

ANNEX

REPORT BY THE ANIMAL PROCEDURES COMMITTEE ON THE USE OF NON-HUMAN PRIMATES UNDER THE ANIMALS (SCIENTIFIC PROCEDURES) ACT 1986: ANALYSIS OF CURRENT TRENDS WITH PARTICULAR REFERENCE TO REGULATORY TOXICOLOGY

**Government Response by Andy Burnham, MP, Parliamentary
Under Secretary of State for the Home Department**

Introduction

Under the terms of the Animals (Scientific Procedures) Act 1986 ('the 1986 Act'), non-human primates, together with some other sensitive species, are given special protection and can only be used where animals of no other species are suitable. The majority of procedures that involve the use of primates are conducted as part of the regulatory testing designed to ensure the safety of pharmaceuticals.

The Government recognises that the use of non-human primates in animal experiments is an issue of public interest and concern. We also recognise that the responsible, limited use of non-human primates for experimental and other scientific purposes still plays an essential part in producing new knowledge and insights that underpin advances in healthcare and bring other benefits not currently achievable by other means.

There is no immediate prospect of an end to this use whilst the benefits to humans, animals and the environment outweigh the costs to the animals involved and until there are suitable alternatives available. In the meantime the Government remains committed to ensuring that non-human primates are only used where it is considered fully justified and to ensuring that the highest standards of animal welfare are applied.

A great deal of time and thought has gone into the Animal Procedures Committee's report on the use of non-human primates. I am grateful to the Committee for the advice that it has provided on this issue. The report has been widely read in the scientific and animal welfare communities. It has succeeded in moving the debate forward by raising many points and highlighting issues that will doubtless serve to stimulate and shape further discussion on the use of non-human primates in scientific procedures.

In responding to the report, I have not attempted to address every point made in the report. Instead, I have thought it best to set out my response against the fourteen principal recommendations presented by the committee in Chapter five of the report (entitled "Conclusions and Recommendations and the way forward"). I hope that this approach proves helpful and addresses the key issues the committee has sought to tackle.

By way of introduction, I can report that recommendations 1, 2, 3, 5, 6, 8, 9, 10 and 11 have been implemented either fully or in part since the date of publication and that

recommendations 4, 7, 13 and 14 reflect existing practice. My comments on the APC's detailed recommendations are as follows.

Recommendation 1

We recommend that the Secretary of State convenes an appropriately resourced forum for all interested stakeholders to address the issues and questions this report contains, to review the recommendations, and to progress these.

Response

This recommendation was accepted in the Government's interim response to the Committee's report in June 2003 (Annex A). A stakeholder forum was convened in January 2004 and a report of the event was subsequently published at the end of March 2005 (Annex B). The views expressed by stakeholders at the forum and the further comments received following publication of the report of the event have been invaluable in informing my response to the remainder of the Committee's recommendations.

Recommendation 2

We believe that the development and implementation of non-animal alternatives to replace the use of non-human primates must be accepted within industry and the international regulatory arena as a high priority goal, which requires immediate and dedicated attention.

Response

I note that the Committee confirmed at the stakeholder forum that this recommendation was not intended to suggest that the development and implementation of reduction and refinement alternatives is not currently seen as a high priority goal. The forum also noted that the commercial sector currently provides the majority of the resources deployed to make progress in this area. There was also concern at the forum about raising expectations that non-human primate use will decrease in the near future, and about losing focus and momentum on reduction and refinement if replacement is seen as the sole goal.

I agree that, although replacement may be the eventual goal, there are no quick wins in sight, and that progress must be made with reduction and refinement in the meantime. Since the publication of the Committee's report and the forum, the Government has established the National Centre for the Replacement, Reduction and Refinement of Animals in Research (NC3Rs) to provide additional focus to work on the identification and development of alternatives to the use of animals in scientific procedures and testing. The NC3Rs has identified the use of non-human primates as an immediate priority.

In recognition of this, its current programme of work includes a number of initiatives aimed at applying the 3Rs in this area of animal use. The NC3Rs' programme includes funding research, convening and co-ordinating working groups, symposia and workshops, and producing training material. In particular, the NC3Rs together with the Association of the British Pharmaceutical Industry (ABPI) is reviewing and challenging the use of primates in drug discovery and development and through this initiative aims to identify ways of minimising primate use and

enhancing the implementation of the 3Rs in this area. In addition, these issues are also with the scope of work being done by the Inter-Departmental Group on the 3Rs, which the Home Office leads.

We believe that these developments, which post-date the publication of the Committee's report, are a significant step towards satisfying the terms of this recommendation.

