Some views On The 3RS in Britain Today

Highlights from CMP's **October 2003** Meeting



Why we **Neec** to use animals in **Biomedical** Research

In real life, our tissues and vital organs are interconnected, our blood vessels contain all manner of natural chemicals, our immune systems get involved.

for people with an interest

Highlights

Meeting

from CMP's

October 2003



is the exception rather than the rule. There are examples where animals mimic or model the whole human situation very well, but most of the time scientists are only interested in one small part of the disease. A single biochemical reaction, for example, that seems to make the difference between health and illness.

My team and I are trying to find better

There's a common belief that people

like me use animals because we think

their version of a disease will inform us

somehow about humans. Actually, that

treatments for asthma and the less well-known, but just as widespread, condition chronic obstructive pulmonary disease. Now guinea pigs and rabbits may not get asthma like a human, but their airways constrict in the same way. We can measure that constriction in a sleeping animal, how much the muscles

around its bronchial tubes contract or how obstructed its airways have become. And this helps us assess whether a new molecule is likely to become a good medicine. We cannot do that in a test tube, and we need to do it before moving on to human patients.



Corbis

Young children can sometimes find asthma inhalers hard to use. A new tablet could help

In real life, our tissues and vital organs are interconnected, our blood vessels contain all manner of natural chemicals, our immune systems get involved. These aspects can only be replicated in an animal. Humans share these characteristics with the other mammals and it is vital new ideas are tested in real life so that we can make progress from the test tube or computer screen to people. You cannot measure blood pressure in a test tube; chronic cough, another research interest of mine, is poorly treated - you cannot get cells to cough.

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I'm sometimes asked "If we've got such good medicines now, why do we keep doing research to develop more?" The answer is that even in asthma, which in comparison to many other diseases is well-controlled, there are unmet needs. Many cases of asthma occur in the first five years of life and young children do not have the co-ordination to use inhalers. Most patients would much rather take a tablet once a day tablet than an inhaler four times a day. But such a tablet would need to treat both the symptoms of the obstruction and the underlying inflammation. For this, more research is necessary, including some in animals.

Clive Page

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the ethical constraints n using humans. It is possible to subject animals procedures and conditions at most societies would not ermit to be done to humans. nimals are small, they produce fast, and they are adily bought. Animals can be bred to be genetically pmogenous and housed ady to use. All of this is provenient for research. ne 3Rs combine to lessen o burden on animale

Reduction

is about minimising the number of animals that are used in studies – for example by having good experimental design. A well-designed experiment means that scientists use no more and no fewer animals than necessary. Too few animals could mean obtaining invalid data and having to repeat the study with even more animals.

Refinement

is about minimising the suffering and distress caused and

Replacement

does away with the animal procedure altogether.

Whilst computer modelling and simulations are sometimes used as replacements not just for experiments but also for teaching purposes, it should be remembered that development of these systems depended on data obtained from animals in the first place. The use of mass computing power enables promising drug candidates to be found quickly. A joint initiative between Intel and Oxford University (http://www.chem.ox.ac.uk/curecancer. html) lets people around the world volunteer their PCs to model the interactions of a huge number of compounds against 12 molecules that have key roles in the development of leukaemia.

In many disciplines, cell culture and other in vitro systems that do not use animals are not seen as replacements but as the norm. This is especially so for mechanistic studies at the cellular and molecular level. In toxicology it is estimated 85% of in vitro work is carried out in freshly-obtained animal cells and tissues and only 15% is done in immortal cell lines, which have slightly altered properties to fresh cultures. This means that animals have to be killed to get the fresh material to put into culture. But even when that's required, at least the animals are being used more efficiently; a single animal can provide tissue for several cultures.

Cell culture systems are ideal when you want to avoid whole body influences. At other times, where the systemic influences are crucial, this can be a disadvantage.



Horseshoe crabs donate blood – and spare rabbits Mary Hollinger/National Oceanic and Atmospheric Administratior

Examples of Non-animal Methods

Tissue culture

Human corneal cells, grown in the laboratory, can be reconstituted to make a tissue that resembles a real cornea. Progress is being made to get different sorts of cells to retain their individual characteristics longer in culture and thus be more useful to scientists. Animal cells can also be genetically engineered to make them more like human ones.

