The **A P C**
Animal Procedures Committee

ANIMAL PROCEDURES COMMITTEE

THE USE OF PRIMATES UNDER THE ANIMALS (SCIENTIFIC PROCEDURES) ACT (1986)
ANALYSIS OF CURRENT TRENDS WITH PARTICULAR REFERENCE TO REGULATORY TOXICOLOGY

DECEMBER 2002

ANIMAL PROCEDURES COMMITTEE
5TH FLOOR, ALLINGTON TOWERS,
LONDON, SW1E 5EB

From the Chairman
Reverend Professor Michael Banner MA Dphil

4/12/02

Dear Mr Ainsworth

ANIMAL PROCEDURES COMMITTEE RECOMMENDATIONS ON THE USE OF PRIMATES UNDER THE ANIMAL (SCIENTIFIC PROCEDURES) ACT 1986

On behalf of the Animal Procedures Committee, I enclose the Committee's report on the use of primates under the Animal (Scientific Procedures) Act 1986, which is an analysis of current trends with particular reference to regulatory toxicology.

I should like, if I may, to draw your attention to the hard work of the members of the APC's Primates Sub-Committee, which considered the issues. The Sub-Committee carried out their work with a great deal of thoroughness and dedicated an enormous amount of time and thought to this report. The Sub-Committee's members are Professor Robin Dunbar (Chair), Professor Christopher Atterwill, Dr Robert Hubrecht, Dr Maggy Jennings, Dr Gill Langley and Professor Alan McNeilly. We were also grateful for the assistance given to the Sub-Committee by Dr Roger Curtis of the Home Office Inspectorate.

The Committee has been to great lengths to formulate helpful, practical recommendations taking into account, as we are required to do, of the legitimate concerns of science and industry and the protection of animals against avoidable suffering and unnecessary use. I hope our advice will prove helpful to your consideration of this difficult subject and I commend this report and its recommendations to you. In particular, I would like to draw your attention to recommendation 1, emphasising the complexity of the issue and the need to engage stakeholders to tackle the unresolved issues raised by the report. I look forward in due course to the Home Office's detailed comments and recommendations.

Yours sincerely

MICHAEL BANNER

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EXECUTIVE SUMMARY

This report has been compiled in the context of the Animal Procedures Committee's (APC) remit to review the use and care of non-human primates under the provisions of the Animals (Scientific Procedures) Act 1986 (ASPA).

It summarises primate use in scientific procedures in the UK over the eleven year period from 1990 to 2000, and attempts to identify any significant trends during that period and likely changes to patterns of use in the future. Since the majority of primate use is in pharmaceutical research and development, particularly regulatory toxicology and other safety assessment procedures, this issue is examined in detail. Other uses of primates will be reviewed by the Primate Sub-Committee at a future date.

The report contains a number of recommendations aimed at reducing primate use and these are summarised below. However, it must be emphasised that this is a complex issue with a multitude of 'players', and that there were many questions and concerns raised during the preparation of the report that remain unresolved. These require further serious discussion with key stakeholders if further progress is to be made. It is recognised that many of the issues discussed and recommendations made refer to some animals, which are not primates.

Statistics of primate use
In the eleven year period covered by this report, 40,659 primates were used in scientific procedures under the ASPA. Most were either marmosets and tamarins (38.16% - mainly the common marmoset, *Callithrix jacchus*) or macaques (59.07% - mainly long-tailed macaque, *Macaca fascicularis*, and rhesus macaque, *Macaca mulatta*). No baboons have been used since 1999. There is no distinct pattern in macaque use over the period covered, but there is a slight downwards trend in number of marmosets used overall.

The major use of primates (around 72% of the total in recent years) is in toxicology procedures, including those for pharmaceutical safety and efficacy assessment. Most of these procedures are carried out to fulfil legislative requirements. Macaques appear to be the primates most commonly used in toxicology, and a greater percentage of macaque use is for toxicology than is the case for marmoset use. No baboons have been used in toxicological procedures for the last five years.

The majority of project licences using primates, granted in the last 5 years, have been assessed prospectively to be in the moderate severity banding.

