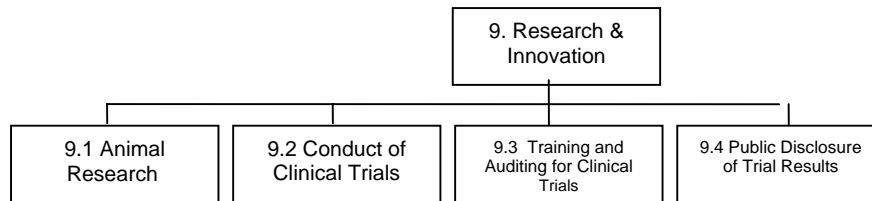


RESEARCH & INNOVATION



Research 9

Research and Innovation

Corporate responsibility principle

In undertaking our research and in innovating:

- We may explore and apply new technologies. We will constructively engage stakeholders on any concerns that may arise.
- We will ensure that our products are subject to rigorous scientific evaluation and testing for safety, effectiveness and quality.
- We will comply with or exceed all regulations and legal standards applicable to the research and development of our products.

Research and development (R&D) of new medicines and vaccines is at the core of our business, and makes a significant contribution to society.

New drugs have brought huge benefits to the health and quality of life of millions of people over the last 100 years. But continued R&D remains as important as ever. There are still many serious, debilitating and life threatening illnesses for which there are no effective treatments or where treatments could be significantly improved.

In 2004 we invested £2.8 billion (\$5.1 billion) in R&D. Nearly 15,000 people work in R&D at GSK.

There are many ethical concerns relating to biomedical and pharmaceutical research - from the use of new technologies to the objective reporting of clinical trial results. GSK is committed to the highest ethical and scientific standards in all our R&D work. This section explains our approach to animal research, the conduct of clinical trials and the public disclosure of clinical trial results. For information on our approach to new technologies see Ethical Issues in R&D in the website.

Case Study

Focus on the Patient

“Everything we do in Discovery Research can make a difference to patients – this is what motivates me,” explains Karen Lackey, Director of Systems Chemistry in Discovery Research.

Karen leads a group of 51 research chemists in the UK, US and Japan. They work at the beginning of the drug discovery pipeline, identifying and creating molecules that have the potential to become new treatments. In her previous role in the organisation, her chemistry team was involved in discovering the lapatinib molecule for use in breast cancer treatments which is now being tested in clinical trials.

Karen believes that the introduction of Centres of Excellence for Drug Discovery (CEDD) at GSK has had an important impact. CEDDs bring together a range of experts in a particular disease area to speed up the drug discovery process. “The way GSK R&D is set up helps us to prioritise our efforts and ensure that we discover the most effective medicines. Through the CEDDs, researchers have access to experts in all our main therapeutic areas. They evaluate every molecule for its value to patients and help us to identify which ones will have the most impact.”

Jill and Eric Wolford understand the importance of this better than most. In 1999 Jill was diagnosed with breast cancer and underwent nine months of intensive treatment including chemotherapy, radiation and stem cell transplants.

Now recovered and back at work as an Associate Director at GSK’s Global Clinical Operations North America, she and her husband Eric, also a GSK employee, are keen to talk about their experiences. They are meeting with R&D managers and leadership teams to talk about how Jill’s illness has shaped their attitudes to life and work.

This is part of GSK’s Focus on the Patient, an initiative that aims to reinforce a patient centred culture across R&D. Employees have the opportunity to hear from patients about their diseases, the GSK treatments that have helped them and the new medicines they need. One of the goals is to motivate employees by reminding them of the benefits they can bring to patients through their work.

Jill welcomes this initiative. “My father was a breast cancer survivor and I’m 99% sure I carry the breast cancer gene. So when I look at my kids I think ‘Please someone find a cure for breast cancer’. For every case report form there is a person, family and network of friends. We treat people not diseases and we need to remind ourselves of this the whole time.”