Eye irritancy

A protein found in the American jack bean is the basis for a test system used to detect chemicals likely to irritate eyes. The Irritection Assay System produces biochemical changes similar to those found in human corneal tissue. Some known potent eye irritants make it cloudy, less potent or non-irritants make it much less cloudy or even clear.

Safeguarding vaccines and biological fluids

There is a danger that an injection, e.g. a vaccine, might cause fevers or even death due to the presence of bacterial debris. So injection fluids are checked for contamination. This used to be done with rabbits but the LAL test uses the blood of horseshoe crabs which clots if pyrogens are present. The crabs themselves can be returned to the water.

Krys Bottrill Fund for the Replacement of Animals in Medical Experiments

Welfare and The 3Rs

Refinement can be considered in **two main ways**.

There are the steps taken to reduce suffering occurring from studies themselves, e.g. post-operative pain relief or training the animal to cooperate voluntarily.

Then there is the refinement of housing and husbandry which concerns suffering not required by the study. Not all laboratory environments meet the needs of the animals kept within them and indicators of poor welfare such as stereotypies (repetitive cycles of identical activity) can be seen in laboratory animals.

While some may see replacement and reduction as the first two options, refinement that reduces residual suffering is extremely important for those animals still destined for use in research.

> Suffering is not always obvious. Prey animals, like rodents, do not fare well in the wild if they display their weaknesses and they retain that characteristic in the laboratory. So well-trained and sensitive staff are needed. Not all suffering is pain related. For example, smell is very important to mice and if they lose the ability to communicate by scent marking it could be distressing and can cause social disruption. This might happen as a result of genetic modification or overzealous cage cleaning might eliminate the smells

Not all suffering is pain related. For example, smell is very important to mice and if they lose the ability to communicate by scent marking it may be very distressing. they value. Other non-obvious suffering includes skin irritation, nausea, fatigue or sensitivity to light.

Refinement of housing and husbandry can have benefits to the quality of science as well as the welfare of animals. Conversely, poor welfare can hinder science. In one study, hamsters housed in smaller cages had a higher baseline temperature than those in larger cages. This compromised their ability to develop a fever when they were challenged with infectious agents. Better welfare improved the quality of the science. Similarly, animals that adapt to test cages or were examined in their home cages have been shown to respond better to other laboratory tests.

Examples of **Refinement**

Visualising tumours

Fluorescence is used to visualise the growth of tumours in mice. The animal can range freely within its cage and it does not have to be put down in order to assess the tumour growth, which means fewer animals required. It also means that experiments can be terminated before the animal shows obvious signs of distress.

Training

Technicians can teach animals to cooperate with routine laboratory procedures. These then become less distressing for both the animal and the technician. Giving young animals, such as puppies, a varied environment makes them less nervous when being examined or dosed later in life.

Changing Standards

There have been seen some quite dramatic changes in terms of enrichment, such as those outlined for dogs. In Denmark there is a unit that not only provides platforms, complexity, chews and so on, but also outside runs for the dogs.

Standards have changed and are still changing. This is partly the result of pressure from welfare organisations such as UFAW, FRAME, RSPCA and others. Regulatory bodies such as the Home Office, animal care staff and the scientists themselves also initiate changes. People are really beginning to realise the importance of an enriched environment, early socialisation, habituating and training and need for a complex environment during development.

Future challenges include: validating welfare improvements; addressing scientists' concerns; examining barriers to implementation; and the education

Providing chews in dog cages.

Chewing is a species-specific behaviour of dogs, and yet there might be little opportunity for dogs to chew in the research environment. It's a fairly simple matter to provide chews in a way that's compatible with the studies that are done. Dogs will use them for about a guarter of their day.

There have been seen some quite dramatic changes in terms of enrichment

Platforms in dog cages.

If you provide dogs with a platform so they get a better view they will typically spend up to 60 percent of their time there. They are much more relaxed than dogs with a restricted view.

> **Robert Hubrecht** Universities Federation for Animal Welfare

of regulators, the public, and scientists. Britain does have high standards and we would not want to see animal studies exported overseas where local conditions may not always be so rigorous. We need to harmonise standards worldwide, and there is evidence that this is happening, in Europe at least.

Dogs given chews will use them for a quarter of the day



Caroline Manning GlaxoSmithKline

Discovery and The 3Rs

It is important and necessary by law to complete safety studies in animals before a novel molecule is tested in humans.

