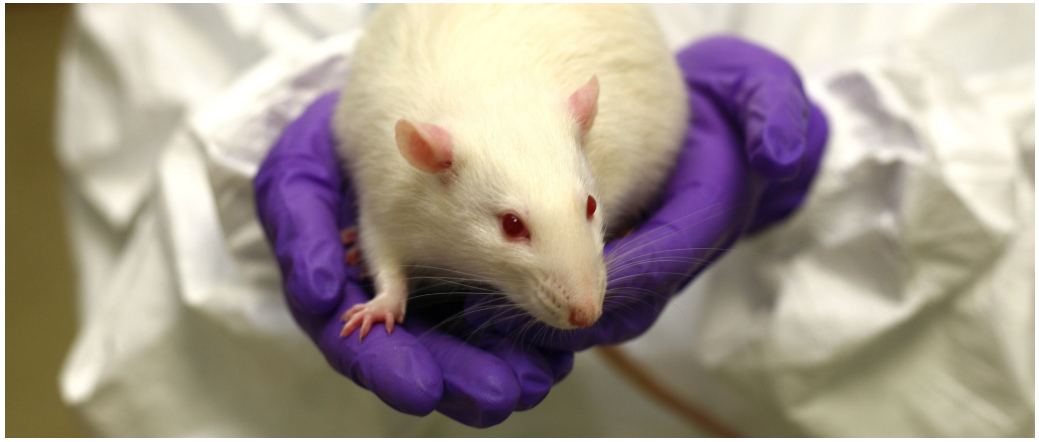
Vascular access button

Surgically cannulated rats are typically used if a substance is administered by intravenous infusion, where the pharmacology or formulation precludes the use of a bolus and/or the intravenous profile requires further definition. The Vascular Access Harness (VAH) was the standard model for dual cannulated surgical rats. The disadvantage of this model is rats are singly housed and permanently harnessed. The Vascular Access Button (VAB) has been introduced to give the opportunity to socially house the surgical rats and improve post-operative recovery. The data generated is used to determine the rate and extent of absorption, the time course of distribution throughout the body and the rate of elimination and excretion from the body.

Development of Organs-on-a-Chip

Producing organs-on-a-chip requires biomedical engineering expertise and draws upon several other technologies, including 3D cell culturing, bioprinting, microfluidics, and induced pluripotent stem cells. One company's Pharmaceutical Sciences group hosted distinguished speakers and guests from across the globe for the Organs-on-a-Chip Symposium focussing on the future of efficacy and safety testing. Experts from the world's most renowned academic centres shared their latest innovations on organoid bio-engineering, microfluidics and advanced in vitro disease modelling. One group have been using biological design principles to develop microfluidic devices lined by living human cells which replicate organ-level structure and functions and can replace animal testing for drug development, mechanistic discovery, and personalized medicine. Going forward, the technology will play a key role in developing complex systems and assessing targets which are not present in animals, which is central to the commitment to the 3Rs principles. This symposium provided an opportunity to exchange experiences and new ideas, to grow expertise and team up with world leading experts and jointly shape the future of efficacy and safety testing.

◊ In drug metabolism/pharmaco-kinetic (DMPK), in vitro assays are successfully used for many different predictions of a drug candidate Absorption/Distribution/Metabolism/Elimination (ADME) with in vitro, physiologic cell-based methods (for passage through gut barrier, liver metabolism and drug-drug interactions, inhibition and induction of metabolic enzymes). There is a close collaboration with safety and QSAR modelling to optimize and characterize target modulation. A model system lacking is the kidney elimination model useful for compound optimization.



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◊ Another company is working on introducing a novel microfluidics high throughput organ-on-chip technology with the aim to extend the knowledge from existing 2D/non-fluidic cell culturing to an advanced level for eADME/PK support, also with a view to drug-drug interaction de-risking for projects in case of kidney-efflux, liver-bile-efflux, blood-brain-penetration for small and large molecules[3].

Development of a non-invasive technique for Automated Detection of Epileptic Seizures in Rodents

Epilepsy is a severe disease with largely unmet therapeutic need and one third of the epileptic patients experience multiple crises every day of their life. Animal models are still essential to understand the mechanisms of the disease and to test potential promising new medications. In most cases, epileptic crises are detected in animals through invasive electroencephalogram (EEG) recordings, requiring preliminary implantation of electrodes in the brain. A pharmaceutical company has developed a non-invasive technique named 'AccelEpi' (for Automated Accelerometric Detection of Epileptic Seizures in Rodents), which allows the detection of these crises in epileptic mice without any surgical implantation. Mice are freely moving in their home cages and are carrying a small silicone 'jacket' containing the AccelEpi sensor, similar to 'Wii' used for some video games. This sensor detects changes in gravitational force, such as the abrupt movements associated with epileptic seizures in mice. An algorithm has been set up that can discriminate the epileptic crises from normal movements linked to animal activities like grooming, eating, etc. This technology is superior to previous methods of monitoring and quantifying seizures in mice, which required being video-monitored around the clock and a human to review all the content and manually score each episode. The AccelEpi system received the Bio-IT World Best Practices Award for Research and Drug Discovery in 2015[4].

Efficient antibody discovery from human material using single-cell expansion techniques

The human antibody repertoire has an enormous diversity and these antibodies can bind a vast number of foreign and self-specific epitopes (part of an antigen molecule to which an antibody attaches itself). In biotherapeutic development, human-derived antibodies are a gold standard due to their compatibility with human patients. Despite recent exploitation of methods for the efficient isolation of human antibodies, limitations in the throughput have led to experimental compromises, including the generation of hybridoma cell lines from immunized rodents, which have either been humanized with respect to their antibody genes, or which must be subsequently humanized in vitro. Scientists have now optimized a technique to maximize flexibility, allowing the production of ready-to-go recombinant antibodies. This allows researchers to work directly with human donor material, effectively replacing animal protocols. Depending on the donor's immunological status, material can be screened for receptors that offset pathogenic threats (such as influenza or polyomaviruses) or antibodies that ceases to recognize one or more of the body's normal constituents such as that which arise during autoimmune disease.

[3] Membrane-free culture and real-time barrier integrity assessment of perfused intestinal epithelium tubes Nature Communications, Volume 8, Article number: 262 (2017) https://doi.org/10.1038/s41467-017-00259-3
[4] https://investors.epam.com/news-releases/news-release-details/epam-life-sciences-awarded-grand-prize-bio-it-world-best

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Using in vitro CRISPR engineered organoids to replace genetically engineered mouse tumour models

In vivo pharmacology or mechanism studies for oncology often involves the use of genetically modified animals. However, the generation of a specific mouse strain takes often more than one year, and it can be very time consuming to breed strains that lack the desired genotype. There is also quite often a very long time until tumour formation after the induction. In order to overcome these shortcomings and animal welfare concerns, the engineering of tissue specific organoids into cancer progenitors via in vitro 3D culture has been developed. These in vitro generated cancer progenitors harbour defined genetic alterations which, when injected in vivo into immuno-competent mouse hosts, can readily form tumours with overall short disease latency. This method eliminates the generation and breeding of genetically modified rodents and has therefore a huge impact on decreasing animal numbers.

Cryopreservation of genetically modified rodent breeding colonies is contributing to Reduction and Refinement while supporting R&D programs

Cryopreservation, whereby preservation of material takes place by cooling to very low temperatures, is used to reduce animal breeding and the number of surplus animals produced for lines for which there is low demand. Applying this strategy, frees up resources to support production of higher priority models and refine animal breeding and study conduct. Cryopreservation is an excellent strategy to re-derive a model when natural genetic drift occurs and ensures backup in the event of a catastrophic loss after a natural or accidental disaster, allowing re-establishment of a breeding colony of specific models, without the need for a new generation or acquisition. Cryopreservation of rodent lines at regular generational intervals ensures that, if genetic integrity is lost, it can be easily and quickly re-established. In addition, cryopreserved material is easily transported with no impact on the welfare of the animal or phenotype of the model. One company currently has a repository of 550 cryopreserved transgenic lines, whereas only 150 models are globally available as live colonies.

Refinement of Jacket Telemetry in Preclinical Safety

Telemetry models are the gold standard for cardiovascular risk assessment for both Safety Pharmacology and Toxicology studies. Telemetry allows for collection of large volumes of quality data, from unrestrained animals. However, unrestrained telemetry models typically encompass either invasive surgical procedures that provide maximum signal parameters, or only electrocardiographic (ECG) collections from wearing jackets which provides for minimal invasive applications. To improve on this process, enhancement of the jacket telemetry model, by way of a minimally invasive implant that collects blood pressure and temperature in addition to an ECG was tested in order to increase the screening capability and deliver refinement of the model used. This led to the development of a minimized surgical procedure to place the implant thus eliminating the need of the invasive procedure to enter a major body cavity, while maintaining a core body temperature collection. A catheter was passed subcutaneously to cannulate the femoral artery in the hind leg to allow for the collection of arterial blood pressure. A special 35cm length catheter was designed such that the tip could be positioned near the diaphragm to allow for respiratory data to be extracted from the collected blood pressure waveform. Simultaneously, a tattoo regimen has been used on the animals while they were anesthetized, marking the optimal ECG electrode location. The tattoo ensures exact lead placement for each subsequent data collection, refining signal quality and

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reproducibility while improving the analysis and reporting.

Refinements to prevent animals chewing equipment and enhance welfare: New type of Electrocardiography (ECG) jacket for dogs

A new type of jacket which is used to capture ECG data for 24hrs, has been refined which prevents the dogs gaining access to their leads and chewing them. Together with refinement to the jacket acclimatisation process, this has resulted in fewer dogs needing repeat 22hr ECG recording and fewer dogs losing ECG signal during data capture.

Switching from analogue external telemetry blood pressure and ECG registration to fully implanted digital devices in canine and NHP cardiovascular drugs safety studies

Drug development cardiovascular safety studies are currently carried out with the subcutaneous implantation of blood-pressure device and sensors measuring the arterial blood pressure in the artery in the thigh of the animals (femoral). The Electrocardiography (ECG) signals are taken from electrodes attached to the chest of the animal. Both signals are sent together from the transmitter that the animal has to carry in a small backpack. This method has been upgraded to a new technology with a fully implanted digital transmitter. This allows simultaneous measurement of animals in group housing conditions without the signal interference which is encountered with analogue transmission technology. The new device is fully implanted into the abdominal wall and connected via wires which run under the skin to ECG electrodes and a blood-pressure catheter which is located within the femoral artery. The surgery itself is only slightly more complex than the implantation of the former device; however, the refinement is based on the fact that the animals do not need to carry a backpack with the transmitter anymore. They do not need to be trained to accept jackets containing receiving and transmitting equipment, manual handled to attach adhesive electrodes to the skin or wear jackets on the day of measurement. Also animals can be group housed whilst measurements are captured simultaneously from more than one animal within the group. Based on the fact that manual handling induces stress, related blood pressure increases, which can take hours to normalise, the fully implanted digital system also enhances the quality and scientific integrity of study data.

