The Association of the British Pharmaceutical Industry

INTRODUCTION

The membership of the Association for the British Pharmaceutical Industry encompasses pharmaceutical, biopharmaceutical and biologics companies that research, develop and sell new medicines and therapeutic interventions in the UK. Members range in size from multi-national integrated pharmaceutical companies down to small growing companies and contract research organisations.

The pharmaceutical industry is a key component of the UK biomedical research base in the UK, spending over £3.2 billion per annum on R&D. In autumn 2002 pharmaceutical companies in the UK were spending £70 million on collaborative research with UK universities and hosting over 700 PhD students in their facilities (excluding contract research).

Through manufacturing, the UK generated a trade surplus of £2.8 billion, with £10.33 billion of exports. Overall the industry currently employs over 69,000 people directly[1], and a further 250,000 in supply industries.

INTRODUCTION

The ABPI fully supports the search to reduce, refine and replace the use of animals in scientific procedures (the '3Rs'). The pharmaceutical industry in the UK has been at the forefront of developing technologies that have replaced or reduced the number of animals required in research to elucidate disease mechanisms and develop new medicines. We estimate that industry expenditure on such technology exceeded £300 million[2] in 2001. It is often forgotten that the use of animals in scientific research is not a cheap option, but is always driven by scientific need and must be justified by the possible benefits of the research to humans and/or animals.

In 2002, the House of Lords Animals in Scientific Procedures Committee produced a significant report following extensive consultation with academe, industry and those

[1] *Annual Business Enquiry,* Office of National Statistics

[2] ABPI estimate based upon investment and recurrent spending in new technologies used in exploratory research within the UK that have replaced or significantly reduced the use of animals – these technologies include, high throughput screening, bioinformatics, genomics and proteomics.

opposing the use of animals in research. This independent inquiry drew a number of conclusions and produced a number of challenges. Critically the Committee found that:

- it is morally acceptable for human beings to use other animals in scientific research, but that it is morally wrong to cause them unnecessary or avoidable suffering;
- there is at present a continued need for animal experiments;
- toxicological testing in animals is at present essential for medical practice and the protection of patients and the environment; and
- there is a need for the UK to strive for "not the tightest regulation, but for the best regulation" in the field of animals research

The challenges made by the Committee included increasing openness and encouraging those involved in the use of animals in research to take further steps to implement the concept of the 3Rs. Although already engaged in these areas, ABPI members have been taken further action to respond constructively to these challenges.

As part of its policy on sharing and enhancing best practice in animal welfare, the ABPI has developed an on-going dialogue with legitimate welfare organisations such as the RSPCA. The RSPCA continues to challenge the industry and although it is often difficult to respond fully, it has introduced new ideas that will bring about further evolution of the already high standards of animal welfare seen in pharmaceutical and related companies throughout the UK.

KEY POINTS

- The use of animals in biomedical research is essential to help us develop our understanding of human and animal disease and to evaluate safety of medicines before they are tested and used in man.
- Animals should only be used where there is no alternative and their welfare must be given a high priority.
- The pharmaceutical industry strives hard and invests heavily in finding alternatives to animal procedures. When validated, such alternatives are rapidly adopted and applied by the pharmaceutical industry – using animals in biomedical research is expensive and it would be unethical to use them wherever a validated alternative existed.
- Good experimental design is critical to ensure that neither too many or too few animals are used – using too few animals would also be inappropriate as it would require repetition of studies.
- Animal models of disease are not perfect and no scientist expects them to be: yet they provide a raft of information that cannot be obtained from elsewhere – they remain essential in the foreseeable future to provide information on how candidate medicines travel through the body, how they reach their site of action(s) and are subsequently metabolised and excreted.
- Pharmaceutical companies continue to strive to reduce and replace the use of animals, but despite advances in informatics, cell and tissue culture and genetics and genomics, it is still impossible to model how a particular candidate medicine will react in a whole body. No computer exists that can model the complex interactions within one cell, let alone in the millions of differentiated cells in a mammal.

- The safety of human medicines is critical - it would be unethical at the present time to test a medicine in humans without first carrying out animal studies. Regulatory agencies around the world recognise this and quite rightly demand certain information from pre-clinical safety studies in animals.
- Every company and scientist in the UK has a statutory obligation to ensure that animals are only used whenever necessary, that procedures are refined to minimise any suffering and that good welfare practices are put in place.

RESPONSES TO THE CONSULTATION QUESTIONS

Q1 What is your view about the use of animals in research?