Animal Research

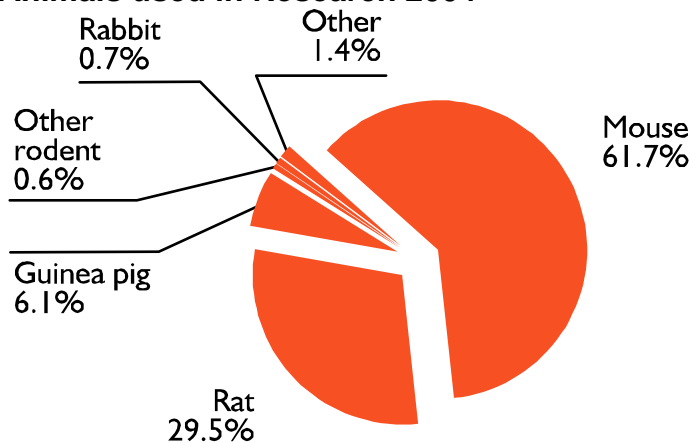
Learn more about animal research in the website

Animal research is essential to understand disease and to evaluate the safety and effectiveness of new medicines before they are given to people. Regulations require new medicines to be tested on animals before being tested on humans for safety reasons. Some vaccines have to be tested on animals each time a new batch is produced. We estimate that animal research accounts for around 5% of all GSK research expenditure.

GSK has 13 animal research laboratories in Europe, Japan and the US. Some research (around 7% of our total animal research) is conducted by external contractors on our behalf.

Over 98% of the animals used in our laboratories are rodents (such as rats, mice, guinea pigs) and rabbits. The remaining 2% includes fish, ferrets, pigs, dogs, cats and primates.

Animals used in Research 2004



The Three Rs

Our animal research laboratories are subject to strict internal and legal controls. GSK is committed to the 3Rs – **reduction, refinement and replacement** – and to achieving the highest standards of animal welfare.

The 3Rs commit us to: **reducing** the number of animals used in each study; **refining** studies to minimise pain and maximise the information obtained from each animal; and **replacing** animal studies with alternative methods wherever possible.

We provide extensive training on the 3Rs to all staff who are involved in the care and use of animals, and we have a number of initiatives to increase awareness of animal welfare. For example, we produce quarterly bulletins which review recently published journal and news items on these subjects. A UK-based 3Rs committee made up of GSK scientists, statisticians, senior managers, animal technicians and veterinarians encourages a 3Rs culture at

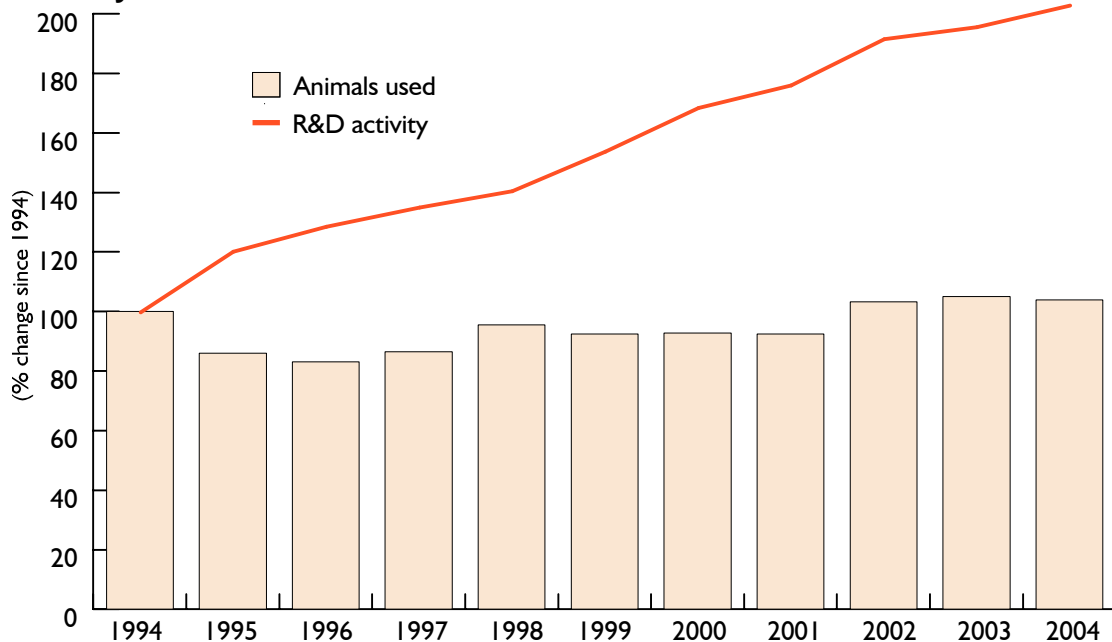
GSK through seminars and production and promotion of 'Recommended Practice' guidelines for scientific procedures and animal welfare.