Combining pharmacokinetic (PK) information with dog cardiovascular (CV) telemetry studies using Automated Blood Sampling

By combining dose escalating dog pharmacokinetic information and dog cardiovascular data collection in a single design, one team has reduced the number of dog studies conducted and enabled the generation of robust PK data from a CV study, increasing the impact of the CV data by improving the ability to define the exposure-response relationship. Combining the commercially available automated blood sampling system with dog telemetry studies is an advance over the standard approach of conducting separate studies and achieving lower quality pharmacokinetic information with single blood samples from the telemetry studies. This approach allows for collection of multiple serial blood samples without disruption or negative impact to telemetry cardiovascular data collection and eliminates the potential stress to the animal caused by multiple blood collection events.

Non-invasive analgesia for minipigs

Standard pain relieving treatment for minipigs typically requires numerous injections to alleviate post-surgical or procedure related pain. In addition to the stress and discomfort of injections, this practice can result in fluctuating concentrations of the analgesic if not injected at correct intervals. Replacing injectable analgesic with formulations that do not require multiple injections or restraint can refine pain-relieving protocols. An oral formulation of the drug meloxicam is available for swine and has proven to be as effective in reducing pain as injectable meloxicam in minipigs. The formulation is well accepted by the minipigs and requires no or minimal restraint. Transdermal delivered fentanyl either as patch or spot on treatment is also well tolerated and effective in providing a long lasting analgesic effect in minipigs and should be considered as alternative to injectable formulations.

Welfare and Study Design Refinements for Evaluation of Blood Sampling in the Minipig by Temporary Cannulation of the Saphenous Vein

Historically, blood samples have been collected from the minipig either by venepuncture

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of the jugular vein or by the surgical implantation of a catheter into the vena cava. Jugular vein sampling can cause stress to the animal due the restraint position that is used in an inverted cradle. In addition, because of the deep positioning of the jugular vein, the technique is a challenge and it is associated with a risk of injury if the sampling is not precise. Vena cava catheters require time consuming introduction and maintenance; can sometimes experience patency problems; and the animals are prone to infection around the implantation site. Due to the invasive nature of the catheters they can only be inserted once, and the animals therefore need to be euthanized following a single short-term study of around 2-3 weeks. The insertion of a temporary cannula into the saphenous vein in the leg is a major refinement to the invasive sampling procedures described above. Cannulation is conducted under inhalation anaesthesia, and the cannula does not impede normal animal behaviours. After a few minutes, and once recovered from anaesthesia, the animals are returned to their holding pens and can be dosed as normal. Several blood samples can be withdrawn from the cannula over 24 hours without the need for further needle insertions. Additionally, animals are held in a natural upright position for sampling rather than the inverted cradle, therefore the experience of the animal is greatly improved. The saphenous cannulas are removed on completion of the sampling regime and can be re-inserted, following a 14-day recovery period, to allow further study sampling. The animals can therefore be used on several phases, leading to a potential 90% reduction in the number of animals used for pharmacokinetic studies.

Reducing the invasiveness of liver biopsy performed in non-human primates to assess drug exposure and drug efficacy in the liver

In humans with liver conditions, harvesting liver tissue by biopsy remains unavoidable, in addition to other biological measures, to assess the liver pathophysiology. It has also proved to be an attractive investigative tool in clinical trials to assess the potential impact of new specific therapeutics on the liver integrity. In preclinical research, in good predictive animal models such as non-human primates, an indication for liver biopsy is the monitoring of liver exposure to drug candidates and the assessment of drug efficacy after administration. To limit the size of liver biopsy to the smallest possible amount, and thus the effect on the animals, a minimal laparotomy approach is carried out with a fully optimized anaesthetic/analgesia/antibiotic protocol, high surgical expertise, clinical pathology (by sampling blood) and clinical signs (such as body temperature, body weight, behaviour) monitoring in order to reduce any surgical complications. In practice, this liver sampling methodology allows the generation of meaningful results offering a refinement alternative while using a limited number of animals.

3Rs Surgical and procedural model refinements

Surgical model refinements lead to better science, the reduction in the number of animals needed, and the overall impact on animal health. Here are some recent examples of surgical model development efforts specifically focusing on incorporating the principles of the 3Rs[5]:

- The development of repair surgeries for animals with long term surgically implanted devices. A minor yet effective repair surgery was developed to restore patency (whereby keeping open) to intrathecal catheters to maintain a passive drip of cerebrospinal fluid (CSF), such that the restored patency would last for the required duration.
- Another minor repair surgery was developed to prolong cardiovascular telemetry implants by removing the transducer and re-implanting it via a new vessel.
- Refinements have been developed to maintain advanced study support techniques. Bile Duct Cannulation is the enduring large animal model for investigating bile elimination of new drug candidates. However, this model may initiate anatomical and physiological changes that may affect the drug pharmacokinetics, so a novel, minimally invasive procedure to collect bile from large animals termed 'ultrasound-guided cholecystocentesis' was developed and validated. In this procedure, ultrasound is utilized to guide a needle transcutaneously through the liver and into the gall bladder, allowing for precise bile sample collection. With this refined method, it is now possible to safely and efficiently obtain bile samples from dogs and monkeys in support of drug pharmacokinetic studies without the previous harmful effects.

[5] *Wanda West, Jon Ehrmann, Wendy Johnson. "Lumbar Intrathecal Catheterization in the Canine". Journal of Investigative Surgery, Volume 27, Number 4, August 2014, pages 226-233*

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Precision cut lung slices as an example of reduction

Precision cut lung slices (PCLS) are lung co-cultures from animals that allow compound testing in the niche of the lung using a reduced number of animals. The lungs of the euthanized animals are flushed with low melting agarose and thin slices are made out of these lungs. These slices represent the whole lung and all cell types in the lung: epithelium, fibroblast, muscle cells, immune cells, endothelium etc. From one animal, many slices can be obtained, as well as material for the positive and negative controls. PCLS from different animal models can be obtained to mimic fibrosis or inflammation. Compounds are tested in this system before determining if in vivo experiments with larger animal numbers are necessary.

New Inhalation Box as an example of refinement

Inhalation boxes are used in safety testing of air-born molecules. The boxes have been redesigned to avoid having to force the animal in from the top as in previous system, which causes them unwanted stress. The new system allows for them to climb into the box on their own via a tube at the side, thus reducing stress levels. The sides of the boxes are also shielded with latticework, so the tails and paws of the animals are not injured during their time in the box.

New feeding regime for guinea pigs as an example of refinement

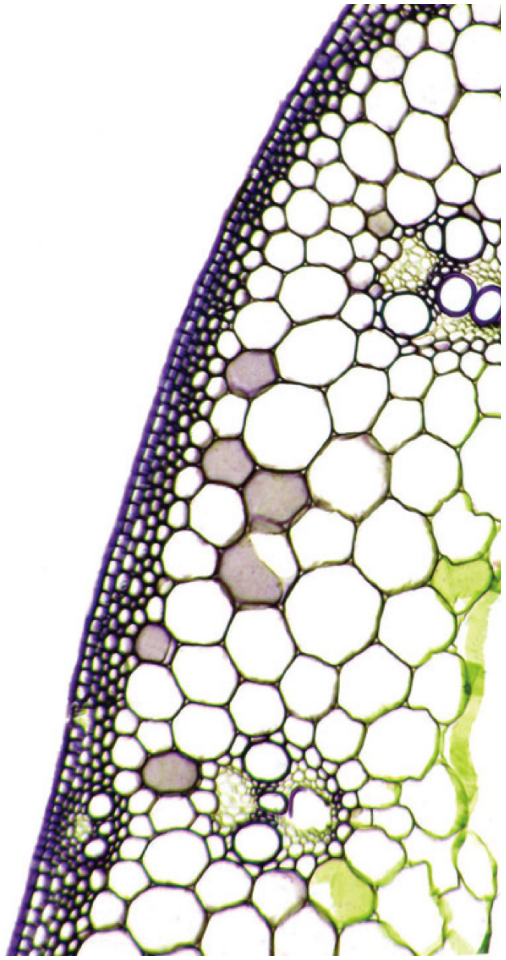
Previously, it had been routine practice to ensure that guinea pigs had an empty stomach for 10 hours before intratracheal application because the food pellets contaminated the whole mouth and food may be inadvertently pushed into the trachea and cause inflammation to the animals. However due to this extensive time without food, as the, guinea pigs would regularly eat their faeces instead leading them to be housed on grid floors the night before the application, causing them even more stress. As a solution, they are now fed hay and cucumber the night before, which can be cleared easily from the mouth with a Q-tip/cotton swab. In addition, as they are provided with food, it is no longer necessary to house them on grid floors.

Rewards based training for pigs

A training programme has been developed and refined to aid both the studies and the welfare and manual handling of pigs The pigs' temperament has improved, they are less vocal and more engaging with the staff. The refinements in the pig area have included changes to the slings used during the procedures to make it more comfortable for the animals, and to also aid jugular bleeds without the need to place the pigs into a V crate - thus reducing stress to the pigs. Finding ways to improve the oral gavage route through new methods of dosing via jellies or capsules and making modifications to slings and stands to aid oral gavage but minimise stress to the pigs are continuing and have shown improvements to the pigs welfare.

Different blood sample technique as an example of reduction

Arterial blood used to be collected from dogs in a final study under anesthesia without revival via surgery of the large artery in the leg of the animals. However this protocol has now been improved and the arterial blood sample is now taken from the ear artery under anesthesia. Bleeding can be stopped easily without swelling by applying pressure at the site of sampling over 15 minutes and the anesthesia is then reversed. This new protocol



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no longer leads to the killing of the animal, instead it is awoken after the procedure.

Reduction and refinement: Implementation of micro-sampling techniques in pharmaco-kinetic (PK) study evaluation and toxico-kinetic (TK) assessment

Micro-sampling is a method to collect a very small amount of blood (typically ≤50 µL) used to measure concentrations of a drug and/or its metabolites, and subsequently calculate the appropriate PK/TK parameters. Minimizing the volume of blood collection can reduce pain and distress in animals and improve the welfare (refinement) of rodents and non-rodents. It can also reduce or eliminate the number of required animals in a TK satellite group when used in rodent studies (reduction) whereby TK assessment is conducted in main study group animals. The benefit is particularly notable for mice, since a significant number of these animals are generally used in satellite groups, in TK studies using conventional sample volumes. For early PK evaluation, micro-sampling method allows serial design studies in mice and rats and the possibility to have a full PK profile on the same animal, thus reducing inter-individual variability assessment. This not only reduces the number of animals needed, this approach also improves the statistical power of the study performed. For more detail see: ICH Consensus Guideline Q&A released for Consultation on 19 May 2016, at Step 2b of the ICH Process.

