Anonymous #27

Question 1. What is your view about the use of animals in research?

It is essential at the present time to use animals in the discovery and development of new human and veterinary medicines. Not only is it required by regulatory authorities that the safety of potential new medicines is assessed in animals, but also studies in animals are critical in the choice of compounds that can go on to become medicines to improve the health and quality of life of both humans and animals.

The importance of animals in providing information that can be transferred to humans may be illustrated by the discovery of amlodipine. Before amlodipine, calcium antagonist drugs were used only for the treatment of angina but had the potential to increase mortality in patients suffering from other cardiovascular diseases, such as high blood pressure and heart failure. This was due to the short-acting nature of the compounds available at the time, such as nifedipine. The rapid fall in blood pressure caused by nifedipine would result in severe reflex neurohumoral activation which, if it persisted chronically, could increase the risk of cardiac rhythm disturbances and sudden cardiac death. Amlodipine works in exactly the same way to reduce blood pressure as nifedipine, but it was found in studies on animals that the onset was slow and prevented neurohumoral activation. Consequently, amlodipine is now saving the lives of patients with not only angina, but also high blood pressure and heart failure. The slow onset of amlodipine would not have been discovered without research involving animals, and the world of medicine would not have had such a useful drug.

There have also been examples of *in vivo* data being predictive of efficacy in humans whereas *in vitro* data was not. Fluconazole, an anti-fungal compound, was not active *in vitro* but was extremely efficacious in mice and, subsequently, humans. This finding led to changes in the *in vitro* testing conditions and eventually resulted in a method that improved the ability to identify effective anti-fungal compounds at the *in vitro* stage. However, these methods still do not fully explain why some compounds are so active only *in vivo*, for example fluconazole is the agent of choice in the clinic for Cryptococcus infection, is very active in animal models of infection, but is inactive or at best weakly active *in vitro*. This has been reported by Troke *et al* in Reviews of Infectious Diseases 12 Suppl 3:S276-80 (1990).

A useful review of the predictivity for humans of pharmacological toxicology carried out on animals has been published by Olsen *et al* (Regulatory Toxicology and Pharmacology 32, 56-67 (2000)).

In most cases, such as in the specific examples above, the results of studies in animals can be transferred to man as the integrated physiological systems of animals are like those of humans in more respects than they are different. On occasion there are differences and these may be revealed in unexpected effects of drug candidates when they proceed to testing in humans. However, these effects would occur many times

more often and to a more serious extent if tests were not first carried out using animals.

The use of animals in research may cause pain, suffering, distress or lasting harm. This possibility is a key factor in the UK's legislation (Animals (Scientific Procedures) Act 1986) but would be unacceptable if there were no potential benefit to either animals or humans arising from the research. In every case where the use of an animal is proposed, the anticipated cost *vs.* the potential benefit needs to be specifically argued. This argument needs to be convincing not only to the scientists themselves, but also to others who are not directly involved in the work, e.g. members of ethical review processes or the Home Office Inspector. The question of cost-benefit analysis has been dealt with in detail by a recent report of the Animal Procedures Committee.

Question 2. What are your views about the use of genetically modified animals in research?

Genetically modified animals can be very valuable in reducing the likelihood of seeing differences in responses to drugs between humans and animals, e.g. replacing an animal gene with a human equivalent in order to predict the effect of a potential new medicine on the human target receptor or enzyme within an integrated physiological system. The cost *vs.* benefit argument has to justify the expected benefit against the suffering that may be caused by the genetic modification as well as the possible effect of the compound and any pain, suffering, distress or lasting harm caused by undergoing the experimental procedure. However, there are no additional welfare issues that cannot be covered by appropriate use of cost-benefit analysis. Furthermore, although there may be a perception that all GM animals are phenotypically abnormal, that is far from being the case as most are phenotypically normal.

It is true that GM animals may be considered 'unnatural' from the point of view of being man-made, but it could be argued that in many ways this is not dissimilar to, for example, pedigree livestock and domestic pets. In addition, spontaneous mutant phenotypes are not new and have a similar potential to compromise animal welfare. Nevertheless, they have been used in research for some considerable time and their use has been dealt with effectively by the cost-benefit analysis process. An example of this is the spontaneously hypertensive rat (SHR), which has been used for many years in research and has been key to the discovery of anti-hypertensive medicines.

It is important to note that GM animals in many cases introduce a refinement as the science can become more mechanistic.

Question 3. What is your view about the use of alternatives?

It is now generally considered that the term 'alternatives' applies to all of the 3Rs of Reduction, Replacement and Refinement.

All scientists should consider the use of alternatives when proposing an animal experiment, at the same time as considering the cost-benefit argument. This aspect should be, and is, an integral part of the Ethical Review Process in the UK.