Our Animal Welfare Awards encourage employees to find alternatives to animal research. The awards, presented twice a year by GSK's R&D Chairman, recognise employees who have made outstanding advances in implementing the 3Rs. In 2004 awards were made for: refinement of an animal model to discover new treatments for brain damage caused by strokes; innovative use of imaging systems to minimise animal use while accelerating drug development; use of computer-generated prediction models and cell and tissue cultures to replace animal testing.

In Europe, we also give a GSK Laboratory Animal Welfare each year to external researchers or laboratories for developing new techniques to implement the 3Rs. The prize this year was won for a project that promoted improvements in husbandry and housing for laboratory animals.

This approach is having an impact. Despite a significant increase in R&D activity since 1994 the number of animals used by GSK is broadly similar to ten years ago.

Change in R&D Activity Compared to change in Number of Animals used by GSK



Recent GSK advances in research techniques supporting the 3Rs and animal welfare:

1. Blood sampling techniques that reduce the number of animals used and the number of injections required per animal and increase the quality and efficiency of sample collection.
2. Refined methods for collecting DNA from transgenic mice, that reduce animal stress and increase productivity.

3. Development of better facilities and refined procedures for ferrets and guinea pigs. Exchange of this knowledge between GSK laboratories in different countries.

Regulation and Internal Controls

Our laboratories comply with strict national laws, guidelines and codes of conduct on animal welfare. Regulators carry out regular unannounced inspections of our sites to check standards of animal care.

GSK laboratories, and any external laboratories conducting research on our behalf, must also follow our Code of Practice on animal research. When GSK sponsors animal research at other companies or institutions, we require that such entities meet all legal requirements to conduct animal based research and we establish to the best of our ability, that best practice standards for animal care and use are followed.

'Best practice' is defined as a combination of what is currently known from the scientific literature, from published recommendations, and from the knowledge of experts from within and outside GSK. In addition, GSK expects these external collaborators to demonstrate application of best practice regarding animal research. Accreditation by the Association for the Accreditation and Assessment of Laboratory Animal Care International is one example of how this can be demonstrated.

To ensure appropriate use of animals, all proposed animal tests must be reviewed by our Ethical Review Committee.

We also obtain independent evaluation from the Association for Assessment & Accreditation of Laboratory Animal Care (AAALAC) International. Ten of our laboratories are accredited by AAALAC including all our animal laboratories in the UK and US. Our laboratories in Belgium, Italy and Spain achieved accreditation during 2004.

Communicating Our Approach

We believe it is important to explain the need for animal research and to be open about what we do.

Our laboratories host visits from schools, colleges, animal welfare organisations and others. In 2004, we also made over 45 visits to UK and US schools to discuss issues around animal research.

We are in regular discussions with animal welfare organisations, our investors and other interested parties. For example this year we have contributed to the work of the Nuffield Council on Bioethics and will be developing our relationship with the new UK national centre for the 3Rs (NC3Rs).

Conduct of Clinical Trials

Learn more about clinical trials in the website

The safety and effectiveness of new medicines must be evaluated in clinical trials before they can be approved for marketing.

Regulators will only give approval if trials demonstrate that a product is safe and effective and that its benefits outweigh any risks from potential side effects.

A new product will typically be tested through three stages of clinical trials. These involve both healthy individuals and patients with the relevant disease. In 2004 there were 140 projects in clinical development.

Traditionally most clinical trials have been carried out in Western Europe and the US. It is however becoming increasingly challenging to enrol sufficient patients in these countries as the increasing number and scale of trials is often utilising most of the available investigators and patients. Therefore as clinical trial capabilities in Eastern Europe, Latin America and Asia have improved significantly in recent years, we are starting to conduct more trials in these regions. We also conduct a number of clinical trials in the least developed countries of the world to evaluate medicines for diseases that disproportionately affect these countries.

During any clinical trial the safety of participants and future patients is our first priority. All our trials, wherever they are conducted, are carried out according to international standards of good clinical practice and applicable laws and regulations. The trial protocols are reviewed by external regulatory agencies in the relevant countries when required and all protocols are considered by relevant ethical review committees whose remits cover the sites where studies will take place. Safety data are routinely collected throughout development programmes and are reported to regulators in line with applicable regulations as well as being reviewed by GSK on an ongoing basis for any safety signals. The GSK Global Safety Board is responsible both for approval of pivotal protocols and internal assessment of any issues related to patient safety that arise during the development programme.