Microsampling for Discovery Pharmacokinetic (PK) Studies in Mice

Capillary micro-sampling (CMS) of 8 µL of blood provides a methodology that can be utilized for serial sampling in drug discovery mouse PK studies. The CMS approach was used to investigate time-dependent pharmacokinetics by dosing mice daily for 5 days with the test compound. On day 1 of dosing nine time points were collected from each mouse and then repeated on day 5 of dosing from the same animals. Obtaining full pharmacokinetic profiles on two different days from the same animals was made possible by this CMS sampling approach. This example highlights the advantage of using 8 µL CMS for reducing the number of mice needed for discovery PK studies, while refining the sampling method in accordance with the standards for blood collection. In this example, a total of four mice were needed for the dosing and PK sampling part of the study. Significantly more animals would have been needed if other methods for obtaining the PK samples had been used. For example, if non-serial blood sampling had been used, a total of 76 mice would have been needed for this study. If a composite (sparse) sampling strategy (where one takes about 100 µL of blood per sample and up to three samples / mouse) had been used, a total of at least 26 mice would have been needed for this study. We are continuing to use CMS sampling as a way to reduce animal numbers for both single and multiple dose discovery PK studies[6].

Microsampling in Minipigs

A team has refined the technique of serial blood sampling in Gottingen minipigs utilizing the tail vein. The conventional method of blood sampling for swine is use of the jugular vein, requiring animals be placed in a supine position and restrained, which can be stressful for both the animals as well as the personnel. Defensive movements throughout this form of restraint can cause hematomas and other possible injury to the animal. The alternative method of microsampling from the tail vein is easily accessible and requires minimal restraint, with a combination of positive reinforcement and a local anesthetic at the puncture site. This refined method decreases the time it takes to collect a sample and minimizes stress to the animal and personnel.

[6] *Capillary microsampling of whole blood for mouse PK studies: an easy route to serial blood sampling - https://doi.org/10.4155/bio.14.275*

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Supporting R&D for better science and more welfare – EU initiatives supported or funded by industry

EPAA – European Partnership Alternative 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-sectorial and multidisciplinary partnership between five European Commission services and eight 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.

- EFPIA and its members play important roles on the EPAA Project Platform focusing their work on skin sensitisation, vaccines and other biologicals as examples.
- EFPIA was involved in the published scientific paper "One science-driven approach for regulatory implementation of alternatives: a mutli-sector perspective" submitted to the journal of Regulatory Toxicology and Pharmacology (RTP)[7] and the published EPAA manuscript 'EPAA Partners Forum - Finding synergies for 3Rs – Toxicokinetics and read-across' which is published in Regulatory Toxicology and Pharmacology[8].
- 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. This led to the publication of a workshop report in the Journal Biologicals[9].
  - Since, the animal tests have been deleted from 49 European Pharmacopoeia monographs in 2018.
  - There are two OIE Terrestrial Manual chapters which state that one of the tests may be waived, and national legislation as appropriate.
- New focus in the EPAA is on pyrogenicity, looking at the opportunity for the EPAA to facilitate the implementation of in vitro alternatives to the Rabbit Pyrogen Test and discussions continue around a new focus on optimal duration of non-clinical studies to assess the safety of monoclonal antibodies.

[7] https://www.sciencedirect.com/science/article/pii/S0273230018302137
[8] https://www.sciencedirect.com/science/article/pii/S0273230018302186
[9] https://www.sciencedirect.com/science/article/pii/S1045105617300647

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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.) are contributing enormously to animal welfare:

- IMI helps to drive animal welfare and 3Rs – Presently numerous IMI consortia impact on the use of animals and IMI projects contribute to the 3Rs.
- IMI successes have addressed and brought results in 3Rs or new research paradigms or more predictive testing tools that do not require – or require fewer – animals
- IMI projects are contributing to a better understanding of the challenges faced in using animal models and are impacting on the use of laboratory animals in research and development.

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In 2018, IMI celebrated 10 years of success in radical collaboration in 100 projects. Specifically, IMI successes have brought results in 3Rs, new research paradigms and more predictive testing tools that do not require – or require fewer – animals and to date has resulted in 34 in vitro models and tools; 70 robust animal models; 316 in silico models; 12 novel imaging techniques; 95 novel robust assays and 1500 stem cell lines[10].

In 2018, to highlight the benefits to the 3Rs, in collaboration with IMI, Sarah Wolfensohn published an extensive review of the contributions of cross-discipline collaborative European IMI/EFPIA research projects to the development of Replacement, Reduction and Refinement strategies[11]. The review outlined whether, and if so, how, scientific research projects organised and managed within collaborative consortia across academia and industry are contributing to the 3Rs and how projects funded by the IMI, are contributing to a better understanding of the challenges faced in using animal models. It identified the value and spirit of collaboration and sharing of information can help address human health challenges and in so doing reduce the dependence on animal use in areas where it has normally been viewed as necessary and in turn, lead to an overall reduction in the use of laboratory animals.

We are proud to be part of the LITMUS IMI project, as we believe such a broad scientific collaboration is the way forward in securing better and safer access to diagnostics and medicines – in this case by developing a more reliable animal model reflecting the human development of non-alcoholic fatty liver disease.

Lars Friis Mikkelsen, CEO, Consortium member of LITMUS IMI project, Ellegaard Göttingen Minipigs

[10] *https://www.imi.europa.eu/sites/default/files/news/Brochure_ResultsImpact.pdf*
[11] *Wolfensohn, May 2018, Alternatives to laboratory animals: ATLA 46(2):91-102*

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Industry commitment to improved experimental design

Improvements to experimental design to reduce the number of animals used

Biological experiments using animals are of great value in helping scientists to understand disease and evaluate new medicines. However, the statistician supporting the design and analysis of these studies has to balance the inherent inter-animal variability, and therefore the need to use sufficient animals to produce robust and reproducible data to give scientists confidence in the results, with the desire to minimise the number of animals used. Variability may be due to any number of factors, and is influenced by both the operator and the environment. The statistician's approach is to exploit this variation and strengthen the study design, allowing the scientist to better control the biological variability by removing or reducing the influence of these factors. Complex experimental designs are sometimes mistakenly associated with increased animal numbers. In fact, exploring the full potential of alternative designs can help reduce sample sizes.

The pharmaceutical industry strives to go beyond what is legally required and works to implement 3Rs to ensure high standards of animal welfare and high-quality science to ultimately improve the lives of the people and animals that stand to benefit from the research.

There are well reported issues with the reproducibility of animal studies with the experimental design and the reporting of studies being highlighted as major contributing factors. If an animal study is not designed to answer the scientific research questions being asked and publications do not contain the appropriate level of detail, then the animals and resources used to conduct that study are potentially wasted. Effective experimental design and statistical analysis are critical means of minimising the use of animals and achieving study outcomes.

Every effort should be made to improve research studies, using the best available guidelines to ensure that all details are recorded and results reported correctly, which will improve the quality of science and maximize the uptake of 3Rs opportunities..

EFPIA companies support the use of the following guidelines and resources when considering study design and reporting/publication of in vivo research:

- **The Experimental Design Assistant (EDA)**. A free online tool designed to guide researchers through the design of their experiments, helping to ensure that they use the minimum number of animals consistent with their scientific objectives, methods to reduce subjective bias, and appropriate statistical analysis. Details available from www.nc3rs.org.uk/experimental-design-assistant-eda
- **Planning Research and Experimental Procedures on Animals: Recommendations for Excellence (PREPARE)** is a newly published aide memoire to remind scientists of all the topics which may be relevant when planning experiments. Details are available from https://norecopa.no/prepare
- **Animal Research**: Reporting of In Vivo Experiments (ARRIVE), which are widely accepted good practice guidelines to improve the quality and reliability of publications from research involving animals. Details are available from www.nc3rs.org.uk/arrive-guidelines

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The pharmaceutical industry works to implement 3Rs to ensure high standards of animal welfare and high-quality science to ultimately improve the lives of the people and animals that stand to benefit from the research. If an animal study is not designed to answer the scientific research questions being asked and then the animals and resources used to conduct that study are potentially wasted. Effective experimental design and statistical analysis are critical means of minimising the use of animals and achieving study outcomes. Every effort should be made to improve research studies, using the best available guidelines to ensure that all details are recorded and results reported correctly, which will improve the quality of science and maximize the uptake of 3Rs opportunities.

EFPIA members acknowledge that improvements are required across the industry and organised a user workshop in 2019 on experimental design in Industry. It brought together research scientists, preclinical biostatisticians, members of ethics committees and animal welfare bodies. The workshop helped increase awareness across industry of the concept and importance of effective experimental design and identified what is being done while identifying the key factors, challenges and gaps. Recommendations developed focused on what would motivate companies to embrace a more formalised system to review design of experiments, which of the good practices and challenges identified are key to developing better experimental design in companies. The recommendations coming from the workshop will be implemented across the industry.

Trends towards a reduction in the use of recovery animals during drug development for human safety assessment

It is a regulatory requirement to assess recovery of animals during drug development, to determine whether effects observed persist or reverse once treatment ends. However, flexibility exists as to how, where, or even if, recovery animals are included. In 2014, a data-sharing initiative identified opportunities to reduce recovery animal use by inclusion later in drug development, and in fewer studies or dose groups. As part of the UK National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) / Association of the British Pharmaceutical Industry (ABPI) initiative to review the use of two species in regulatory toxicology packages, the international expert group (representing 37 pharmaceutical / biotechnology companies, contract research organisations and regulatory bodies) has analysed the dataset to examine current approaches to the inclusion of recovery animal groups. There are some positive indications that fewer recovery animals are being included, with a higher proportion of compounds that did not include recovery in any first-in-human toxicology study in 2017 compared to the earlier dataset. Likewise, when recovery was included, reduced study designs used fewer animals via fewer dose groups. Further examples of compound-specific cases for minimal approaches were also noted, along with a decrease in the inclusion of recovery animals for monoclonal antibodies[12].