The use of primates in regulatory toxicology
The reasons that primates are used in regulatory toxicology and other pharmaceutical safety studies are examined. The main issues discussed include: the requirement for a second species in regulatory toxicology; species selection (including scientific considerations, practical issues, regulatory influences and ethical concerns); study design and timing (particularly the scheduling of rodent and non-rodent studies); alternatives to primate use; and the role of regulatory bodies and their inter-relation with the pharmaceutical industry.

The licencing of regulatory toxicology procedures under ASPA is also discussed. A key question is whether the process of species selection does indeed result in the use of primates 'only when it is fully justified' as required by ASPA, i.e. whether the current system allows an adequate evaluation to be

made of the justification for the use of primates in regulatory studies. The use of 'generic' licences for regulatory toxicology studies is identified as a source of concern, and the need to gain a better oversight and monitoring of procedures that involve large numbers of primates is emphasised.

Future use of primates in pharmaceutical development

Since so much of current primate use is for the development and testing of pharmaceuticals, it is clear that the numbers of primates used in the future will be closely linked to developments in the pharmaceutical industry. The industry's view is that its future lies in developing entirely new classes of neuroactive drugs to combat the increasingly important neurological diseases of old age. Developments resulting from, for example, the human genome project may also have an impact, such that the demand for primates as models in basic research, and in drug development and safety assessment, may actually increase over the next decade or so.

However, there are serious ethical and animal welfare concerns regarding the use of primates in experiments, and considerable public disquiet with regard to such use. These concerns are also likely to increase as more is discovered about their advanced cognitive faculties, complex behavioural and social needs, and the difficulties of satisfying these in a laboratory environment.

Summary conclusions and recommendations

The drive to produce pharmaceuticals for human benefit, and the associated primate use that this currently entails, clearly conflicts with the desire to minimise and eliminate the use of primates in experiments, and thus with the APC's stated goal of "minimising, and eventually eliminating primate use and suffering". If the predictions of an increased demand for primate use are realised then this conflict becomes more intense. The APC believes it is extremely important to recognise this conflict,

and *absolutely essential* to more determinedly and actively seek ways of resolving it. However, it must be recognised that this is a global issue, which needs to be tackled on an international basis.

If, as seems likely, the vast majority of primate use continues to be in the development and safety assessment of pharmaceuticals, then it is clear that this is where the focus needs to be if major reductions in use are to be achieved. We recognise that progress has already been made in this respect and that some of our recommendations reflect existing practice. However, we believe that significant in-roads could still be made in reducing the numbers of primates used in toxicology if there was sufficient international commitment to this goal. We believe it is essential to establish such a commitment, together with a mechanism that will ensure that primates are only used when the objective of ensuring the safety of human subjects cannot be achieved by any other means. In such cases, every effort should be made to ensure that safety evaluation programmes are designed to minimise the numbers of primates used, reduce suffering, and eliminate the possibility of wastage of animals.

The Committee's recommendations are set out in full in Section 5 of the report. A brief summary of these is given below, but it is essential that they are reviewed in the context that they appear in the full report.

Taking the issues forward

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.

Development of alternatives

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. To achieve this goal, involving the pharmaceutical industry (ABPI, EFPIA and others) regulatory bodies (EMEA, USFDA and Japanese Ministry of Health and Welfare) and scientific societies (e.g. the British Toxicology Society and the Society of Toxicology). The International Conference on Harmonisation (ICH) should adopt a co-ordinating role in the development of this strategy.

Species selection and associated issues

Recommendation 3

It is essential to instigate a detailed examination of regulatory policies on species selection in toxicity testing (requiring regulators to justify their need for primate data). This should incorporate the points and questions identified in Section 3.2 and 3.3 of this report. The aim must be to introduce a harmonised, consistent, scientifically justified policy for species selection both nationally and internationally.

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.

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.

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.

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.

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.

Validity and necessity

Recommendation 8

The use of primates in the safety assessment of pharmaceuticals can clearly only be justified under current UK legislation if the data obtained are both valid (relevant for humans) and necessary in order for a safety assessment to be made. 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. The international pharmaceutical industry, in collaboration with regulatory authorities, has the major responsibility, and the necessary access to data, to make these crucial assessments."

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.

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.

Regulatory toxicology and the ASPA

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.

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.

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.

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.