We all benefit from treatments that have depended on animal research. All new prescription medicines are developed with the help of animal studies that provide essential information about their efficacy, quality and safety (level of toxicity).

This is so, regardless of the particular company developing the medicine or the country in which that company is based. It is with good reason that the pharmaceutical industry needs to conduct research in animals and that governments around the world demand data from this research before they will allow medicines to be tested and used in people.

Pharmaceutical companies work at the forefront of technology and scientists search for, and use, non-animal methods wherever possible. These methods play an important role in the research process but they only give some of the information that is needed. For the present, and the foreseeable future, animals remain an absolutely essential bridge between the computer and test tube work at the beginning of the research process and the testing in patients towards the end.

A recent report (by Olson H et al "Concordance of the toxicity of pharmaceuticals in humans and in animals" in Regulatory Pharmacology and Toxicology 2000, 32 56-57) of a collaborative study addressing the question of the relevance of animal toxicology studies for humans showed a concordance of 71% between preclinical animal model species and humans. This level of concordance is much closer than it would be using non-animal methods alone and supports the value of in vivo toxicology studies to predict many significant human toxicities associated with pharmaceuticals.

Some effects of medicines can only be evaluated in the living body because of the complex biological reactions that cause them to occur. It is recognised throughout the world that well designed and carefully interpreted animal studies enable researchers to get much closer to the human situation than is possible using non-animal methods alone.

As a result, pharmaceutical companies that bring a new treatment from an idea, to a real medicine that doctors can prescribe, are all in the same position. They must either do the animal work to assess the likely effects of potential new medicine in-house or they must contract outside organisations to do so on their behalf.

You may ask "do we not have enough medicines already?" The answer to this question is definitely NO since we may control some diseases, thanks to existing medicines (e.g. polio, some microbial infections, stomach ulcers), but research into new medicines is essential for several reasons.

- While great progress has been made, treatment remains inadequate in major areas eg: cancers, arthritis, cardio-vascular diseases, multiple sclerosis, a number of tropical diseases and myopathies.
- Diseases largely associated with an aging population e.g. Parkinson's and Alzheimer's disease are on the increase.
- Some infections become resistant to currently used treatments: this is the well known case of antibiotic resistant infections which require continuing research into new antibiotics (e.g. MRSA).
- New diseases will always emerge: AIDS, Legionella, SARS etc.
- People living with chronic conditions are likely, over time, to need to change the medicines they take to treat their condition.
- Through pharmacogenetics: we are gaining a real understanding of the underlying reasons why people respond differently to different medicines and why some people are more likely to experience unwanted effects than others. Having a number of different medicines that treat a particular disease is therefore essential.

The World Health Organisation estimates that there are 18,000 known diseases in the world (excluding genetic variation within a particular disease phenotype). We are able to treat 6000 and to cure 2000 of them. Research for new treatments cannot stop tomorrow.

There is an impressive list of successes in human and veterinary medicine that have been achieved thanks to animal experimentation. In particular:

- development of many vaccines for man and animals (rabies, polio, diphtheria, rubella, measles, mumps, hepatitis, meningitis, animal respiratory infections);
- repair surgery (heart surgery) and organ transplantation (heart, kidney, liver, pancreas);
- discovery of the role of insulin in diabetes, of the role of cholesterol in cardiovascular diseases; evidence of the responsibility of asbestos in lung cancer;
- development of many medicines for cardiovascular diseases, central nervous system disorders, cancer (including leukaemia and Hodgkin's disease), diabetes, AIDS etc.

All these important advances from biomedical research have contributed to cutting child mortality by half in less than a century.

The importance of animal experimentation can also be demonstrated by the work of numerous laureates of the Medicine and Physiology Nobel Prizes. Between 1901 and 2000, it was granted 66 times to scientists who used animal experimentation in their research, which led to important breakthrough discoveries, such as:

Year	Scientist	Animal used	Contribution
1905	Koch	Cow, sheep	Origin and development of tuberculosis
1919	Bordet	Guinea pig, horse, rabbit	Immunity mechanisms
1932	Sherrington, Adrian	Cat, dog	Neurone function
1938	Heymans	Dog	Respiratory mechanisms
1945	Flemming, Chain, Florey	Mouse	Penicillin
1964	Block, Lynen	Rat	Metabolism of cholesterol
1974	De Duve, Palade, Claude	Hen, guinea pig, rat	Structural and functional organisation of a cell
1997	Prusiner	Mouse, hamster	Discovery of prions
1998	Furchgott, Ignarro, Murad	Rabbit	Regulation of tension by NO

It is impossible to completely end animal testing. Not only would it stop the development of new medicines but it would also:

- Make it impossible to diagnose certain human and animal conditions
- Stop the manufacturing of numerous human and veterinary vaccines
- Stop medical student training and, particularly, the training of surgeons (e.g. cardio-vascular surgery, transplantations)

Every researcher, and the organisations for which they work, has a moral and legal obligation to use as few animals as possible and to ensure that welfare is given the high priority it deserves. But most people would accept that it would be immoral to endanger human life in order to avoid using animals.