The validation of biomarkers to avoid invasive or terminal examinations

The diverse human pathology and disease progression of non-alcoholic steatohepatitis (NASH), a liver disease, challenges scientists to identify suitable pharmacological approaches to mimic the disease characteristics. Although rodent models were established, it was necessary to use designated groups of animals to characterize the state of the disease, and to use additional small cohorts of animals to document disease progression and efficiency

[12] *https://www.nc3rs.org.uk/reducing-use-recovery-animals and Sewell, F et al. (2014) Recommendations from a global cross-company data sharing initiative on the incorporation of recovery phase animals in safety assessment studies to support first-in-human clinical trials. Regulatory Toxicology and Pharmacology 70:413-429. doi: 10.1016/j.yrtph.2014.07.018*

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of the test compound. To spare these animal cohorts, a set of biomarkers, measurable in plasma to avoid any invasive or terminal examinations were validated. Consequently, the level of protein was correlated disease severity. These biomarkers allow individual characterisation of each animal enabling a randomization of experimental treatment groups. This approach also allows the definition of the best window of effectiveness and the direct monitoring of treatment success, in contrast to being limited to an endpoint analysis and killing representative animals along the study. Establishing this minimally invasive analysis regime to document disease burden and treatment efficacy throughout a study has led to a reduction in animal use and using a minimal number of animals.

An international collaborative project to review the use of two species in regulatory toxicology packages

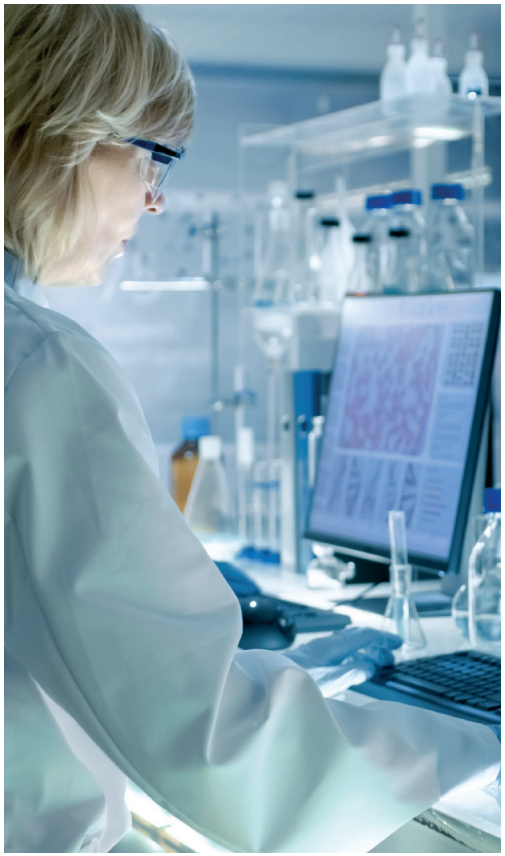
The collaboration of over 13 years between a pharmaceutical association and the NC3Rs which includes an international working group representing 37 pharmaceutical / biotechnology companies, CROs, consultants, academia and regulatory bodies which are exploring opportunities when data from a single animal species would be sufficient for progression without compromising human safety leading to a reduction in animal use. The background and plans for the project are outlined in a recent publication (Prior et al 2018). Data have been shared for a range of molecule types across different therapy areas and initial work has investigated the potential for one species to be used for long-term toxicity studies supporting Phase II preclinical trials. This is currently permitted for biological molecules if toxicity profiles are 'similar' in two species in short term studies. By identifying the incidence and types of molecules with similar target organ toxicities identified in two species within short term studies, it may be possible to encourage further adoption of this principle, as well as widening it for different molecule types or therapy area[13] [14] [15].

Combination of two experiments in one as an example of reduction

Passive cutaneous anaphylaxis (PCA) is an animal model used to test for inflammatory reactions to the skin, for in the example in testing reactions to allergies, while the passive respiratory anaphylaxis (PRA) model is used to test respiratory reactions. In the PCA, inflammation and swelling were tested in the ear of animals, while in the passive respiratory anaphylaxis model was tested in the lung of animals. Often both studies were performed with the same compound in two different experiments. By combining both studies into one by sampling the lung and ear from the same animal, half the number of animals are used leading to a reduction in the number of animals required.

Significant reduction in animal usage for regulatory respiratory safety assessment by a change in study design

A collaboration with a contract research organization to fundamentally re-design regulatory studies resulted in reduced animal numbers yet maintained quality data. Evidence of the change in statistical planning was provided that made the new design robust and provided a clear demonstration that even established methods can be improved, resulting in modest, but important changes. The collaboration means that the design is shared across industry through the contract research laboratory, ensuring wider impact for reducing animals.



[13] https://www.nc3rs.org.uk/review-use-second-species-regulatory-studies , Prior H et al. (2018).
[14] Reviewing the Utility of Two Species in General Toxicology Related to Drug Development. International Journal of Toxicology 37(2): 121-124. doi:10.1177/1091581818760564
[15] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S6_R1/Step4/S6_R1_Guideline.pdf

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Prediction of blood-brain-barrier penetration by combining physicochemical and in vitro parameters

Blood-brain-barrier penetration of a drug candidate is generally determined in many projects by in vivo experiments. This research program can however be usefully accompanied by in vitro systems or the study of physico-chemical properties. In vitro data show penetration through in vitro cellular blood-brain-barrier models or correlate Efflux in vitro to Efflux in vivo, whereas physico-chemical data are used to guide optimization of chemistry. In many cases the endpoint of simple approaches is not the intended in vivo brain to plasma ratio of the compounds of interest. Therefore, a multi-dimensional integration of in vitro mechanistic Efflux data using a cell line was developed, and calculated physico-chemical descriptors into a computer generated in silico regression model. With this complex modelling, it was possible to project multiple input parameters on in vivo brain to plasma ratio as the endpoint. The model has been used in different projects to drive optimization of small chemical molecules and decreased the reliance on animal use.

Tissue Slice Culture: use of slices of tumours grown in dishes to replace animals

One team has refined culturing slices of tumours grown in dishes to provide a more realistic model that functions more like a cancer in the body. This project has been used to successfully predict and validate targets, and help prioritise compound selection before carrying out animal experiments. Since these technologies are using human tissue and functionality, they are likely to provide a route to answering questions that animal experiments simply cannot address. Animal studies have ceased in some cases and there is potential for further replacement of animal studies using this method.

Evolving the in vivo mouse model for personalized medicine clinical trials, reducing the number of animals used

Patient-derived xenografts represent a frontier of personalized medicine, where tumors from patients are cultured in the laboratory. Traditionally patient's cells were grafted into many mice. However, because the correlation with human drug response is so much greater in this model compared with traditional laboratory grown cell lines, a more clinically relevant statistical method could be applied, that strengthens the data translation from animal to human and dramatically reduces the number of animals used. The team have developed an approach where cells from 1 patient are grafted to 1 mouse, and the overall population assessed much as a clinical trial would, embracing the variation to find the effective drug, and in doing so reduce the mouse numbers six fold. Moving towards replacement, one team have developed a robust in vitro alternative to generate stable cell lines to assess chemical sensitivity. This means that early screening of compounds that would traditionally be carried out in mice is now done in vitro. This has the potential to reduce mouse use in this area by ~90%.

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

Mechanisms used to promote the development of 3Rs through training

The pharmaceutical industry has invested in numerous mechanisms to improve animal welfare and understanding of the necessity for 3Rs implementation through various training initiatives:

- Staff training opportunities, both external and internal, are strongly supported across the company's employees in research and development who handle or care for animals, or develop and agree project proposals.
- Many companies organise veterinary consultations and one on one sessions with scientists.
- Numerous training campaigns have been initiated (e.g. on Bleeding techniques, severity assessment).
- Scientific seminars are organised to inform on methodologies and new technologies.
- Clearly defined terminology and common language is developed for 3Rs-relevant categories and respective definitions for the following: non-animal models, animal models, animal care, animal procedures. For each category, an implementation plan to collect, collate and communicate 3Rs-relevant advances was developed to better inform users.
- Indicators of 'Success' have been established to identify positive change through surveys, training completion, increased discussion and participation in activities.
- Companies have taken on the initiatives to host Internal and external courses by subject matter experts (e.g. handling, training and working with specific species or techniques).

Highly trained staff beyond the minimum requirement

Many pharmaceutical companies employ veterinarians, veterinary technicians, operations staff and animal care technicians whose qualifications go well beyond the minimum level required and have extensive additional credentials in order to provide the best care to the animals.

For global companies, many of the veterinarians are board certified through the American College of Laboratory Animal Medicine (ACLAM), have completed advanced degrees in addition to their veterinary degrees, and actively participate in annual continuing education. Veterinary technicians often hold varying levels of certification, and may also be certified or licensed veterinary technicians, hold advanced degrees or certifications and participate in continuing education. The majority of surgical and anesthesia technicians are certified through the Academy of Surgical Research as Surgical Research Scientists and/or Surgical Research Anesthetists. Operations staff and animal care technicians may hold advanced degrees, certification with the American Association of Laboratory Animal Science (ALAT, LAT, LATG, CMAR) and participate in continuing education.

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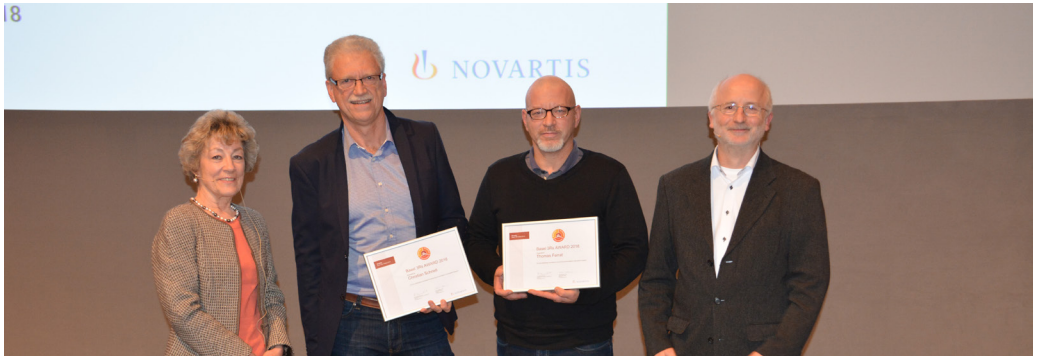
Dissemination beyond own department and own establishment drives improvement in welfare and general quality of science

Sharing best practice and presenting novel solutions to benefit a pro-active approach to animal welfare

There are several ways and initiatives whereby the pharmaceutical industry contributes to sharing best practices[16 17 18 19]:

- Internal 3R award: Many companies promote 3R implementation through annual 3R Awards. The awards are in recognition of teams or individuals and their projects that have contributed to bringing the commitment to the 3Rs principles into action. Scientists are interested in promoting their 3R achievements and over the years companies have seen an increase in the number of applicants and level of work. Often the awards are presented at events organised to promote the work of the institutions to colleagues, external partners, CROs, regulators and NGOs. These events stimulate an active discussion on the topic and highlight activities. Often external speakers are invited and participants get the opportunity to meet and discuss animal welfare with key members of ethical and veterinary organizations.
- Many countries have a national 3Rs centre which provides a forum for collaboration, discussion, exchange and dissemination of information on the 3Rs and initiates research projects and recommends allocation of resources within the area.