Industry researchers use a wide range of tools. Computer modelling, human cell lines, animal tissues, research in whole animals and clinical trials in people are just some of them. The starting point is understanding the disease or disorder in order to identify a target for a new medicine. The challenge is then to identify a chemical that will interact with that target, manipulating it in the desired way.

Before that part of the research programme using animals can start, scientists must submit a detailed licence application to the Home Office. As part of this process, the pharmaceutical company completes a cost-benefit analysis, considering both the potential benefit to mankind in the treatment of diseases and disorders and the ethical considerations in using animals. Research is only approved if the benefits outweigh the possible harm to the animals.

Within GSK, at the centre of the ethical review process is CARE – the Committee on Animal Research and Ethics. CARE is made up of senior people who are responsible for animal research and animal husbandry. It also has lay members – people who do not work with animals and external experts, such as veterinary surgeons.

It is important and necessary by law to complete safety studies in animals before a novel molecule is tested in humans. Ethical review within the company and at the collaborating hospitals will scrutinise the animal and non-animal safety data before giving approval to proceed. These tightly controlled studies, conducted in healthy human volunteers, allow the scientists to see for the first time what the molecule does in humans. Animal and non-animal work will have given confidence the new chemical is fit for its job but it is not until results from patients start to appear that there begins to be some certainty as to the medical value of the new treatment.

Research into the 3Rs is part of everyday work at GSK and time and resources are allocated to specific research projects. Each year there is an internal animal welfare award for the best 3Rs innovation or practical application. A specialist interest group, drawn from scientists, vets, technicians, statisticians and information scientists, has been set up to promote the 3Rs and educate scientists within the Company. Taking an idea and turning it into a vaccine or medicine that can be prescribed by a doctor takes 10-15 years. Broadly speaking there are two main phases – first, finding a chemical that might become the active ingredient and second developing and testing that chemical to see that it is safe and does what it is supposed to do clinically.



Most R&D does not involve animals

As part of our efforts to promote the 3Rs, specialist information scientists publish a monthly scientific literature review on animal alternatives and welfare. Researchers also submit specific requests for such information. This is particularly useful when new project licences are being written, or new techniques are being set up or a new animal model is being designed.

Examples from Industry

Co-ordinated tissue supply

A well-managed and regularly updated tissue sharing and storage service ensures that people working in different groups can make use of all the tissues from a single animal. This avoids harvesting tissue separately from different animals – thus reducing the numbers of animals that are used.

Better animal models of human disease

Even though scientists are usually only interested in one aspect of a disease, the closer the animal models the human situation the better. With regard to Alzheimer's disease, a mouse has been bred with two key genes altered. Like humans with the disease, the mouse develops protein plaques in the brain and has the associated memory decline - some of the hallmarks of this terrible disease. In the past, researchers had to wait for mice or rats to age naturally and then look for the ones showing signs of natural memory decline. With the transgenic animals that stage is reached much more quickly and more consistently. Fewer animals are needed and they are kept in the laboratory for a much shorter time.

Sophisticated measurement systems

LABORAS (Laboratory Animals, Behaviour, Observation Registration and Analysis system) is an innovative piece of equipment that allows scientists to monitor rodent behaviour within the home cage environment, without disturbing the animal. The platform at the bottom of the cage is very sensitive to vibrations and different normal behaviours, such as grooming or feeding, produce specific patterns of vibrations. Using LABORAS, it is possible to track animal behaviour in normal animals, determine behavioural changes after treatment with new medicinal chemicals. and to characterise behaviours in animal models of disease. It has been used to develop non-invasive test methods for many neurological research projects.

Absolute figures are misleading

Despite ever-increasing numbers of new chemicals being assessed to see if they have potential as medicines, the animals total has not risen. In fact, the number of animals used in the discovery and development of a new medicine has fallen sharply. For example, animal use in safety testing of new medicines has fallen by one third since 1995. Molecules likely to cause side effects in people can increasingly be weeded out without using animals. Computer modelling and cell-based assays in particular have allowed us to screen out problem compounds before reaching the toxicology stage. Those that continue will, of course, still need to be tested in animals, but their chances of success are higher than used to be the case.

For more info on the 3Rs at GSK see: http://science.gsk.com/about/animalresearch.htm

Funding Body's Perspective



If we are to minimise suffering then we need to be better able to recognise signs of suffering in animals.