Q2 What are your views about the use of genetically modified animals in research?

Throughout history, humans have modified the genetic integrity of animals using selective breeding to develop specific domestic strains for purposes such as farming and keeping as pets. Likewise, for biological research, various genetically defined organisms have been developed, from the most simple viruses and bacteria to laboratory and agricultural animals. The use of these model organisms has been fundamental to all aspects of biomedical research in the 20th Century, from the study of basic biological mechanisms, to the understanding of disease pathology (since some human pathologies do not occur naturally in animals), and the development of new pharmaceutical therapies for human and animal use.

Traditionally, genetically-modified animals such as laboratory rodents were developed through the use of classical inbreeding strategies or by identifying naturally occurring or induced mutant strains e.g. the SCID mouse (Severe Combined Immune Deficient). Recently, a more targeted and proactive approach has emerged with the development of recombinant nucleic acid technologies permitting the establishment of many new and unique genetic types of animal throughout transgenesis and targeted homologous recombination (gene knockout). Transgenesis is the science of integrating new genetic information (the transgene) in to the genome of a host recipient (within or across and

species or phylum), and the stable inheritance of the new gene, via the germ line, by resulting offspring. Several methods exist for transferring transgenes, for example, viral vector mediated transfer, pronuclear microinjection and targeted homologous recombination using embryonic stem cells. Transgenesis frequently results in a loss of gene function in the host (hence the term, gene knockout). Already, many hundreds of genetically manipulated and selectively bred transgenic mice have been created to provide new models for study in almost every biomedical discipline e.g. human gene function and regulation, disease pathology and toxicology.

Other examples of benefit of their use include:

- New ways of studying arthritis, with pathological features of greater specificity and lesser severity than previously existing models.
- Numerous examples of enhanced understanding of the function of different genes (e.g. much improved understanding of the immune system).
- Experiments for carcinogenicity in genetically modified rodents and neurodegenerative disorders are of reduced duration and cause less distress and pain for animals compared to traditional studies.
- Rodent models with genes expressing human diseases reduce the need to use higher mammalian species (such as primates) during drug development.
- Developments with transgenesis in mice will contribute to the further reduction in the use of "higher" animals, such as dogs and non-human primates, in biomedical research.

Technological advances such as transgenesis, along with those like the Human Genome Project and Combinatorial Chemistries, have revolutionised biomedical research and provided a major impetus to the pharmaceutical industry because of the unprecedented potential for discovery of new drug therapies and allowing drugs to be used in humans earlier. Thus biotechnology, and genetic modification of animals in particular, are viewed as a very promising, arguably, crucial technology, with far reaching consequences for our society.

The animal welfare issues associated with the use of genetically modified animals are the same as those associated with other animals in biomedical research. It is the minimising of any pain or distress to individual animals in medical research that is most important, not the manner in which the animals are bred. The pharmaceutical industry is committed to the application of current best practice at all times. Therefore it recommends the application of the following practices for the use of genetically modified animals:

- As with all other animal experiments, such animals must only be used in biomedical research where no other scientifically valid means of obtaining the required information is possible;
- Only trained and competent people may be involved in the use and care of all animals in research;
- Regulations controlling the production and use of genetically modified animals must be strictly observed;
- The most efficient and refined techniques should always be used;

- The publication of details of new genetic variants and strain characteristics should be encouraged by the pharmaceutical industry to avoid duplication and to distribute knowledge to a wider scientific community.
- Storage (e.g. cryopreservation of embryos, freezing of sperm) of strains should be carried out when they are no longer needed, with cataloguing and access to other researchers.
- Careful consideration should be given to the health status of transgenic strains. Producing new strains to high health status may remove the need for starting again at a later date.
- Avoid stresses and risks related to the transport of live animals by transporting strains as cryopreserved embryos.
- Dialogue and proactive sharing of information about why and how genetically modified animals are produced or used should be established between the public and researchers.