The pharmaceutical industry is a frequent contributor, either financially and/or scientifically. Likewise the pharmaceutical industry is participating in and supporting national knowledge sharing platforms or 3R competence centres (such as CALAR, NC3Rs, Danish 3Rs centre and Norecopa). For example, the NC3Rs is leading a data crowdsourcing project for animal technicians to collect data on the prevalence and potential triggers of cage aggression in group-housed male mice. By contributing to the pilot study that shaped the final survey, a global project within one company is sharing data on male mouse aggression, thus providing for a better understanding of the triggers for, and approaches to, reducing this aggression[20].

[16] *https://www.novonordisk.com/research-and-development/bioethics/animal-ethics/responsible-use-of-animals.html*
[17] *https://www.nc3rs.org.uk/*
[18] *https://en.3rcenter.dk/*
[19] *https://norecopa.no/*
[20] *https://www.nc3rs.org.uk/laboratory-mouse-aggression-study*

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Leading by Example | Sharing | Enforcing

Open Communications | Dialogue | Reporting

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◊ National networks for Animal Welfare Bodies also play an important role in promoting and sharing on 3Rs and culture of care.
◊ Strengthening the strategic approach to work with the 3Rs has been achieved for example by forming dedicated 3Rs departments or 3Rs centres within individual organisations.
◊ By creating job descriptions for veterinarians that balance both the operational and strategical activities, this ensures that future initiatives are rooted in realistic everyday situations from the animal house.
◊ Animal welfare goals make good sense for employees directly involved in animal studies but they also make good sense at senior management level. The deployment of balanced scorecard goals at Corporate Vice President level ensures that attention and focus on animal welfare activities are effectively cascaded to the lower organisational levels. This ensures the involvement of employees directly involved in animal studies, such as animal care technicians and veterinarians, in progressing animal welfare on the practical level, and is crucial for successful achievements.
◊ Organising workshops and seminars where the participants can Define, Discover, Dream, Design and Deliver how their future work with a pro-active animal welfare mind-set can be accomplished are useful ways to generate high impact ideas.

Leading the way in animal welfare globally

A forum on animal welfare and non-clinical quality was held in Shanghai. The aim of this event was to engage in open discussions with leading Chinese contract research organizations (CROs) and key opinion leaders on the current status of animal welfare and quality systems in China and to explore future opportunities for improvement in their operation. At this First China Forum the Charter on Non-Clinical Quality & Animal Welfare where signatories committed to foster awareness and endeavour to maintain the highest ethical and scientific standards in animal experimentation and non-clinical quality in China.

Stimulating natural behaviour of minipigs in a laboratory environment

Companies have been investing in improving the housing and care to minipigs with the aim to improve their welfare. Straw is an excellent enrichment material for minipigs as it prompts natural behaviours such as rooting, foraging and exploration. Typically, rooting material is placed on the floor, but by combining this practice with hayracks and plastic balls with large holes, all filled with straw, the minipigs can be occupied for a longer duration. Multiple animals can access the racks and balls at the same time, and lower ranking animals benefit from the racks and balls when the straw is spread gradually on the floor. Hay given to sows by the hayrack a few days before the expected farrowing date has furthermore shown to increase nest building behaviour. By giving animals the opportunity to engage in natural behaviours and with a degree of control, their welfare is significantly improved.

Transgenic mouse breeding and sentinel programme

Following review of the sentinel screening programme, which is used to monitor the background health status of animals held in research facilities, the use of surplus animals generated during breeding (e.g. genotypes not used for study or wildtype animals) for sentinels has been adopted and now results

As funders, working as a community across Europe, can help promote high quality science, which the 3Rs are integral to. Sharing good practice on issues like grant making, and pooling our resources improves animal welfare and scientific outputs.

Sam Alvis, Policy Officer, Wellcome Trust

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in no animals being purchased from vendors for the purpose of sentinel health monitoring in the transgenic breeding area. Using a robust process of animal monitoring, animals are preselected from stock that are at the end of their scientific use – these animals are culled prior to tissues being harvested for health monitoring. Animals are not kept beyond their scientific use for this purpose. This process saves the need to receive approximately 200 mice from vendors per year solely for the purpose of health monitoring of the barrier facility.

Using Novel Home Cage Recording to Investigate Rat Acclimatisation

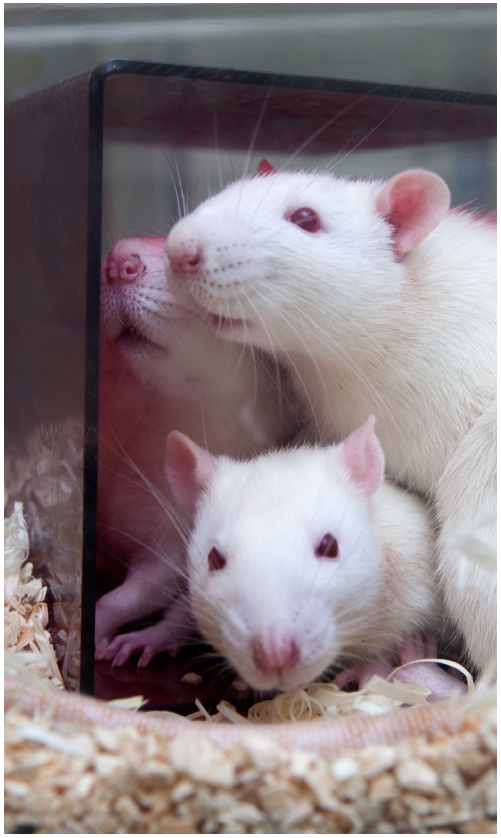
Using the 'Rodent Big Brother' video tracking system, (an automated non-surgical system, which can be used in rats and mice, to measure activity and temperature over a minimum of a 24 hour period)[21], the team studied rats as they acclimatised to a new environment and established the time needed for them to settle. Observations related to feeding, resting, nesting and play led to a number of recommendations to minimise weight loss and stress throughout the transport process. One recommendation was the use of timed lighting units in the transport containers to maintain circadian rhythm and feeding patterns. Five days appeared to be the minimum acceptable time for animals to be acclimatised sufficiently for study inclusion. Although the animals had not fully gained pre-shipping weight, their behavioural parameters had stabilised and they were actively exploring their environment.

Rat Playtime

Rats that were used in telemetry studies and housed in the facility for up to 9 months (long term, reuse animals) were provided an area in the form of a pen to exercise, play and socialize outside of their home cage environment. The pen was designed with care to allow and encourage the animals to carry out natural behaviours whilst ensuring they felt secure. The rats were put into the "play" area 1-3 times weekly for between 20 and 40 minutes in groups of up to 10 animals. In the pen, rats were constantly busy, occasionally stopping to groom or a quick pause to look around before moving off again. Rats in the pen explored, chewed, groomed, played with each other, climbed, dug, paddled in the water tray and foraged through various substrates provided. Both in the pen and the home cage as well as during procedures there was a very apparent increase in the confidence and friendliness of the rats. They became more used to and amenable to being handled and were much more likely to voluntarily interact with people. There has now been a workshop for the Institute of Animal Technology on this topic[22].

Continuous rodent monitoring: capturing critical observations

Continuous rodent monitoring technologies are being evaluated that are enabling 3Rs impact by innovatively determining optimal housing conditions, and improving study reproducibility by collection of more relevant data. These technologies enable 24/7 measurement of behaviour and the detection of subtleties in behaviour that often go unnoticed by standard observations. Researchers may miss important health signs by observing the animals during the day and not during the rodents' natural wakefulness overnight. Furthermore, presence of researchers may inadvertently create behavioural and physiological variations, potentially altering study results (often known as the "white coat" effect). Industry is sharing common strategic interests related to continuous monitoring in order to identify



[21] *https://crackit.org.uk/challenge-3-rodent-big-brother*
[22] *https://www.nc3rs.org.uk/iat-congress-2017-workshop-summary-playtime-rats*

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meaningful endpoints and disease specific metrics which would increase knowledge gained from animal studies. When integrated in meaningful ways, such technologies could also reduce animal use, reduce pain and distress and decrease probability of loss of important data points by enabling earlier endpoint detection.

A Novel Pairing Strategy for Aged Male Cynomolgus Macaques

Cynomolgus male macaques have historically been single housed due to the concern of aggression between cage mates, territorial disputes and hierarchical differences. There were several female macaques that were reaching their retirement age that were no longer able to breed. This team identified an opportunity and worked diligently over the course of nearly a year to reduce aggression in the males by successfully pairing 9 females with the aged males. During the course of this time, stress was greatly reduced for both the males and females through different enrichment opportunities and a well-developed practice to pair the aged animals. This is a significant refinement due to reducing the stress that was historically observed in the males and the team was successfully able to accomplish socially housing this species.

Managing Ulcerative Dermatitis in mice

A team has integrated cold laser therapy in the treatment of ulcerative dermatitis (UD), which is a medical condition that severely impacts the well-being of mice with a certain genetic background and negatively affects study data. Cold laser therapy has been known to be effective as an adjunct treatment for inflammatory conditions in multiple species, particularly skin lesions and wound healing. This process we understand is the first time to attempt treatment of UD using the cold laser. When combined with the standard therapies (nail trim, moisture barrier, etc.), laser therapy produced a greater degree of healing, or at least significantly slowed/halted wound progression. Through the new application of an existing technology, innovative use of the cold laser, and attention to the care and welfare of mice, the team involved has been able to reduce the numbers of animals used for studies by reducing the number of extra/replacement animals required, and to refine animal use by providing pain relief and improved wound healing.

Data donation to enhance the effectiveness of database-dependent property prediction tools

The research based pharmaceutical companies represented in EFPIA are in possession of physicochemical, toxicological and ecotoxicological data on chemical substances which is no longer of economic value.
The publication of this data is intended to extend the variety of publicly available high-quality hazard data on chemicals to, among other things, enhance the effectiveness of database-dependent property prediction tools. Through this, there is an opportunity to improve the hazard characterization of structural analogues, optimize their safe use and can potentially lead to a reduction in animal testing. Mechanisms for the delivery and secure dissemination of the data have already been developed under the REACH regulation and will be used for data donation. As a voluntary non-profit industry initiative, the project is run under the patronage of EFPIA and led through Roche. ECHA is an active partner in this initiative.

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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

Kirsty Reid, Director Science Policy, EFPIA blog[23]

EU legislation and science further the protection of laboratory animals

EFPIA's goals are to accelerate the development of and access to integrated healthcare solutions for unmet medical needs in the interests of patients and society at large. This often requires a paradigm shift in research, regulatory and medical practice. The paradigm change also encompasses furthering the welfare of animals used in research and testing, which in turn contributes to high quality science. Having recently joined EFPIA, I have seen already that these goals of accelerating innovation and protecting laboratory animals are interconnected and reflected in EFPIA policies and scientific activities.