CHAPTER 1

INTRODUCTION

This report was prepared by the Primate Sub-Committee of the Animal Procedures Committee (APC) **and has been endorsed by the full committee**. It forms part of the Sub-Committee's remit to review the use and care of primates under the provisions of the Animals (Scientific Procedures) Act 1986 (ASPA). This remit was developed during the APC's ten-year review of the ASPA when it was agreed that the Primates Sub-Committee should:

"take on a more strategic role, particularly given the current concern about the arrangements for transporting primates to the UK and the fact that the European Commission has turned its attention to all aspects of the use of primates in scientific procedures. The Sub-Committee would lead on issues such as:

i)   *"how to minimise, and eventually eliminate, primate use and suffering;*

ii) *acquisition of primates (availability of animals in the UK, the suitability of overseas sources and transport arrangements);*

iii) *housing and care;*

iv) *the use of wild-caught primates (should this be allowed at all and, if so, what should constitute the specific and exceptional justification needed if such use if to be authorised); and*

v)   *the use of primates in regulatory toxicology."*

(see Appendix F, Chapter 3, Annex 2 para 5 of the APC Annual Report for 1997, Home Office, 1998b),

The statement about eliminating the use of non-human primates (hereafter referred to as primates)

in experimental procedures has attracted concern among some users. However, we consider this to be a justifiable goal because it requires those who use primates to justify their need to use them, rather than to assume that such use is acceptable, and it should act as a stimulus to seek alternatives. We consider this to be especially appropriate in the case of primates because with their markedly more advanced cognitive faculties compared to other animals, and the difficulty in satisfying their behavioural and social needs in a laboratory situation, experimental situations are likely to be more stressful for them. However, it is recognised that many of the issues discussed and recommendations made refer also to some animals, which are not primates.

1.1 Aims of the report
The Sub-Committee believed that a useful starting point for its deliberations would be to review and summarise current primate use in the UK and to identify any significant trends and likely changes to patterns of use in the future. This was the initial aim of this report. However, it became obvious that the majority of primates are used in pharmaceutical research and development including regulatory toxicology which accounted for the largest single category of use. The Sub-Committee decided to focus attention on regulatory studies, drawing out a number of conclusions and recommendations with regard to what could be done to reduce primate use in this area.   Other uses of primates will be examined by the Sub-Committee at a future date.

1.2 Method of working

1.2.1 Statistics on primate use

Information on primate use in scientific procedures was obtained from the annual statistics published each year by the Home Office (HO). These provide details of the numbers of animals of each species (or group of species) used for the first time each year, together with a breakdown of the broad categories of types and purposes of the procedures carried out. They are based on annual returns made by licence holders at establishments designated under ASPA, and are thus a complete account of all animals used in those scientific procedures that fall under the remit of the Act. It should be noted that the annual statistics are necessarily retrospective. Thus, for example, the statistics for the year 2000 were published in 2001. (Note, full details of what is contained in the statistics and how the information therein is obtained, collated and presented are contained in HO 2001a).

This report presents a summary of the information available in the HO Statistics for the eleven-year period from 1990 to 20001 (see section 2). The numbers and types of primates used, and the main purposes for which they were used are described and any obvious trends identified. Only the statistics for mainland UK are presented here - the statistical returns for Northern Ireland have not been included. This is because no primates were used in Northern Ireland between 1990 and 1994, and post 1994, primates are not listed as a separate taxon and none have been used.

1.2.2 Use of primates in toxicology and possible future trends

Details of the use of primates in toxicology (section 3) and discussion of the likely future usage of primates in scientific procedures (section 4) is based partly on discussions with: Dr Krys Bottrill (who in 2000 carried out a review for DG Environment of the use of primates within the EU, in particular their use in regulatory toxicology and

related biomedical areas); representatives from the Association of British Pharmaceutical Industries (ABPI); and individual *in vitro* and *in vivo* toxicologists. A recently published report: The Use of the Marmoset in Pharmaceutical Toxicology prepared by Drs D. Smith, P. Trennery, D. Farningham and J. Klapwijk for the ABPI (Smith et al. 2001) also provided much useful information. In addition, members of the sub-committee have visited contract research laboratories using primates in regulatory toxicology, and some members have direct experience in this field.