Q3 What is your view about the use of alternatives?

The ABPI fully supports the search for alternatives to using animals in scientific procedures. The pharmaceutical industry in the UK has been at the forefront of developing technologies that have replaced or reduced the number of animals required in research to elucidate disease mechanisms and develop new medicines. We estimate that industry expenditure on such technology exceeded £300 million[3] in 2001. The ABPI believes that every effort should be made to practically apply the concept of the 3Rs – reduction, refinement and replacement.

Some people may think that researchers have a choice between animal and a non-animal method. But the researcher has no such choice. Both European and UK legislation prohibits the use of an animal if a validated alternative can provide the necessary information. Whole areas of medicines research that used to have to be done in animals are now done in other ways. The pharmaceutical industry is known to work at the forefront of technology and use it to the full.

The use of alternatives in the process of biomedical research is outlined in Figure 1.

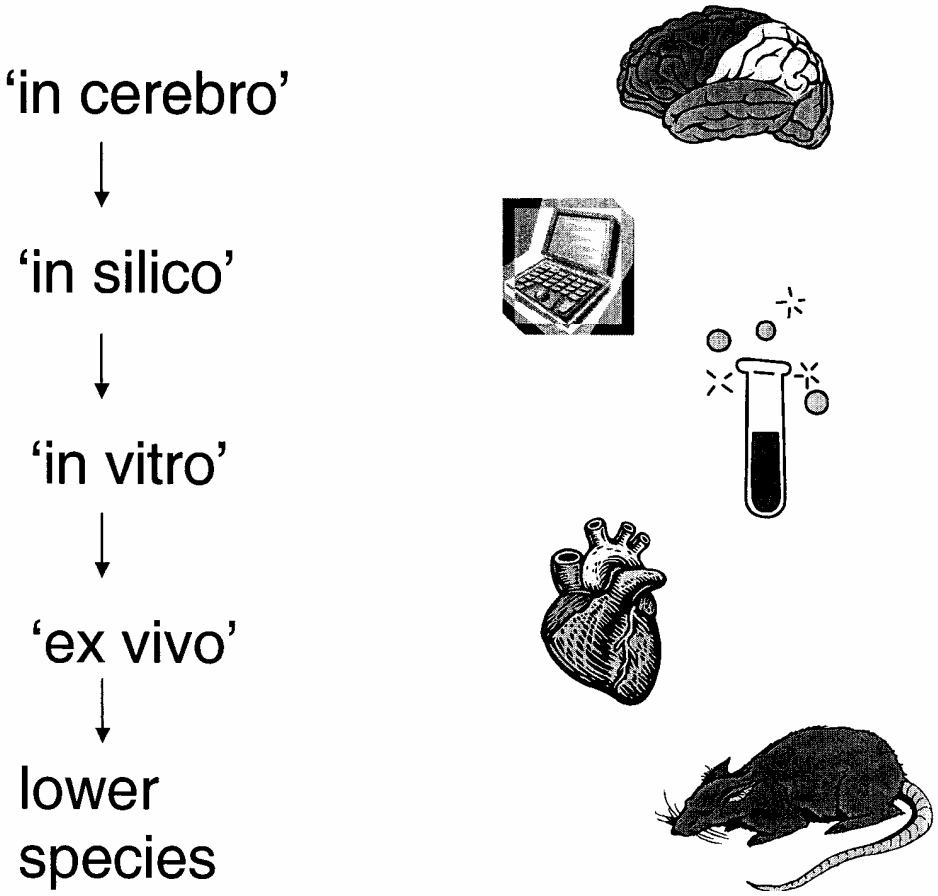
Replacement alternatives have employed the following methodologies and the value and limitations of each are briefly reviewed.

Computer/Molecular Modelling

It is now possible using computers to help design potential medicines. A 3D molecular image of the receptor/target of a disease tissue can be modelled and the structure of a chemical modified to 'dock; with the receptor. Using this technique it is possible to design in desirable features (e.g. drug absorption) and design out adverse features (e.g. potential toxicity).

This fast growing area of drug discovery is limited by the power of the computer and since it is a theoretical model it lacks biological knowledge.

FIGURE 1: Use of alternatives to animal procedures in biomedical research



Mathematical Modelling (Bioinformatics)

This can best be described as the prediction of beneficial and/or unwanted effects using data generated from in vitro databases or previous animal studies. Interactive database can be used to predict drug kinetics (absorption, metabolism) and potential toxicity. This process is limited by the information in the database.