Good Clinical Practice standards

All clinical trials are conducted according to the Good Clinical Practice (GCP) guidelines developed by the International Conference on Harmonisation (ICH).

These guidelines provide an internationally accepted ethical and scientific quality standard for designing, conducting, recording and reporting trials. They cover issues such as the selection and training of trial investigators, gaining informed consent from trial participants, monitoring and quality assurance.

All trials must be approved by an independent ethics committee to ensure the trial is justified and that it is designed and will be conducted according to

appropriate ethical standards. These committees have the power to reject or stop a clinical trial. An ethics committee is typically composed of lay people, medical professionals and scientists.

We conduct audit activities to ensure clinical trials are conducted to the appropriate standards, see [Training and Auditing for Clinical Trials](#) in the website.

Clinical Trials in Eastern Europe, Latin America and Asia

The pharmaceutical industry is starting to perform more trials in regions such as Eastern Europe, Latin America and parts of Asia.

There are several reasons for this. Clinical trial capabilities in these regions have improved significantly in recent years and trials in these countries can help to speed up the research process and ensure new medicines get to patients more quickly. Fewer patients are enrolled into trials in these countries so it is easier and quicker to find patients to participate. These patients have often used fewer medicines compared with those in Western Europe and the US. This makes them good candidates for a clinical trial because it is easier to assess the effect of the products being tested. Cost is also a factor, with operating costs in these countries being lower. Our objective is to carry out more of our clinical trials in Eastern Europe, Latin America and parts of Asia by 2005.

There are concerns that trials in these regions may not be carried out to the same high standards as those in Western Europe and the US. All GSK clinical trials are carried out to the same standards of GCP everywhere in the world. This is vital to protect patients and ensure that we can gain regulatory approval for new medicines.

Clinical Trials in Diseases of the Developing World

GSK has seven products in clinical development for diseases that disproportionately affect the developing world. For more on R&D for developing world diseases see [Access to Medicines](#) in the website.

Clinical trials for diseases of the developing world need to be carried out in countries where the disease is prevalent, and these can include some of the world's least-developed countries. All trials that we sponsor, irrespective of location, are conducted according to the standards applied in developed countries.

In some of the least-developed countries extra efforts may be required to ensure that we meet global standards. For example, in areas with low literacy levels it can be difficult to obtain informed consent from trial participants. In these cases investigators work with independent witnesses to make sure that the trial is properly explained to participants and that they understand what is involved.

For more information on our policy and procedures in this area see [Clinical Trials in the Developing World](#) in the website.

Training and Auditing for Clinical Trials

We provide training to ensure that clinical trials are performed to high ethical and quality standards. We also audit the conduct of clinical trials to ensure they are carried out according to Good Clinical Practice (GCP) guidelines.

All employees involved in designing, conducting and monitoring GSK-sponsored trials are trained in GCP. Training is mandatory and employees must have completed the required training before starting or changing jobs. In 2004 there were 11,239 training activities related to GCP. Each "training activity" represents a successful completion of an e-learning module or instructor-led course related to GCP by one of our employees or complementary workers.

We keep detailed training records which are routinely requested by regulatory authorities when undertaking an inspection to assess the competence of employees undertaking clinical trials.

GSK has an internal audit department (independent of the departments responsible for conducting clinical studies) which conducts audits of GSK systems and processes involved in the conduct of trials, as well as auditing clinical research organisations and investigators performing clinical research on our behalf. In 2004, 176 audits were conducted:

- 102 audits of investigator sites conducting GSK-sponsored trials (representing approximately 5% of investigator sites participating in pivotal clinical trials)
- 17 audits of internal GSK systems and processes used in managing clinical trials / data
- 26 audits of clinical research organisations carrying out clinical trials on GSK's behalf
- 17 audits of GSK Country Medical Departments
- 14 audits conducted in response to suspected irregularities

Audit results are reported quarterly to the R&D Risk Management & Compliance Board, and annually to the GSK Audit Committee. Any concerns or issues identified during audits are fully investigated and appropriate action taken.

In 2004 these audits resulted in 144 findings that needed further investigation, and 4 investigators were reported to regulatory agencies.