The Sub-Committee has also been able to benefit from work the Boyd Group were doing on primates at the same time as we were preparing this report. The Boyd Group produced a series of five detailed discussion papers covering issues such as the moral status of primates, a comparison of the welfare considerations with respect to the use of marmosets and macaques, and the use of primates in regulatory toxicology (Boyd Group, 2002). The RSPCA were also preparing a detailed report on the trade in primates for research and testing and provided additional analysis of the HO Statistics (Prescott, 2001).

We are grateful to all the individuals and organisations concerned for taking the time to speak to the Sub-Committee and/or allowing us early sight of their documents.

CHAPTER 2

ANALYSIS OF PRIMATE USE 1990 - 2000

2.1 Total numbers of primates used each year

A total of 37,317 primates were used in scientific procedures during the eleven-year period covered in this report. The total number used per year has remained fairly constant, averaging 3,392 animals, though usage has varied by around 16% either side of this mean from year to year (Figure 1). Overall, there is no obvious trend (either increasing or decreasing) in the numbers of primates used per year during the 11 year period, although there has been a decline since 1994.

2.2 Species used

The tables presented in the HO annual statistics currently list primates under four main headings: Prosimians, New World monkeys, Old World monkeys and Apes. Further subdivisions into nine different groups (generally taxonomic families) are provided in the breakdown of procedures and of animals by primary purpose (Tables 1 and 1a of the Statistics), by field of research (non-toxicology - Tables 5 and 5a of the Statistics), and by toxicological purpose (toxicology - Tables 10 and 10a of the Statistics). These subdivisions also appear elsewhere in the Statistics.

Note that the nine family groups may each comprise several related species and that these are not identified individually. Generally primates listed in the family group 'marmosets and tamarins' are common marmosets (*Callithrix jacchus*); those in the family group 'squirrel, owl and spider monkeys' are common squirrel monkeys (*Saimiri sciureus*); the macaques are either long-tailed macaques (Macaca fascicularis) or rhesus macaques (*Macaca mulatta*); and the baboons are olive baboons (*Papio hamadryas anubis*).

Table 1 below gives the numbers of prosimians, marmosets and tamarins, other New World monkeys (e.g. squirrel, owl and spider monkeys), macaques, baboons, and other Old World monkeys (e.g. vervet monkeys) used in scientific procedures each year for the period 1990 to 2000. There is a significant decline in the numbers of prosimians, New World monkeys other than marmosets and tamarins, and baboons over time. The decline in the use of these species probably reflects the costs of housing species that are relatively more ecologically specialised (prosimians and many New World species) and the rising cost of buying and housing larger bodied primates such as baboons. There are few captive-breeding centres for baboons, and the

Figure 1.
Total number of
primates used
each year,
1990-2000
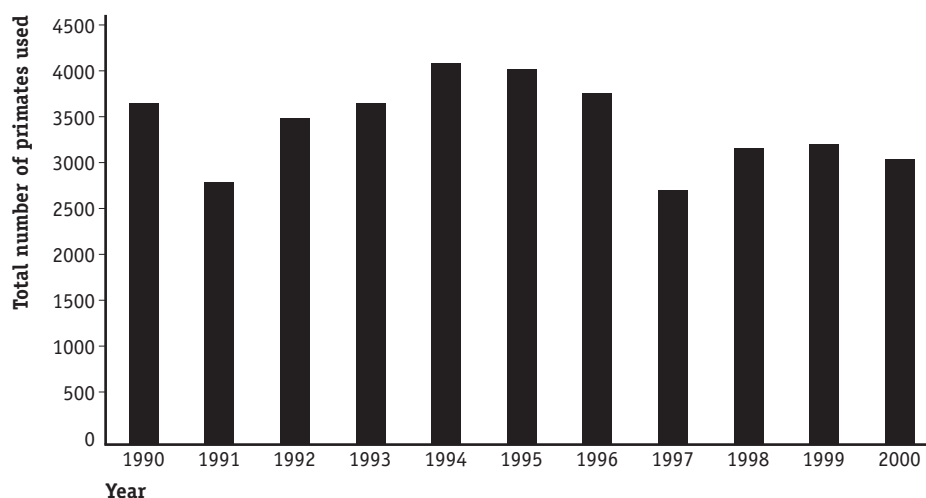
desire for purpose-bred, disease-free, more homogeneous animals may also have been a factor, as may the restriction on the use of wild-caught primates under the UK legislation in 1995.