The Medical Research Council (MRC) is the UK's principle source of public funding, spending about £400m a year on research and training to improve human health and medicine. Approximately one-third of MRC-funded research involves the use of animals, predominantly rodents. From the perspective of a funding body, the 3Rs are important for scientific, ethical, legal and economic reasons

There is increasing recognition in the scientific community that the way animals are housed, handled and used can have an impact on their physiology, behaviour, immunology, and biochemistry. And this, in turn, can affect the validity and reproducibility of the data obtained. This can be exemplified by research using mice that have been genetically modified to mimic some aspects of Huntington's disease. If the Huntington's mice are provided with a complex cage environment that provides opportunities to hide, build a nest, gnaw, and forage they mimic the disease more accurately. This means the mice are better "models" of the disease than those housed in a less complex environment. Thus, providing animals with a better environment can

not only have benefits for animal welfare but also the science for which they are being used.

The MRC incorporates the principles of the 3Rs into its research. The main input is when applications for funding for research using animals are reviewed by scientific experts. Those reviewing the applications on behalf of the MRC are asked to consider whether the use of animals is justifiable, whether the use of that particular species is necessary and whether the applicant has fully considered the 3Rs. This review focuses on the scientific aspects of the project and whether the 3Rs have been implemented. For example, considering questions such as is it possible to do this research without involving animals? Has the applicant minimised the number of animals

involved? And, is there a different way of refining the techniques and the research to minimise any suffering? These issues are also considered by 'the Board', which is essentially a panel of experts that provides advice to the MRC on whether the research should be funded. For some applications, for example those that involve the use of primates, welfare experts are also involved.

The MRC makes significant contributions to the 3Rs by funding research. "Indirect" contributions refer to research which is carried out for a specific scientific purpose but where a spin-off has contributed to the development of the 3Rs. "Direct" contributions are where the primary motivation for doing the study is contribute to and improve the application of the 3Rs.

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> Vicky Robinson Centre for Best Practice for



Non-invasive techniques to study the brain

MRC scientists are at the forefront of developing non-invasive techniques to study the brain. One example is transcranial magnetic stimulation. Here, magnetic stimulation is used to temporarily and safely disrupt brain function. This can be done in human volunteers whose ability to do various cognitive tasks is then assessed. In some instances this technique has replaced the use of monkeys in comparable brain function studies.

Cryopreservation

The MRC has been leading the development of techniques to reduce the number of mice that are used. One example is cryopreservation.

increasing rapidly. Freezing the embryos and gametes (eggs or sperm) of such mice when the initial research has come to an end avoids continuing to breed the mice until they are needed again. This can help reduce the number of mice that are used overall

The use of genetically-modified mice is

Archiving genetically-modified mice, either as frozen sperm or embryos, has another benefit in that it eliminates transporting live animals to other establishments, which can be distressing. Instead they are sent as frozen sperm or embryos. In addition, it means that scientists worldwide do not need to generate the same types of geneticallymodified mice over and over again at their own laboratories - they can import the frozen sperm or embryos instead

Direct contributions

Better housing for mice

Scientists at the MRC National Institute for Medical Research have designed "red houses" for mice – a development recognised by the annual award of the Swiss Laboratory Animal Science Association. The transparent, plastic red houses provide the mice with somewhere to nest, hide and to climb. They have two entrances to avoid one mouse dominating and stopping others entering.

Tests have shown that mice prefer shelters to have a dark interior - probably because it provides somewhere to hide. The problem for animal care staff is this means they have to disturb the mice in order to carry out daily welfare checks. However, mice apparently do not see red and once inside a red house they are in a dark environment. The transparent walls mean mice can be checked without being disturbed. Simple but effective!

Improved cage – cleaning regimes

Researchers at the University of Oxford are being funded by the MRC to investigate improved cage-cleaning regimes as part of husbandry refinement for mice. In the past, the emphasis has been on keeping mice in a clean environment with frequent cage cleaning by animal technicians. Mice rely on their sense of smell; they use it for maintaining social hierarchies, for communicating with each other and for establishing territories within the cage. Thus cleaning out the cages too often might be distressing for mice because of the disruption to scent cues. Understanding how often it is best to clean out their cages will benefit the mice.