Cell culture

This ranges from the use of bacterial cells to those from humans. In all cases the systems are much cheaper than using animals and the advent of robotics has enabled some screens to be automated e.g. High Throughput Screening for biological activity using cell fractions/components. These applications have revolutionised drug discovery with millions of assays being performed in a matter of weeks, a process which could not be replicated in animals. Other examples of the use of cell culture are:

- The 'Ames' test using the bacterium Salmonella to predict the potential of a chemical to induce mutation (and hence possible carcinogenesis or teratogenesis);
- The replacement of the so called 'Pyrogen test', used to detect endotoxins in injectable drugs/infusions, by the LAL test. The rabbit has been replaced by the Horseshoe crab;
- The use of liver cells (hepatocytes) from animals and man to study the fate of drugs given to man.

However, cell cultures cannot replicate the complex living body and even simple biological mechanisms (e.g. blood pressure) cannot be studied in this way at the present time.

Tissue/organ culture

Both tissue and organ culture offer substantial supplementary methods in the search for new medicines, both in the area of discovery and safety evaluation. It has been possible to replace the need for skin irritancy using animal models and sophisticated in vitro models are available to study drug absorption (Caco-2 monolayers). The use of human disease tissue is increasing e.g. arthritic joints and will aid our understanding of pathogenesis and possible cure.

However, as with cell culture, these methods only allow for a limited part of an organism to be studied. These methods are very useful for studies on particular organs and help considerably to limit the number of animals used in experiments. The majority of these alternatives have been and are still being developed by industry.

Industry is firmly committed to using validated non-animal alternatives and to minimising the number of animals used in research. However, irrespective of their level of sophistication, these methods would never be able to simulate an entire complex organism, nor could they guarantee that all the systems and their interactions have been taken into consideration. It would always be necessary at a certain stage of any research to study the living organism in its entirety, and therefore to use an animal to acquire as much understanding as possible before clinical trials in man begin.

Industry feels strongly, that before any non-animal alternative method of research is adopted, it must be proven to be a truly valid substitute. At the very least, each non-animal alternative must be capable of providing researchers with data comparable in quality, reliability and validity to those currently available through the use of animals. The complexities and intricacies of the entire mammalian system are beyond our present capability to simulate in either man-made models or by the use of tissue cultures or lower organisms. Until such capability is demonstrated, we cannot support the elimination of animal use in research.

Q4 What is your view about ethical issues relating to the use of animals in research?

Man has the duty to treat sick people as well as save lives of people and animals. In order to do so, he must improve his knowledge of biology, and human and veterinary medicine. That is why man carries out animal research where there are no other appropriate investigational methods.

The pharmaceutical industry strives hard and invests heavily in finding alternatives to animal procedures. When validated, such alternatives are rapidly adopted and applied by the pharmaceutical industry. However, as the House of Lords Committee has found, the appropriate and ethical use of animals remains essential to elucidate mechanisms of disease and to ensure the safety and efficacy of medicines to safeguard patient and volunteer safety.

Over the last ten years, significant efforts have been made by industry to reduce the number of animals needed, refine techniques to minimise discomfort and replace them

with alternatives. During this period for every new chemical entity identified, there have been reductions of around 70% in the number of animals used in exploratory research.

Researchers understand that the use of animals in research is a privilege and must be carefully guarded to assure human and animal relief from the spectre of disease and suffering. To ignore human and animal suffering is irresponsible and unethical. Nearly every major medical advance of the 20th century has depended largely on research with animals. Our best hope for developing prevention, treatments and cures for diseases such as Alzheimer's, AIDS and cancer will also involve biomedical research using animals.

The use of animals in medicines research is a complex ethical issue with no easy answer. Most of us want to do the best we can for people and animals, but most people would accept that human health and well being come first. As few animals as necessary should be used in research and they should be spared all unnecessary distress. Scientists must be aware that an animal has sensitivity and memory and can suffer without being able to escape the pain. Scientists should therefore be guided by respect for the animal and prevent unnecessary suffering. But if we want to have new and better medicines without taking unacceptable risks with human life, then for the foreseeable future, we have to accept that animals will be needed.

Research on animals is in many cases an obligation. According to the Nuremburg Code, drawn up after World War II, any experiments on humans "should be designed and based on the results of animal experimentation". The Declaration of Helsinki, adopted in 1964 by the 18th World Medical Assembly and revised in 1975, also states that medical research on human subjects "should be based on adequately performed laboratory and animal experimentation".