Part of this paradigm shift is grounded in the 3Rs Principles. The Rs stand for: reduction (using fewer animals); refinement (modifying procedures or husbandry and care practices so as to minimise the suffering of animals); and replacement, whereby methods, strategies or approaches that do not use live animals are employed). Established in 1959 by William Russell and Rex Burch in their book "The Principles of Humane Experimental Technique", the Principles remain relevant and continue to drive progress.

Europe is known as a leader in the 3Rs and the welfare of laboratory animals. Directive 2010/63/EU on the protection of animals used for scientific purposes, which replaced the legislation of 1986, integrates fully these principles in all stages of research processes. Thanks to the Directive (and trust me it's happening), questions, tools and regulations are evolving, driven by scientific progress and collaboration. The legislation challenges scientists to change their perspectives and way of thinking, to drive for change.

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The inclusion of the 3Rs is clearly extensive and very impressive, however, nothing is effective if the Directive is not implemented and enforced fully. A mere two years since the deadline for national transposition passed, it is at this point too early to measure the impact of all its provisions. A preliminary Commission report is expected in November this year and a full evaluation of the legislation has been promised for 2019. In the meantime, our energy should go into appropriate and effective implementation.

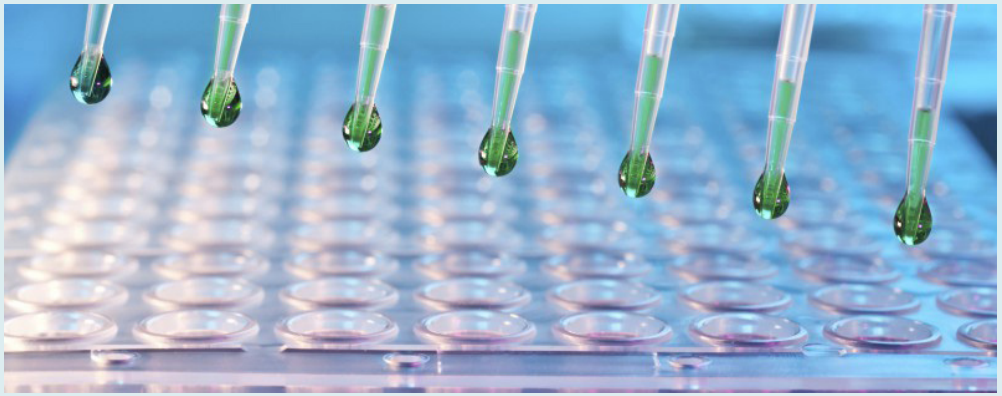
How?

- Certainly through engagement, dialogue, transparency, and the sharing of good practices. EFPIA is already involved in or champions several related initiatives.
- Then there is the use of guidance. Following the adoption of the Directive, guidance was produced on specific provisions of the Directive, and endorsed by all the Member States. The guidance is readily-available on the Commission website, in all the major languages of the EU. It is our joint responsibility to make sure that all those involved in planning and running research know about it and apply it.
- Finally, by challenging continually research paradigms in order to improve and accelerate translation from discovery to clinical research. The EU invests extensively – sometimes jointly with the industry, as is the case in the Innovative Medicines Initiative (IMI).

Pharmaceutical companies and their research partners take measures proactively to minimise the impact on animals, in cases where animals remain important for specific purposes in medical research and testing.

This stands out in our recent report on "Putting animal welfare principles and 3Rs into action". The health and welfare of animals remain important, as do the personnel involved and the pharmaceutical industry engage strongly in the Culture of Care. They also contribute by providing resources and workmanship to the Innovative Medicines Initiative which has injected millions of euros into successful projects, many of which offer direct and indirect benefits for the 3Rs, leading to refined animal models, computer-modelling, non-invasive imaging, safety biomarkers, stem cells and real world evidence, which help to generate a better understanding of numerous chronic diseases as well as to produce more effective medicines.

But it goes still further. Medical research continues apace. It needs to, as many health challenges still remain unmet. Animal studies continue to play an invaluable role in meeting these challenges and they remain a legal requirement. However, the change in mindset is ongoing and science continues to evolve. In fact, scientific advances are leading to fewer tests and experiments on animals, as well as to new ways of reducing the impact on animals. This is why dialogue and transparency about the use of animals for medical research and developments in science must remain at the forefront of debate and scrutiny for all those involved.



[23] *https://www.efpia.eu/news-events/the-efpia-view/blog-articles/31082017-eu-legislation-and-science-further-the-protection-of-laboratory-animals/*

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Open Communications | Dialogue | Reporting

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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

EFPIA and its members

EFPIA and its members remain committed to full and correct implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes and enhance the cultures of care, and challenge and openness for research involving animals. The Directive is vital to ensure that necessary research involving animals can continue whilst requiring enhanced animal welfare standards.
On the 8th November the Commission adopted their report on the impact of Directive 2010/63/EU. The published report is in response to the Directive's Article 58 that requires a review of the Directive by 10 November 2017. The report concludes that the timing of the review of the Directive's implementation was premature therefore no amendments and no phasing-out timetable for the use of non-human primates were proposed, however a number of recommendations were put forward.
EFPIA supported the conclusions of the report and has undergone a full analysis of the recommendations to align industry commitments. To achieve the objectives laid down in Directive 2010/63 and implement the recommendations, EFPIA calls upon all stakeholders to join forces and

- Facilitate access to guidance and information for those responsible for research programmes;
- Support and provide resources to EU and national initiatives that enable the development and validation of new research paradigms and the integration of new sciences or technologies into research and regulatory practice;
- Support the exchange of good practice;
- Promote continued open dialogue about the realities of current scientific research and future prospects of science and technology.

Activities of EFPIA

- EFPIA's Research and Animal Welfare group (RAW): works to enhance connections between 3Rs, animal welfare and R&D. It is essential the group is proactively engaged in policy debates on animal use and welfare to ensure license to operate for members. The work of the group ensures there is an understanding by policy makers of the opportunities and limitations of alternative approaches in life sciences. Through the RAW group, industry remains proactively engaged in 3Rs and animal welfare and are recognised to conduct responsible research and innovation.
- EFPIA's 3R focus group: proactively promotes 3Rs and shares experiences and best practices between companies to learn from each other and implement change.
- EFPIA user community workshops: experts from industry, academia, research funding organisations and regulators to exchange good practice including enhancing the implementation of welfare and 3R provisions of the Directive; Culture of Care and in 2019 a workshop on improving experimental design in industry.
- Culture of Care: industry have worked on defining the concept of Culture of Care and how it is understood and applied across Europe. A Framework has been developed with the aim to help organisations identify gaps and areas within their establishments

Our work to develop, and promote, practical ways of reducing the impact of science on animals is underpinned by constructive liaison with those involved in the care, use and regulation of animals in research.

Barney Reed, Senior Scientific Manager, Research Animals Department, RSPCA

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to further improve on which will help in promoting a positive Culture of Care.

◊ Newsletter: EFPIA informs members and other collaborators through a monthly newsletter of the recent relevant news on Directive 2010/63, animal use and welfare

EFPIA collaborating with stakeholders:

◊ Learning from others: EFPIA invite external stakeholders to share tools and educate industry. Recent external experts were NC3Rs (experimental design), ETPLAS, and AniMatch.

◊ EFPIA activities linked to EU institutions: EFPIA remains a leading stakeholder with EU regulators in Commission services of DG environment, DG Grow, DG RTD and JRC EU Science Hub, specifically engaging with EURL ECVAM (EU reference laboratory for alternatives to animals). We provide support work at level of NCP meetings. In 2018, EFPIA provided expert participation in Commission working groups including an expert Working group on Genetically altered animals and in a workshop to review and develop templates for Non-technical Project Summaries and the results of Retrospective Assessment. EFPIA promote the EU endorsed guidance documents for implementation of Directive 2010/63. In addition, EFPIA Works with the JRC through participation as a stakeholder on their ESTAF (Eurl ECVAM stakeholder forum) and participation in the JRC initiative, BEAMS (Bridging across methods in biosciences). EFPIA members respond with expert advice and information to regular calls for information on alternative methods in the areas of biomedical research.

◊ 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 are formed with diverse stakeholders focusing on areas to bring about positive change.

◊ 11th World Congress on alternatives and animals in the life sciences: EFPIA sits on the Local organizing Committee and International Scientific Committee of the 11th World Congress on Alternatives and Animal Use in the Life Sciences that will take place on the 23-27 August 2020 in The Netherlands. The focus will be on 3Rs in transition from development to application

◊ External communication on 3Rs: EFPIA has been an invited speaker to conferences and symposiums of our members (Roche – Global 3Rs symposium – November 2018), other sectors (Cosmetics Europe – Science Symposium – 2017), user community (Infrafrontiers – Nov 2017; SPCAL – June 2018).

◊ FEAM Forum: EFPIA is a member of the Federation of European Academies of Medicine (FEAM) European Biomedical Policy Forum. In March 2018, they held a round table discussion on the use of animals in scientific research and the implementation of Directive 2010/63/EU which was jointly coordinated and moderated by EFPIA. A report summarising the key points can be accessed here link.

◊ Life Science Community: EFPIA Jointly coordinated and signed a Call for Action by the life science community which called upon the scientific community, including research funders, to enhance implementation of Directive 2010/63, and support the culture of care, challenge and openness for research involving animals; and called upon the European Commission

Discussions, debates and collaborative activities among stakeholders is a key to a deeper understanding of the polarity and diverseness of issues, the tool for building trust and willingness to seek mutual ground, and the basis for policies that everyone can relate to and be committed to.

Susanna Louhimies, Policy Co-ordinator, European Commission, DG Environment Unit Sustainable Chemicals

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and Member States to provide the necessary resources to fully implement Directive 2010/63/EU, ensuring that Europe remains a world leader in, responsible and innovative biomedical research.

◊ EARA working group on non-technical summaries: EFPIA was a member of a non-technical Summaries working group coordinated by EARA and chaired by Javier Guillén, AAALAC International. Members included AAALAC International, EARA, EFPIA, FELASA, FENS, LERU, RSPCA and University of Manchester. The group identified opportunities to improve the language, used in NTS, so that it is more understandable for the lay person/general public and its recommendations were fed directly into a Commission working group -examining the template used in non-technical project summaries.

Assessments within the pharma industry:

◊ Industry mapping on rehoming of animals: The EFPIA research and animal welfare group carried out a survey to determine the level of rehoming of laboratory animals within the EFPIA member companies. Conclusions from the survey indicated that the majority have rehoming policies in place, which differ between companies however they are seen as a value to the animals eligible for rehoming and play a valuable part of the 3Rs and Culture of Care efforts. There are opportunities to share and learn from each other to improve processes.