More research into alternatives would be desirable, however it should be appreciated that progress is continually being made as biology advances and the knowledge gained from both molecular biology and physiology are applied to research paradigms. It would not be productive to dissociate research into alternatives from the general progress made in understanding biological systems: 'Alternatives' is not a discipline in its own right and a multi-disciplinary approach will maximise progress. In this respect it is important to note that the vast majority of alternatives now in use were developed within the scientific community, as part of the ongoing search for 'better' ways of performing the science. Specific examples of this in the pharmaceutical industry would include computational chemistry and high throughput screening. The amount of money actually devoted to 3Rs research is therefore normally grossly underestimated.

Within this question of the consultation document, a separate issue has been raised with regard to the duplication of experiments, as any duplication without a scientific justification would mean an unnecessary increase in numbers of animals used. However, because of the vast number of variations in chemical structure, the possibility is extremely remote of two pharmaceutical companies working on exactly the same chemical entity and therefore of duplicating experiments on the same compound. In any event, new chemical entities are patented at an early stage in the research process. Therefore, within the pharmaceutical R&D process, duplication of experiments on animals is highly unlikely to occur. It may, however, be necessary to repeat experiments to validate previous results, take account of new variables, or where an existing compound is used as the control compound in an experiment. In all of these cases, the cost-benefit analysis would apply.

For all experiments, a peer-review literature approach is adopted. However, in some cases, insufficient information may be provided in papers published in scientific journals, often as required by the editor. It is essential that the published information, particularly in the materials and methods section, is sufficiently detailed. Adequate explanation of any refinements carried out in experimental protocols should also be required.

Question 4. What is your view about ethical issues relating to the use of animals in research?

Within the UK, society in general has made the decision, in the form of the UK's enabling legislation, that animals may be used in research. Those companies, universities, other institutes and individuals carrying out research involving animals therefore work within that ethical framework. Each of these organisations or individuals will then make their own ethical judgements.

It would be difficult to argue that animals should share the same moral status as humans. Equally there will be seen to be differences in moral status between different species of animals, taking account of the neurophysiological capacity and how their ancestry *vis a vis* man is perceived. However, regardless of this, society and individuals have a responsibility to use animals in the most humane way possible. Within research, the cost-benefit analysis is the practical application of this.

It is difficult to tell whether animals experience pain and suffering in the way that we do. It is generally accepted that most vertebrates and perhaps some invertebrates experience pain, however suffering and distress are more difficult to determine and happiness is probably a specifically human concept. These are all aspects that have to be considered within the cost-benefit analysis when deciding to what extent animal welfare may be compromised by an experiment.

Question 5. What is your view about the UK regulations on research involving animals in the UK?

The current UK legislation provides a robust legal framework and an appropriate level of protection for animals used in research. However, there is an unnecessary amount of detail and bureaucracy involved in the process. This could be reduced and the application process simplified without detriment to animal welfare. This aspect was commented on in the recent House of Lords Report, which considered the UK should aim for the best and not the most stringent legislation. There is no doubt that some research has already moved abroad purely because of bureaucratic factors building in unacceptable delays. This must be addressed, not only to protect the scientific base in the UK, but because animal welfare standards in research in the UK are as high, if not higher, than anywhere else in the world.

However, of greater importance than the legislation itself is the attitude towards animal experimentation within a company. This is normally termed the 'culture of care' and is based upon all involved acknowledging their strong personal responsibility to the animals they are using or which are under their care. Factors that will encourage a good 'culture of care' include an active community of peers who exchange knowledge and information, good understanding of animal needs and active attention to housing and husbandry, confidence in the robustness and efficiency of the ethical review process, respect for the relevant legislation, provision of training opportunities, and the support and encouragement of senior management.

Question 6. What do you think about the information that is available to the public about research involving animals?

Adequate information on the use of animals in research should be made available to the general public to enable them to make their own moral judgements about the research carried out and how the animals have been used. A considerable amount of information in the form of numbers of animals used is already provided in the Home Office annual statistics, however numbers *per se* are far from helpful and may only confuse and provide scope for mis-interpretation. The presentation of these statistics is the subject of a current consultation by the Animal Procedures Committee.

Information is also available on regulatory websites, such as those of the EMEA and the FDA, however this information is neither particularly accessible nor understandable for members of the general public.

It has been proposed by the ABPI that the current project licence application form should be revised so that non-confidential information, i.e. not compromising personal security or commercial/academic confidentiality, may be easily extracted and published on the Internet. This would probably be the most effective way of better informing the public, however it should proceed in conjunction with other initiatives, such as that of the Coalition for Medical Progress, so as to broaden the level of public understanding as to how animals are being used and to balance this against the benefits to human and animal health that accrue. Unfortunately, the activities of a small number of extremists have deterred scientists from speaking openly about their work and it is essential the activities of these extremists are controlled by sufficiently robust legislation and the effective application of that legislation by the Police and the judicial system.