The use of marmosets and tamarins shows a sharp increase in 1993, but a decline in numbers used thereafter. The numbers of macaques used fluctuates from year to year and there is no consistent pattern of increase or decrease.

Note that the number of each species given is the number of individuals animals on which procedures were carried out *for the first time* in any one year. In some cases, where animals are on ongoing use, the number actually undergoing procedures during the year is slightly greater than that given. Thus, in the case of squirrel monkeys, although 0 *animals* are recorded for 1997, 1999 and 2000, in actual fact 14, 24 and 26 *procedures* respectively were carried out on squirrel monkeys.

2.3 Purposes of procedures and numbers of primates used in each category

2.3.1 Classification of procedures
The Home Office's annual statistics comprise a series of tables which classify the species of animals used and the purposes of that use in a number of ways. The initial classification divides the procedures into a large number of different categories according to the scientific discipline and/or purpose of the study (see Home Office 2001a). The procedures are subsequently broken down further by different criteria, for example with respect to whether they were carried out for a legislative purpose.

Until 1994, the initial breakdown was according to the body system being studied (e.g. nervous or mental, reproductive, skin, bone) with fundamental and nearly all applied research listed together. Some applied studies such as safety testing and surgical technique were listed separately (see Table 2). After 1994, some of the tables in the statistics were changed to try to provide more detail of the uses to which animals were put. The body system classification was expanded, toxicology and non-toxicology procedures were separated more clearly with the latter divided according to the purpose or discipline/field of research (e.g. anatomy, genetics, pharmacology). To simplify this for the purposes of this report, we have summarised the categories into five for 1990-1994 and nine for 1995-2000, as shown in Table 2.

Table 1. Numbers of each family group used in scientific procedures, 1990-2000	Year	Prosimians	Marmosets and tamarins	Other New World monkeys	Macaques	Baboons	Other Old World monkeys
	1990	23	1252	52	2065	238	0
	1991	37	1207	19	1323	177	1
	1992	0	1182	19	2023	210	10
	1993	0	1873	24	1699	8	0
	1994	0	1866	9	2215	45	0
	1995	0	1544	8	2403	80	0
	1996	0	1330	18	2410	28	0
	1997	0	1004	0	1658	17	0
	1998	0	849	8	2237	4	0
	1999	0	1073	0	2118	0	0
	2000	0	1060	0	1891	0	0

Table 2. Classification of scientific procedures – abbreviated terminology	This Report	Home Office Statistical Returns
	1990-1994	
	Body-system studies	All body-system studies (fundamental and applied[a])
	Clinical science	Diagnosis, surgical technique
	Safety	Safety[b]
	Production	Production
	Education	Education
	1995-2000	
	Biology	Anatomy, biochemistry, pathology, microbiology, parasitology, genetics, molecular biology, nutrition*, zoology*, animal science*, ecology*, animal welfare*, tobacco*, alcohol*, other
	Physiology	Physiology
	Pharmacology	Pharmacology
	Immunology	Immunology
	Psychology	Psychology
	Clinical	Therapeutics, clinical medicine, clinical surgery*, dentistry*, cancer research
	Pharmaceutical R&D†	Pharmaceutical R&D†
	Toxicology research	Toxicology research, tobacco safety*, medical device safety, method development, other
	Toxicology testing	all topics listed under General+/pharmaceutical safety/efficacy evaluation

a) includes development, safety and efficacy testing of pharmaceuticals
b) toxicology which is not related to either fundamental research or the solution of medical or veterinary problems (e.g. pesticides, food additives)
* No primates were used in research under these categories during the sample period
† Pharmaceutical research and development
+ including safety testing for non-pharmaceuticals

Despite the apparent detail in the HO statistics, it is difficult to define, and hence analyse, the exact purposes for which animals are used. This is partly because the classification of procedures is based on a 'self-classification' by users. Thus, for example, studies that involve recording from single brain cells could legitimately be classified as psychology, physiology or anatomy, according to the inclination and/or disciplinary affiliation of the licensees concerned. Although users follow a flow chart given at the back of the annual statistics on how procedures should be classified (see Home Office 2001a) there will inevitably be a certain amount of subjectivity in this classification.