Inspections of investigators, clinical research organisations, independent ethics committees (IECs)/Institutional Review Boards (IRBs) and sponsors of clinical trials are also carried out by regulatory authorities to ensure the safety of trial participants, the quality of data, and that trials are conducted according to GCP. During 2004 there were 29 such inspections of GSK and investigators used by GSK to conduct clinical studies.

Public Disclosure of Trial Results

More on GSK's Clinical Trial Register in the website

The pharmaceutical industry is legally required to disclose all relevant data from clinical trials to the appropriate regulatory authorities when seeking approval for a new product.

After approval, sponsors have a continuing obligation to provide regulatory authorities with updated safety information from clinical trials. This ensures regulators can accurately assess the safety and effectiveness of new medicines and monitor their safety after approval. Safety and efficacy information is provided to doctors through prescribing information which is approved by regulators.

In addition there is a need to use ways other than prescribing information to appropriately communicate the results of our clinical trials to healthcare practitioners and others who use or evaluate the use of our medicines.

GSK has taken a significant step this year to respond to concerns about access to trial results.

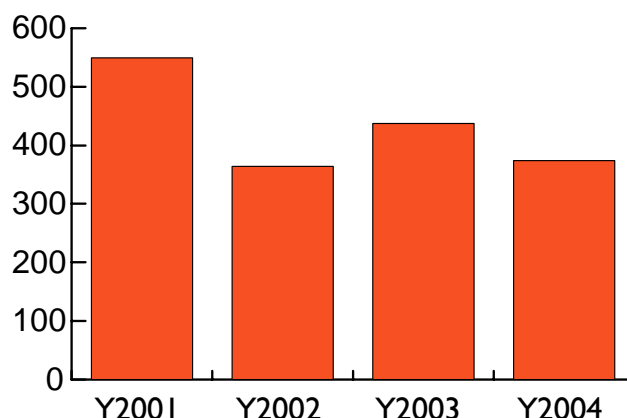
Our Approach

GSK follows the PhRMA Principles on the Conduct of Clinical Trials and the Communication of Clinical Trial Results and is committed to timely communication of results for all products approved for marketing.

Wherever possible we publish our clinical trial results in peer-reviewed scientific and medical journals, or in conference abstracts and proceedings. These are used by research and healthcare communities to obtain the latest information on treatments.

In 2004 there were 374 such publications describing the results of GSK's clinical trials. The number of publications each year depends on the number of trials completed and the number accepted for publication.

Number of publications of GSK clinical trials



GSK cannot guarantee publication of trial results by these methods since this is at the discretion of journal editors and conference organisers. That is why we launched our online Clinical Trial Register in 2004, to supplement prescribing information and publications in the scientific literature (see Clinical Trial Register in the website).

The Register contains results and protocol information from GSK-sponsored trials of marketed medicines. It also provides references to publications that have appeared in medical journals. Anyone can use the internet to access the Register.

By the end of 2004 results for 143 clinical trials had been published on the site. We aim to post, by the end of 2005, the trial results from all clinical trials of marketed products completed since the merger of GSK as well as earlier trials of these products if they are likely to inform medical judgement. Trial results for new products approved for marketing will be posted on the register by the time that medicine is first launched in a major market.

To maximise access to our clinical trial data, we have also committed to posting trial results on the PhRMA clinical trials results database (www.clinicalstudyresults.org).

GSK is legally required to post summary protocol information for ongoing studies of treatments for serious or life-threatening diseases conducted under a US Investigational New Drug Application on the National Institutes of Health website (www.ClinicalTrials.gov) when the trials initiate enrolment. This provides information about the trial's purpose and contact details for further information, enabling patients and investigators to take part. In addition to posting summary protocols for serious or life-threatening diseases, in 2004 we made an additional commitment to post summary protocol information for all other GSK-sponsored clinical trials on the site. This will facilitate participation and enable interested parties to track the trials taking place and the subsequent public disclosure of their results.

We are dedicated to assuring that our results Register and our posting of summary protocol information of trials initiating enrolment are consistent with our stated commitments. To that end, we are establishing a means of providing third-party compliance verification that information being posted to the public databases is in agreement with the principles that we have established. This will be conducted with the assistance of an external organisation - we expect to complete the first full compliance verification exercise in Q3 2005.

Additionally, GSK will assemble an international advisory board to provide input on matters related to the public disclosure of information arising from our clinical research activities.