Recommendation 3

We recommend that the Home Office continues to pursue the issue of species selection and the justification for the use of primates with the relevant regulatory authorities. Since regulatory toxicology operates at supra-national levels, we encourage the relevant groups, bodies and/or competent authorities to take forward our recommendations in the European and international regulatory arenas.

Response

The stakeholder forum understood that the thinking behind this recommendation was that pharmaceutical companies often used primates for reasons other than scientific necessity, but it was not clear to participants what the evidence for that view was. Nevertheless, the forum supported the aspiration expressed in the recommendation.

We also recognise the Committee's concerns in this area and that in order for its aspirations to be achieved efforts need to be made at national and international levels. We are pursuing these concerns through the Inter-Departmental Group on the 3Rs (IDG3Rs). Indeed the Inter-Departmental Group is already one of the main means we have to ensure that opportunities to promote good animal welfare, good science, and sound regulatory decisions are identified and progressed, particularly at the international level. In addition, the licensing process will continue to ensure that species selection is based upon scientific justification.

Recommendation 4

The Home Office should insist that a full range of in vitro toxicokinetic/metabolism screening be done before, and used to assist in, the selection of a second (non-rodent) species for drug safety evaluation.

Response

I understand that, when producing their report, the Committee believed that there are occasions when irrelevant work is done, but that this was not supported by the experience of the representatives from industry and UK regulators present at the stakeholder forum. Those participants confirmed that background studies already assist and are used to inform and justify species selection to ensure that the species used are as relevant as possible to the specific test material and its intended use. I am happy to provide the assurances sought by the Committee that this is the current Home Office requirement. It is implemented through the project licensing system under the 1986 Act as part of the measures ensuring that a clear scientific justification for the use of primates is the key determinant in every case where their use is proposed.

Recommendation 5

We strongly recommend government support for the concept and practice of human tissue donation for research. We urge the Minister to progress this recommendation in discussion with his ministerial colleagues in relevant departments particularly the Department of Health.

Response

This recommendation was accepted by Bob Ainsworth in the Government's interim response to the Committee's report provided in June 2003 (Annex A). As the issue does not fall squarely within any Minister's area of lead responsibility, although a number have an interest from different perspectives, Bob Ainsworth wrote to the Government's Chief Medical Officer, whose remit cuts across several of the key departments concerned, asking him to take it forward.

Recommendation 6

The availability of animal tissues for comparative in vitro studies should be improved. We urge the pharmaceutical industry, the Home Office and ethical review processes to promote in-house tissue sharing and establish tissue banks.

Response

I understand that some establishments already have effective methods of in-house distribution of tissue and that scientists present at the forum gave examples of current good practice. We agree that in-house tissue sharing represents good practice. Although we cannot mandate it, we have drawn the Committee's recommendation to the attention of all Designated Places. We will feed back to the Committee any progress reported to us as result.

Recommendation 7

The use of highly sensitive analytical methods to provide pre-phase human pharmacokinetic data should be further developed and resources provided to move the technologies from the research phase to the stage where they can be routinely used. Early microdose studies in human volunteers should be encouraged by governments, the EU, ICH, clinical research companies and the drug industry.

Response

The stakeholder forum saw this recommendation as reflecting current practice and trends to incorporate technical progress into drug discovery and development. However, micro-dosing currently has significant technical limitations, and its predictive value has not been established and there is an on-going debate about the ethical and technical acceptability of this approach to early human studies.

The use of these methods would not guarantee an absolute reduction in animal testing. Microdosing in man could help to avoid the use of animals (rodents and primates) in testing by eliminating compounds with poor pharmacokinetic properties at an early stage from the discovery/development cascade. However, this might lead to a greater number of (better) candidates being tested, which would require increased use of animals both for preliminary toxicity data (ahead of microdosing) and subsequent regulatory safety assessment. The brunt of the additional testing burden would be borne by rodents rather than primates.

The Committee subsequently sought assurances that these developments are being given priority. I am happy to confirm that this issue is being addressed in work being taken forward by the NC3Rs (see recommendation 2) and that regulatory aspects are being taken forward with the IDG3Rs. We will review licensing policy as and when technical progress is made.

Recommendation 8

Validity and necessity should be continuously monitored by retrospective comparison of test data with clinical experience, and the need for studies specifically on primates should be critically assessed before tests are carried out

Response

The stakeholder forum noted that regulators, in routine post-marketing surveillance, and individual manufacturers already carry out retrospective comparison of test data, but that to co-ordinate this and make it openly available on an international scale would be a very big undertaking and would involve substantial investment. The forum also noted that the necessary investment may be difficult to attract, as potential benefits in the form of improved decision making or scientific progress are likely to take some years to become apparent. The Committee recognised this in its supplementary comments and suggested that less resource intensive retrospective assessments could be carried out. These matters may be best considered as part of post-marketing surveillance. I have, therefore drawn this recommendation to the attention of the Department of Health.