Knowing when an animal is in pain

It is extremely important to ensure that any pain caused in research is kept to an absolute minimum. In order to do this one has to be able to identify animals that are suffering, so that they can be given appropriate pain relief. Most animals used in research are rodents and identifying pain in rats and mice can be surprisingly difficult.

Rodents are prey species and concealing signs of suffering is an important evolutionary adaptation. So how can rodents in pain be identified? To help answer this question, MRC is funding research at Newcastle University to identify subtle signs of pain in rats. Rats that have undergone surgery as part of research studies are videotaped and the way they behave closely analysed.

A number of behaviours that could be associated with pain have been identified, including back arching. This has been substantiated by the finding that the frequency of back arching is significantly reduced when pain relief is given.

Spreading the word

While funding bodies such as the MRC make significant contributions to the 3Rs, both indirectly and directly, it is equally important to collate that information, disseminate it to appropriate audiences and ensure implementation. The MRC's Centre for Best Practice for Animals in Research (CBPAR) has been able to help achieve this. CBPAR provides independent advice and guidance on all aspects of laboratory animal use and welfare, and the 3Rs. It acts as a focus for co-ordination and collaboration between organisations that have a similar philosophy to the MRC. In addition, CBPAR manages the MRC 3Rs funding scheme.

Further information on CBPAR can be found at http://www.mrc.ac.uk/publiccbpar.htm

Regulation of Animal Research

Considering pain on its own is not enough.

Animal research was first regulated in the UK under the Cruelty to Animals Act 1876. This was the first piece of legislation that addressed animal welfare, rather than dealing with animals simply as property or in relation to public order offences. It was particularly significant because the main legislation relating to animal welfare in other contexts did not appear until 1911. The Animal Scientific Procedures Act 1986 currently regulates animal research in the UK. Its purpose is to make provision for the protection of animals used for experimental and other scientific purposes when that use may cause the animal pain, suffering, distress or lasting harm.

Considering pain on its own is not enough. Thus, the current legislation is framed in terms of pain, suffering, distress and lasting harm. It regulates not just the use of animals but the breeding and supply of the commonly used laboratory animals. The Act covers any living vertebrate animal, the common octopus and some immature forms. Interestingly, in the United States the Animal Welfare Act, which regulates animals and science, does not protect rats, mice or birds used for scientific purposes.

The 3Rs are at the centre of the UK regulatory system: good welfare and good science are inseparable. The Home Office legislates on and regulates this issue because it has no conflict of interest. It is one of the very few Government departments that does not commission animal research, require animal test data in order to discharge its statutory function, or own and operate test laboratories.

Within the Home Office, matters relating to the 1986 Act are the responsibility of the Animal Scientific Procedures Division (ASPD). ASPD operates the licensing systems and enforces the legislation; its Animal (Scientific Procedures) Inspectorate assesses and advises on proposals for animal use and inspects work in progress. In 2004, the Inspectorate will have 33 professional staff, operating from five locations around the UK. All are either medical or veterinary graduates with higher academic and professional gualifications.

The licensing system operates at three levels. The places where work is performed must have a certificate of designation. Each and every programme of work is issued a separate project licence that goes down in detail as far as the protocols and the end points to be applied. And the Home Office requires

that project licence holders undergo mandatory training before applying. Licensees are expected to keep up to date and adjust their welfare practices as progress is made. For example, primates, dogs and cats are no longer singly housed in the UK – other than for welfare or veterinary reasons, or for very specific and justified scientific reasons.

At any one time, there are about 3500 project licences valid. Eighty five percent of the animals used are rodents, with the addition of birds and fish these classes of animal account for over 90% of the animals used. There are 240 or so designated places where animals are produced or used – and of the order of 2500 visits of inspection are undertaken annually by Home Office inspectors. The frequency of visits to individual establishments depends on the size, the complexity and the nature of the work done. Two-thirds of the departmental visits of inspection are without notice, i.e. the inspector looks round and checks things as they are on the day. Inspectors spend a lot of time with the junior animal care staff and the personal licensees who actually do the work as they are the ones interacting with the animals day-in and day-out.