◊ Industry considerations to define metrics to assess the progress of 3Rs: The EFPIA research and animal welfare group carried out a survey to assess how industry measures progress and impact of 3Rs. This was a follow-up from what already took place in 2016 where they carried out a collaborative attempt to define how to measure investments in 3Rs and their impacts. The companies support the 3Rs principals and many of them either measure or support the importance of measuring 3Rs by measuring progress either yearly or more than once a year, externally or internally. Ultimately, it was recognized that a common set of principles to measure progress would be valuable and was acknowledged that numbers of animals used alone would not give accurate picture of 3Rs efforts. Assessing the impact of and communicating about 3Rs efforts/ investments requires a set of quantitative and qualitative KPIs. The attempt to

collaboratively define meaningful 3Rs metrics is an unprecedented effort, demonstrating EFPIA members' ongoing determination to further progress the enforcement of the 3Rs principles. Having common, harmonized, easy tools for KPIs on 3Rs in pharma industry (or more globally in animal research) would be very useful. It's for each company to decide whether and how they measure 3R implementation.

◊ Experimental design: The EFPIA research and animal welfare group carried out a survey with companies and identified that industry often lag behind on implementing a policy or strategy for good experimental design. Acknowledging the need for improvement, the RAW group invited the NC3Rs to share with them their various tools and organised a workshop to share practices, identify gaps and challenges to improve experimental design in companies.

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Incorporating Culture of Care Programmes

"Caring for Animals. Caring for People." is the embodiment of the mission of the pharmaceutical industry in Europe. Animals are to be treated with respect- Respect for their environment, respect for the needs that the scientists can provide for, and respect for the contributions they bring to medical research and drug development.

Assessing engineering standards like cage-size, the use of environmental enrichment, health monitoring etc. may be considered as generally straight forward, however, when it comes to assessing the way we think and behave in terms of animal welfare – our culture of care – it is less simple. Several pharmaceutical companies have developed different assessment tools, each providing one way to portray the individual company's culture of care. The pharmaceutical industry has initiated workshops in order to discuss 'what is culture of care' and to share learnings from the use of the different tools.

Company-wide programmes feature discussions on everything from how to talk about animal research to dealing with compassion fatigue; featuring the enrichment program, 3R's initiatives, participation in Biomedical Research Awareness Day and the animal rehoming programme. The care staff is kept engaged and motivated by involving them in activities that promote areas such as teamwork, mental health, inspiration and personal growth. Veterinary staff care is carefully considered by empowering them to bring pride to their work, address compassion fatigue, and raise moral.

EFPIA and its members have developed a framework to help companies identify gaps and areas within their establishments to further improve on, which will help in promoting a positive Culture of Care.

Culture of Care Network - An international network was established following the FELASA Congress in 2016 and now has an extensive global membership of experts from industry, academia and NGOs. The primary goal of the network is to share and publish examples of activities fostering a Culture of Care which make a difference in terms of improved animal welfare[24]. The discussions within the group aim to:

- Promote animal welfare and the 3Rs, and foster a 'Culture of Care' throughout the organizations;
- Stimulate active exchange between the companies and external experts on topics related to animal welfare and the 3Rs;
- Share highlights from each company's ongoing activities in the 3Rs, and promote the 3Rs Awards.

Collaborating though EFPIA helps us understand some of the main successes and challenges around animal research, laboratory animal welfare and how it is communicated to the public across many companies, states and regions. It ensures insight into what works well and what does not, supporting the community to resolve some of the key issues around the welfare of research animals.

Bella Williams, Head of Engagement, Understanding Animal Research

Auditing to improve animal welfare

Assessing the current state of animal welfare is essential to monitor the progress and efficiency of initiatives. Internal audits by independent auditors, sometimes including animal welfare NGO representatives, assures that internal standards are followed and that they meet corporate expectations. Likewise, monitoring external collaborators, such as CROs and/or academia, is essential to assure that corporate animal welfare standards are globally applied just as if they were conducted in-house.

[24] *https://norecopa.no/more-resources/culture-of-care*

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Open Communications | Dialogue | Reporting

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Global collaborations

Improving global standards

Some companies have established official corporate policies on various ethical areas, including animal ethics. To further support an effective and efficient operational performance of the policies they include an extensive governance set-up. For example, one company has set-up a Non-Human-Primate Focus Group that deals with NHP studies; one of their working tools is a document where justification for using NHPs must be documented. Additionally the Animal Welfare Body have a broad composition in terms of competencies, including a statistician whereby they review all external protocols and new in-vivo models and those models with a high degree of severity[25].

Driving the science and sensible regulation - promulgation of better practice by close participation with other organizations

A number of companies have members of their Veterinary Sciences departments actively participating in outside organizations to help drive the science and animal welfare at a high level. The veterinarians may volunteer on the Council on Research, AAALAC International, and volunteer at the state and local levels. The technical staff get involved as well serving on various committee at the local and national levels. Additionally, the technical staff routinely present annually at national meetings and instruct wet labs on current surgical models and advanced study support techniques. Operations staff also volunteer with similar organisations, serve on various committees at the local and national levels and give presentations at regional and national meetings. These activities use the refinement loop ensuring implementation, evaluation and dissemination of good practice.

A significant reduction in animal use and an example of reduction is the sharing of tissues and organs from euthanized animals from studies or projects that were completed or animals that were no longer needed. Such animals were put on Tierbörse (Animal exchange) for other departments and technicians to order.

Today's over-reliance on animal tests and lack of adaptation to technical progress is recognised by all stakeholders. Collaboration is key to get the machinery of progress in safety sciences running faster.

Dr. Francois Busquet (PhD), Policy Coordinator, CAAT-Europe

Collaboration across the International Pharmaceutical Industry to co-evolve new housing methods

The majority of EFPIA companies are international and have several research sites around the world. It is important for them to ensure they globally implement high corporate standards for animal welfare, veterinary care, education and training. In the USA, facilities are AAALAC accredited and outsourced work abides to the same guidelines.

The Global Pharmacology Council is responsible for approving standard pharmacology models and technologies in order to achieve Global Standards. This body has issued internal guidelines and hosted a

[25] *https://www.novonordisk.com/rnd/inside-r-d/bioethics/ethics.html*

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Leading by Example | Sharing | Enforcing

Open Communications | Dialogue | Reporting

Leading by Example

'Pharmacology Day', providing an opportunity to co-evolve procedures such as new housing methods for animals in studies. For example, a metabolic cage has been developed for dogs allowing two dogs to be housed in the same cage, and a cage for non-human primates allowing them to be group-housed, instead of the traditional single housing in these studies. Habituation and training of larger animals, such as pigs, dogs, and NHPs, has long been an integrated part of the care and use programmes within the pharmaceutical industry, as required by European legislation, and recent activities have also looked at how this can be applied to rodents with programmes suitable for the animals, the procedures and length of the project. Some examples include:

- The considerate deployment of re-use of animals and use of control animals for tissue and organs instead of using naïve animals.
- The use of swivel-systems for continuous infusion studies allowing the individual animal a high degree of freedom of movement instead of a confined and fixed set-up.
- The use of telemetric devices which avoids repeated capture, fixation and sampling to measure scientific relevant parameters.

Many of these examples are implemented in close collaboration with CROs. At a particular facility every effort is made to provide the best environment possible for the animals. They have increased cage space for larger animals as well as the ability to spend time each week in a dedicated play cage. For the non-human primate caging space exceeds the legal guidelines. The rooms are enriched with adequate music, television, and novel enrichment items and their diets enriched daily with fresh fruit, and vegetables. In addition, a positive reinforcement-training program is implemented to facilitate voluntary participation by the animals in research activities and decrease stress in daily routine activities. The dogs all are housed in runs and are able to spend time in a play area in addition to their daily interaction with care staff.

Collaboration to facilitate the distribution of genetically modified mouse models

The sharing of genetically modified animal models on a collaborative basis assists with encouraging commitment to the 3Rs principles, and colonies are regularly shared between pharmaceutical companies and academic institutions. Examples of model sharing with academic institutions are the collaborations with transgenic mice overexpressing human CatA and on transgenic mice for Disc1 gene (human proteins whose altered structure may lead to the development of schizophrenia, clinical depression, bipolar disorder, and other psychiatric conditions). In another example, Six CRE-Luc strains have been made available through a commercial supplier's repository to the scientific community which offers a panel of luciferase reporter mice to assay G-protein-coupled receptors (GPCR) ligand binding and pathway activation in various tissues. GPCRs mediate many important physiological functions and are considered as one of the most successful therapeutic targets for a broad spectrum of diseases. The design and implementation of high-throughput GPCR assays that allow the cost-effective screening of large compound libraries to identify novel drug candidates are critical in early drug discovery[26] [27].

Innovation and Quality 3Rs leadership group

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium) has ten leadership groups, one being the 3Rs leadership group. The 3Rs leadership group has representatives from many biopharmaceutical companies and they work to advance 3Rs efforts across the drug development industry. Several working groups exist to promote the 3Rs not only in member companies but also within the animal programs at CRO partners. In 2018, several benchmarking surveys have been conducted to assess supportive care of animals on toxicology studies, rodent housing and enrichment strategies, as well as to assess potential pinworm effects on toxicology studies. There are ongoing efforts to promote the use of a tool to assess CRO/academic research programs for due diligence and to align animal welfare risk assessment practices to uphold high standards for animal care and use. EFPIA participates in their regular calls to exchange on EU initiatives.

[26] *Cardiovascular Research, Volume 110, Issue 3, 1 June 2016, Pages 371–380: https://doi.org/10.1093/cvr/cvw071*
[27] *Translational Psychiatry, Volume 8, Article number: 184, 2018: https://doi.org/10.1038/s41398-018-0228-1*

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Communication, transparency and dialogue with the public

Corporate statements - Communicate on the 3Rs through dedicated sections in publicly available Corporate Social Responsibility (CSR) reports.

Disseminating openness and transparency - Many companies have signed transparency agreements and their websites are important tools in making available information and explaining the use of animals in experiments and including videos of housing and animal handling.

Open laboratories - The general public, NGOs and policymakers are offered the opportunity to visit laboratories or take virtual tours to see the housing and learn about the uses of animals and multiple efforts of industry to enhance the 3Rs in daily practice.

Dialogue with NGOs - Companies proactively engage in constructive dialogue with NGOs. They inform each other and share experiences and expertise through various collaborations on practical and operational issues.