Recommendation 9

It is essential to promote the development of comparative species information in biochemical, pharmacological and toxicokinetic databases. We urge the Secretary of State to progress this in discussion with his ministerial colleagues in relevant departments.

Response

The principle underlying this recommendation is the Committee's belief that the use of primates, which are given special protection under the 1986 Act, should always be rigorously justified. However, although species selection is clearly given serious consideration by the pharmaceutical industry, the Primates sub-committee considered, for the reasons set out in chapter 3 of the Committee's report, that the choice is currently insufficiently justified. We share the Committee's concern that the use of primates should always be rigorously justified. Indeed, this is required by the 1986 Act. However, we are not aware of any problems in practice. We will continue to ensure that the appropriate checks are in place through the licensing system and that they are rigorously applied.

Recommendation 10

The predictive value of data from primate studies should be investigated by comparing the results of pre-clinical and clinical studies on drugs that have progressed to clinical use.

Response

I understand that the stakeholder forum concluded that, while such a comparison could provide an indicator of study validity with respect to materials that subsequently make it into humans, simply acquiring the data would not provide sufficient information to critically appraise decisions on whether or not to use primates. An informed choice of second species would have been made before the data was generated, and it would be difficult to determine what the findings might have been if another species had been used. As clinical studies are not designed to produce or evaluate toxic effects in humans, correlation of findings related to toxicity would not be expected. In addition, as the findings in the second species can prevent materials reaching clinical trials, and prior to this many compounds will already have been screened out based on other species' toxicity in vitro/in silico, such a study would also not be informative about the decisions not to proceed to humans taken on the basis of the findings in the second species.

Along with recommendation 8, these matters may be best considered as part of post-marketing surveillance. I have, therefore drawn these recommendations to the attention of the Department of Health.

Recommendation 11

We consider that the granting of 'generic' licences as the primary means of controlling primate toxicity studies is unsatisfactory. The use of primates in regulatory toxicology should be more specifically justified prospectively in order to achieve better oversight of procedures and facilitate a more considered cost-benefit assessment. The local ethical review process should explicitly review the justification for using primates in all types of procedures for each substance tested.

Response

I understand that this issue was discussed at length at the stakeholder forum and that the Committee now accepts that the granting of 'generic' licences, within the meaning intended in their report, is not a practice adopted by the Home Office. Having reviewed our current processes and practices we believe that the checks and balances inherent in the current system of thematic licences are appropriate.

With regard to the role of the local ethical review process (ERPs), I agree that it is good practice for them to take an active interest in the justification for the use of primates in all types of procedures and we have drawn this recommendation to the attention of user establishments.

Recommendation 12

The numbers of primates actually used each year for each project should be reported retrospectively to the local ethical review process, together with the numbers that reached the maximum severity limit for each protocol.

Response

The stakeholder forum noted that this approach has the advantage of allowing a comparison of predicted and actual adverse effects, such as incidence, severity, effectiveness of proposed control measures, and can generate feedback useful in promoting refinement or reduction. We agree that this represents current good

practice and that it is already being done by some ERPs. We have, therefore, commended it to all licence holders.

Recommendation 13

The design and sequence of pre-clinical safety studies needs to be reviewed. We ask the Home Office to consider whether measures need to be taken to prevent overlap of rodent and non-rodent studies, actively discouraging any simultaneous testing in rodents and primates in order to shorten the time course of drug development.

Response

I note that the stakeholder forum felt that this recommendation was based on a misapprehension that unnecessary testing was being carried out simultaneously on primates while rodent tests were being carried out. In practice, and in accordance with licence terms and conditions, no second species testing takes place unless there is adequate pre-existing data and justification. We are satisfied that tiered and hierarchical testing strategies exist and are deployed that prevent the inappropriate or unnecessary use of non-human primates.

Recommendation 14

The opportunities for re-use of primates in pharmaceutical safety assessment as a means of reducing the numbers used should be further explored by the Home Office in conjunction with project licence holders and local ethical review processes, taking into account all of the advantages and disadvantages for individual animals.

Response

The stakeholder forum considered this a sound principle, provided the re-use was responsible.

We already encourage responsible re-use within the letter and spirit of the 1986 Act. Although we cannot require the re-use of animals, we will continue to encourage this practice where it is appropriate and as far as the 1986 Act permits.

**ANDY BURNHAM
Home Office**

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