There are currently 14,300 personal licence holders in the UK, using 2.7million animals and, in 2002, there were 31 infringements – half of which were self-reported. It is exceptional for non-compliance to be shown to have been wilful. The Home Office response to infringements varies from admonishing in writing, changing licence authorities,

The 3Rs are at the centre of the UK regulatory system: good welfare and good science are inseparable

taking authorities away, and imposing
new conditions and restrictions. The Home
Office can also revoke personal licences.
In the case of a project licence being
revoked this means the research group
being unable to continue its work.
If a certificate of designation were to be
taken away there would be serious
commercial problems. The Home Office
can, and does, prosecute those who
breach the Act not only under the 1986
Act but also under the 1911 and 1912
Protection of Animals Act

Through this regulatory system, licensed animal work in the UK is justified, the benefits are maximised, the suffering is minimised and we have high standards of care and accommodation.

Jon Richmond Animal Scientific Procedures Division The Government view is that while replacement should, of course, be the ultimate goal, we do not believe it should be made a priority at the expense of reduction or refinement.

Government **Perspectives**

The regulation of animal research in the UK is based on the belief that it is morally acceptable for human beings to use other animals but it is wrong to cause them unnecessary or avoidable suffering. Of all my responsibilities in the Home Office, probably the greatest number of letters I get from MPs on behalf of their constituents concerns animal research.

The Government view is that while replacement should, of course, be the ultimate goal, we do not believe it should be made a priority at the expense of reduction or refinement. These are the areas where progress can be made more quickly. The statistics show since 1987 the number of animal procedures started each year fell by 22%.

Home Office officials are currently leading a review across government to improve the application of the 3Rs. One focus is to help resolve the legal and other obstacles to introducing the 3Rs and to encourage data sharing so as to reduce animal testing. The inter-departmental group is also considering the recommendation by the House of Lords Select Committee that a UK centre for research into the 3Rs should be set up.

The Home Office keeps abreast of developments in the 3Rs through the Inspectorate, the Animal Procedures Committee and through discussions with other government departments and the many others engaged in the field. For example, in the international arena the government continues to support the work of the European Centre for the Validation of Alternative Methods (ECVAM).

Home Office officials are currently leading a review across government to improve the application of the 3Rs.

The United Kingdom has a good record in the promotion of replacement tests. We played a leading part in the deletion of OECD Guideline 401 (the so-called 'LD50 Test'), a particularly unpleasant toxicity test, and its replacement with a more humane alternative; and the development and promotion of the local lymph node assay using mice – a more humane replacement for a guinea pig test for skin sensitisation.

I acknowledge that the general progress of getting alternatives accepted into regulatory testing is far slower than it should be and not always for the right reasons. There is sometimes too much propensity to conservatism, as well as a reluctance of the regulators of one country to accept decisions made by regulators of another country.

A full transcript of Ms Flint's speech can be found at: http://www.homeoffice.gov. uk/docs2/carolineflint3rs2003.html

Caroline Flint Home Office





Speaker Biographies



Caroline became the MP for Don Valley in May 1997. She is Parliamentary Under-Secretary of State with responsibility for regulation and licensing of scientific procedures on animals. Clive is Professor of Pharmacology at King's College London, where he conducts research in the field of immunopharmacology – focussing on asthma, chronic obstructive pulmonary disease and bronchitis. His work has resulted in the publication of more than 150 peer-reviewed papers and he has contributed to over 30 books. Clive co-heads the Sackler Institute of Pulmonary Pharmacology, is the Honorary Secretary of the RDS council, and has an active role in the British Pharmacological Society.

Dr Vicky Robinson

Centre for Best Practice for Animals in Research

Home Office

Dr Jon Richmond

Vicky has a background in molecular biology. Following five years of postdoctoral research, Vicky spent three years working at the RSPCA where she was responsible for promoting the implementation of the 3Rs in biotechnology. In May 2002, she became the Director of the MRC Centre for Best Practice for Animals in Research (CBPAR). Jon is Head of the Home Office Animals (Scientific Procedures) Division. A physiology and medical graduate, and a Fellow of the Royal College of Surgeons, he trained in plastic, reconstructive and trauma surgery. He was also involved in clinical practice and research in the UK, Australia and the USA, before joining the Home Office.

Dr Caroline Manning GlaxoSmithKline

Caroline trained as a pharmacologist and has 13 years' experience of medicine discovery in the pharmaceutical industry. She has developed and utilised behavioural models of neurological disorders including epilepsy, anxiety, sleep disorders and chronic pain. Caroline has an active role in the ethical review process within GSK.



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