2.3.2 Numbers of primates used for each purpose

A breakdown of the numbers of primates used in the different categories of scientific procedure during the two periods 1990-1994 and 1995-2000 is given below in Tables 3 and 4 respectively. A detailed comparison of the purposes for which primates were used, and analysis of trends in their use, across the whole period is not possible because of the change in the way procedures were classified from 1995.

For the period 1990 to 1994, it is not possible to ascertain the number of primates used for toxicity testing. This is because the only analysis of *animal numbers* that is given incorporates pharmaceutical safety and efficacy testing into *body system studies*,

which also includes fundamental studies and some non-toxicological applied studies. However, the more detailed analysis of *scientific procedures* indicates that 37.1% of all procedures on primates during this period were for toxicological purposes. Of these toxicology procedures, 98.9% were carried out in response to legislative or regulatory requirements. The great majority (95.5%) of toxicology procedures were for the safety and efficacy testing of medical/veterinary products, and most (92.6%) of these were conducted to satisfy specific legislation or regulations.

From 1995-2000, the number of animals used in toxicological procedures is recorded as well as the number of scientific procedures. The majority (72.3%) of the 19,740 primates used in this period were used in toxicology, which accounted for a roughly constant proportion (67.7% to 76.5%) of each year's total number of primates. The majority of toxicology procedures were associated with *regulatory toxicology*. Thus, for the period 1995 to 2000, the vast majority (94.7%) of toxicology procedures on primates were carried out in response to legislative or regulatory requirements.

Table 3. Number of primates used per year for each type of scientific procedure, 1990-1994		1990	1991	1992	1993	1994
	Body system studies	3370	2351	3268	3167	3879
	Clinical science	45	6	4	25	19
	Safety	67	251	19	223	33
	Production	148	120	152	188	204
	Education	0	36	1	1	0
	TOTAL	3630	2764	3444	3604	4135

Table 4. Number of primates used per year for each type of scientific procedure, 1995-2000		1995	1996	1997	1998	1999	2000
	Biology	171	177	110	169	120	75
	Physiology	126	123	145	95	151	158
	Pharmacology	65	80	51	33	59	75
	Immunology	82	199	235	225	142	109
	Psychology	229	139	131	152	98	88
	Clinical	173	80	26	111	38	36
	Pharmaceutical R&D	458	228	126	28	181	153
	Toxicology research	29	54	9	56	72	22
	Toxicology testing	2702	2706	1846	2219	2330	2235
	TOTAL	4035	3786	2679	3098	3191	2951

### 2.3.3 The division between toxicology and non-toxicology procedures

Figures 2-5 show the numbers of primates of each major taxon used in toxicological and non-toxicological procedures between 1995 and 2000.
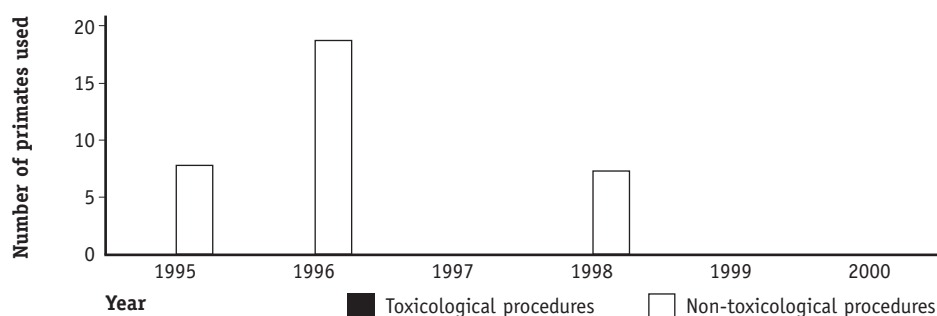
New World monkeys
Of the 6,860 marmosets and tamarins used during this period, 3,816 (55.6%) were used in toxicological procedures (Figure 2). They show a steady decline in usage over time up to and including 1998, with the decline being greater for non-toxicological procedures (see also below). New World monkeys other than marmosets and tamarins (mainly common squirrel monkeys) were used *only* in *non-toxicological* procedures during this period, with use being variable from year to year, and none being used at all in 1997, 1999 and 2000 (Figure 3).