There is much philosophical debate about whether animals do or do not have rights. However this is not the real issue – scientists and indeed the public at large, have the obligation to prevent or minimise suffering of animals and to practice high welfare standards.

Research conducted by the pharmaceutical industry is based on legitimate, compelling and entirely ethical grounds. Laboratory animals are used in research as part of the drug discovery process from which we hope to find the treatment and/or cure for specific diseases.

Q5 What is your view about the UK regulations on research involving animals in the UK?

The 1986 Act provides what is considered to be on of the strongest and most comprehensive regulatory frameworks in the world for the control of animal research. The Act created a climate where optimal animal welfare was recognised and valued. The recommendation from the House of Lords Select Committee that "the UK should strive not for the tightest regulation, but for the best regulation", is fully supported by the ABPI.

As the House of Lords' Committee has recognised, the UK is the only country that requires an explicit cost/benefit assessment of every scientific procedure that requires the use of animals. This coupled with the dedication of the scientists and animal technicians to improve animal welfare puts the UK as a world leader in the ethical use of animals in scientific procedures. A tight regulation does not necessarily led to improved animal welfare. A more flexible project licence application in terms of the generic details, coupled

with the ability of the regulatory framework to respond rapidly to changes in protocols by delegation of interim authority to local Ethical Review Panels to approve routine or minor amendments would benefit both research and animal welfare.

The ABPI also welcomed the House of Lords recommendation "that urgent consideration should be given by the Home Office to the simplification of project licences, with the aim of reducing the length of a typical licence to 10 pages".

The ABPI believes that an escalation in the bureaucracy of the operation of the Act has led to increasing complexity of the system, a certain inflexibility of approach and resultant delay in the approval system. This increasing complexity has led to delays in the time taken before research could be initiated. Of concern to the Association is the belief that this approach and the increased regulatory burden has not necessarily resulted in any benefits to animal welfare. The implementation of appropriate IT systems could improve the efficiency and effectiveness of the Home Office.

The ABPI does not consider that any changes to the legislation *per se* would be required at present in order to reduce bureaucracy. Although there have already been a number of changes to the implementation of the Act, including the introduction of a formal Ethical Review Process at each Establishment, we consider that the major weaknesses in the current operation of the Act can be addressed through amendments to its implementation. What is needed is a continued effort by the Home Office to identify ways of simplifying what has become a very complicated project licensing system and, whilst maintaining animal welfare, to reduce the administrative burden currently associated with the operation of the Act.

Q6 What do you think about the information that is available to the public about research involving animals

The ABPI supports the principle of enhancing the flow of information and openness. However we have serious reservations that the current project licence, after removal of personal identifiers and confidential information as identified by the applicant, would not achieve a useful outcome.

We note that while the House of Lords recommended the disclosure of as much information as possible while "specific justification should then be made for each class of information that needs to be kept confidential, such as the identify of researchers and matters of confidentiality and intellectual property", it is critical that applicants can define what should remain confidential. For example, for smaller biotechnology companies, information relating to a new therapeutic area may be commercially sensitive and may cause severe problems if competitors become aware of new areas of research before a new concept is proved and protected. For small biopharmaceutical companies this type of disclosure could severely compromise their future viability.

We believe there is an opportunity to fundamentally review the current project licence application. The licence could then be refined so that it consists of two parts – an upfront explanation of the work required, which excludes details on the applicant, site and confidential information as defined by the company or organisation involved. The second part could include the information required by the ERP to review the application and the Home Office to consider the cost-benefit involved.

The ABPI agrees that the availability to the public of regularly updated, good quality information on what animal experiments are done and why, is vital to create an atmosphere in which the issue of animal experimentation can be discussed productively. Further efforts are required to disseminate accurate and good quality information that provides the necessary details and is couched in language that lay- audiences can understand. The recent establishment of the "Coalition for Medical Progress", an alliance of organisations that share the common aim to ensure the UK continues to lead advances in human and animal medicine, has a goal to explain and illustrate the need and benefits of research involving animals. However, it remains difficult for individual scientists, whether from academia or industry, to publicly discuss what and why they are using animals in scientific procedures when the threat of harassment, intimidation and violence against themselves and their families remain. Continued focus on illegal and intimidatory behaviour by a minority of animal rights extremists by appropriate authorities would help enormously in allowing more scientists to speak publicly on the value of their work.