Openness across the industry on animal use and 3Rs

The use of animals in research and testing is a controversial subject and to support an open dialogue on the use of animals for scientific purposes a high degree of transparency and openness is important. The corporate web-sites are important tools to EFPIA members to making information about the use of animals easily accessible. Telling what we do and how we do it, is crucial to explain and justify why the use of live animals is still an indispensable requirement to develop drugs for serious diseases or chronic illness. One way this is done is by posting on company websites the actual numbers of the different species used and presenting pictures or videos of housing and even a virtual tour in an animal research laboratory .

Dialogue with academia

An event, bringing together a variety of academic and pharmaceutical organizations to share the impact of in vivo research across their organizations and to discuss ethical practice is a great example of openness in practice. In total 31 posters were displayed from five different establishments showcasing the in vivo science and its impact with the 3Rs initiatives. Participants were encouraged to take part in an ethical discussion about the use of animals in medical research. The event was extremely successful in raising the awareness of the in vivo research and enabled ideas to be shared between other in vivo establishments within the same geographical area. By actively supporting openness this event not only raised awareness of a potentially controversial and emotive area, it also built a culture of respect, recognition and learning which for staff working with animals is a key factor in a great place to work.

Openness and transparency: communication and dialogue with the public

Transparency on the use of animals in research starts at the highest levels within each organization and continues at every level. All employees within each company should be educated on the role animals play in drug development: their use on study, the high level of care they receive throughout their time in research facilities, as well as the adoption and retirement programs that are sponsored. These are accomplished through not only Corporate Statements and Standards on animal use, but through outreach such as presentations and interactive events at Take Your Child to Work Day, Biomedical Research Awareness Day Events, Culture of Care events throughout the facilities, and animal house tours for other departments:

- Biomedical Research Awareness Day is attended by employees across all disciplines at various company sites. The teams achieve a high level of engagement on all aspects of animal care and use and developed novel ways of promoting R&D work through games, quizzes and presentations. In one example, attendees signed a pledge to support the humane use of animals in research, respecting the role laboratory animals play in the quest for new treatments for people and animals and to highlight careers in biomedical research.
- An invitation to an open dialogue on the use of animals for scientific purposes is

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a beneficial two-way street. The public, NGOs, decision-makers and other stakeholders should get a realistic picture of the responsible use of animals by the pharmaceutical industry and the companies get valuable in-put on concerns from the public and also constructive ideas and suggestions to improve animal welfare. These invitations can be proactively targeted or actively posted for a more general audience. Reaching out and an invitation to contribute to this dialogue is achieved by arranging facility visits for all those interested outside the company, by offering to reply to questions from student's assignments or by offering presentations at schools' science days or similar.

◊ One member company offers medical students in their 2nd year the opportunity to attend the course "Medicine and Animal Testing". The course was held for the 10th time at a company in Switzerland in cooperation with the Medical Faculty of the University of Basel and the Vice-President of the cantonal animal testing commission. As in previous years, the students dealt with the various aspects of animal experiments in medicine including the legal requirements, theoretical and practical aspects for the performance of animal testing, ethical aspects for the attitude of humans towards animals in general, scientific gain from animal testing and drug safety. After visiting the animal husbandry facilities of the member company, they were able to spend a day in a research laboratory. The assessment by the students has been positive each year. The students emphasized the open and transparent information policy in the field of animal testing and the extremely responsible handling of the experimental animals. In particular, the students have very much appreciated to get an objective impression for the performance of animal testing.

3Rs Promotion and openness

Companies are making considerable strides in communicating not only what is happening in animal research facilities but also why the work is required. In order to increase transparency with colleagues, animal facilities have opened up in a variety of ways.

◊ One way is through the Community of Science (CoS) that provides educational opportunities for employees providing a monthly lecture describing the regulations, oversight, training, maintenance, and 3Rs initiatives that impact the animals entrusted in their care. Immediately after the lecture, a tour is provided which includes a look into rat, mouse, and dog rooms as well as viewing of Cynomolgus macaques in their housing area. The indoor and outdoor dog socialisation areas are always popular with guests, such that it is now offered several times each month for individual employees as well as for departments and other groups. The Comparative Medicine staff also offer a "Family Day" experience for family members of employees. Experiences include a lecture, tours of the animal facilities, interactions with research dogs, as well as multiple stations setup throughout the facility to inform visitors about the types of research that are ongoing at the company.

◊ At many workplaces, it is traditional to participate in the annual "take your child to work day". During this day many activities are arranged across the site to help employees' children engage in science and to learn more about what their parents do every day. Historically animals in science has not been a part of this, but in 2018 the site took the bold step of actually allowing groups of children to tour the animal facilities and learn more about how animals are used in research, their housing and their care. The event was billed as a great success with lots of positive feedback from the parents and children. This is a new level of openness in a US animal facility.

◊ One company has formed a relationship with a local wildlife rehabilitation centre in order to provide them with rodent carcasses, such as unused breeding stock animals, to help feed the animals in their care including local wildlife in rehabilitation. This program helps to take an enormous financial burden off a sadly underfunded

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service and spreads goodwill to the local community. The company also participated in Biomedical Research Awareness Day, that raises awareness of, and pledges support for animals needed for biomedical research. Additionally they hosted a station during Take Your Child To Work Day where the children received goodie bags with educational material provided by Kids4Research, made enrichment items for the animals, learned about how to dress up for surgery and monitor patients and ask questions about the research animals. Similar outreach has been done at local schools to help educate the benefits of medical research.

Berlin prize for 3Rs 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 focuses on 3Rs 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. In 2017 the prize was awarded to the in vitro platform "FluType" for the detection of influenza subtypes and a platform for two- or three-dimensional human brain models based on human stem cells

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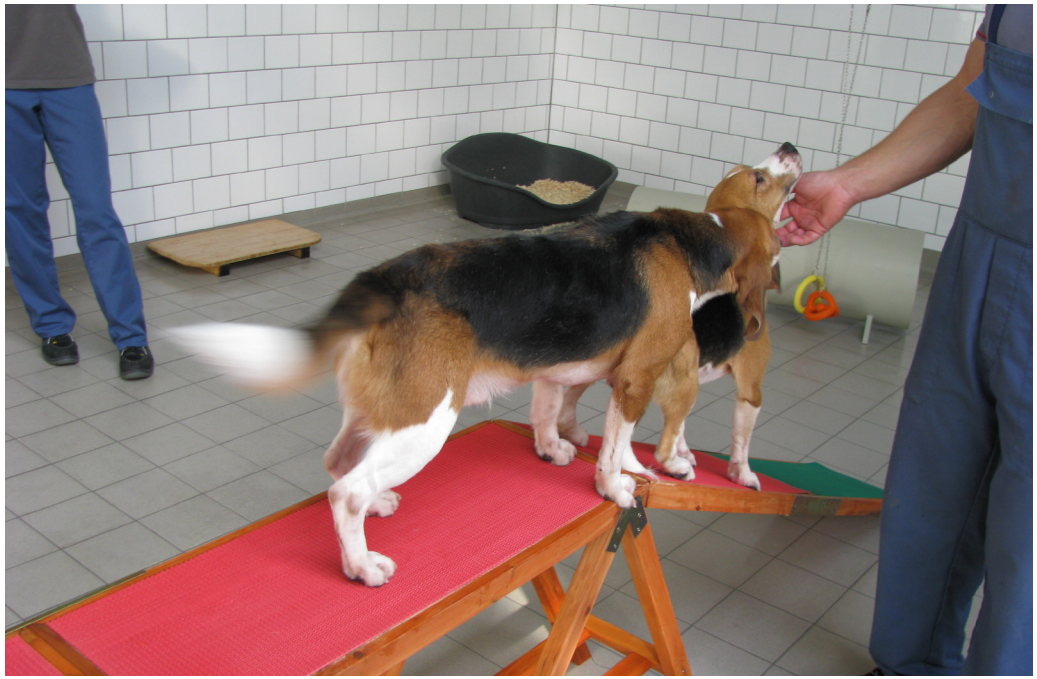
Transparency of Animals in Research – use of the Dog Training Area

Two separate teams within one company have been recognised for their work, in parallel and collaborative efforts, to create outdoor dog play areas in the EU and US. After 2-4 years in research, dogs are rehomed by adoption to private owners through animal welfare organizations. The research dogs are well socialized to humans through daily interactions with study and animal care personnel; however, until recently, the dogs in the US facility have only been habituated to the inside area of the animal unit, while the dogs in the EU also having access to outdoor concrete runs. To help them have the best possible start in their new lives, outdoor dog training and socialisation areas were set up. In these areas, the dogs experience different kinds of surfaces (grass, soil, etc.) and run freely, enhancing their physical and psychological well-being. The training area also allows for the dogs to become accustomed to vehicles and people passing. Another advantage is that the dogs are visible to employees, increasing the transparency of animal research, awareness of the enrichment program and of the adoption program. Employees can volunteer to socially interact with the dogs inside the training/socialisation area. These experiences have already had a notable positive effect of the well-being of dogs as well as humans.



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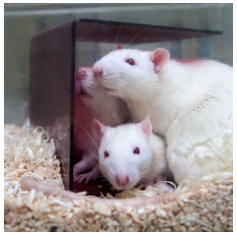
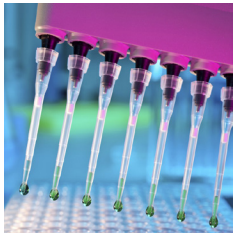
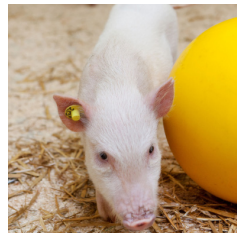
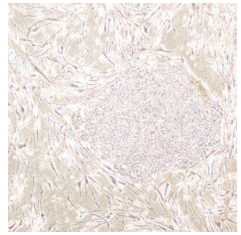
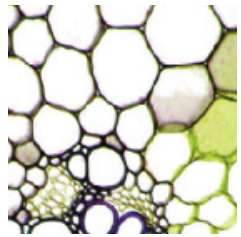




In addition to participating in international events and platforms, the pharmaceutical industry is communicating on the 3Rs through there websites and Corporate Social Responsibility (CSR) reports. Often, there is a dedicated section on animal welfare and the 3Rs are included in these reports. Furthermore, some 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.

A few examples can be found here:
* AbbVie
* AstraZeneca
* Bristol-Myers Squibb
* GlaxoSmithKline
* Interpharma
* Novartis
* Novo Nordisk
* Merck
* Sanofi
* UCB

EFPIA have produced four previous reports on Putting animal welfare principles and 3R into action since 2011 (available on EFPIA's website).



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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**

For more information, contact

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Photos have been sourced from a number of sources, including EFPIA, EFPIA member companies and Understanding Animal Research. EFPIA would like to thank the members of the EFPIA working group on Research and Animal Welfare and the 3Rs Topic group for the valuable contributions to this report. In addition we thank Sarah Wolfensohn for her invaluable contribution in editing and proof reading the examples in this brochure.

June 2019