Figure 2. Number of marmosets and tamarins used in scientific procedures each year, 1995-2000
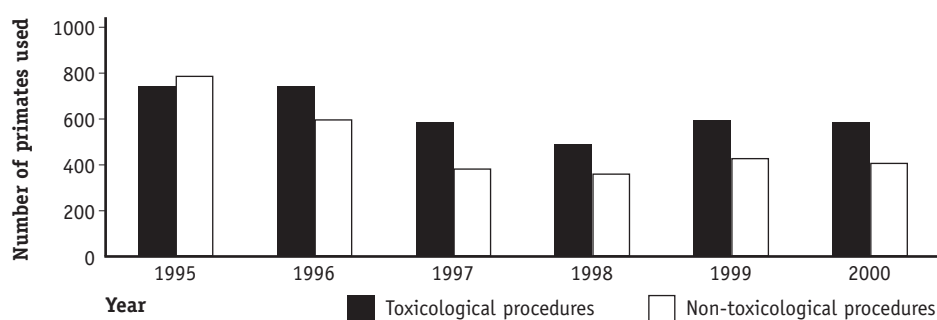
Figure 3. Number of New World monkeys other than marmosets and tamarins used in scientific procedures each year, 1995-2000


Old World monkeys
Of the 12,717 macaques used during this six-year period, 10,384 (81.6%) were used in toxicological procedures (Figure 4).

Relatively small numbers of baboons (157) were used. There was a striking switch from their use exclusively in toxicological procedures (for pharmaceutical safety/efficacy testing) in 1995 to exclusive use in non-toxicological procedures (in immunology research) from 1996 onwards (Figure 5).

Figure 4. Number of macaques used in scientific procedures each year, 1995-1999
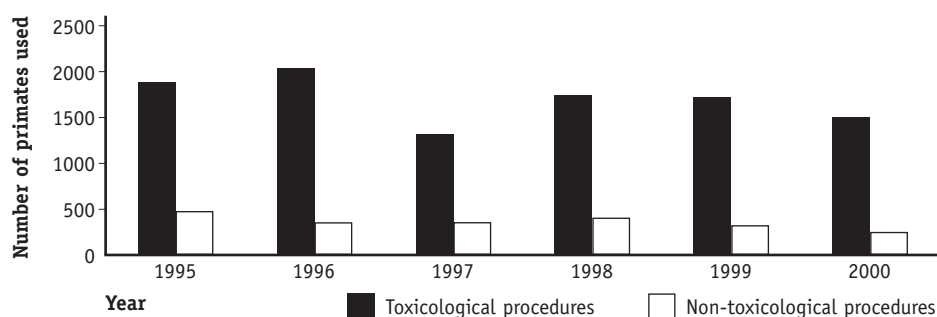
Figure 5. Number of baboons used in scientific procedures each year, 1995-1999
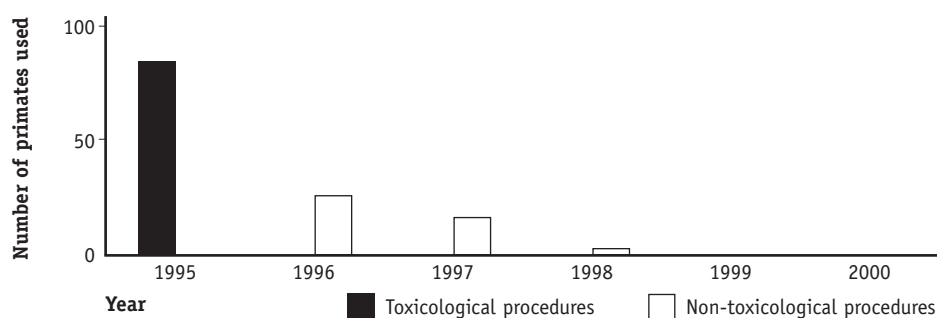
2.3.4 Use of primates in relation to other species in toxicology

There are a number of different species of animals used in toxicology (see Table 10a in the HO statistics). The majority are rodents (mainly rats and mice, but also guinea-pigs, hamsters, gerbils and 'other' rodents), rabbits and birds; but fish, dogs, and 'other' species (including ferrets and pigs) are also used. On average (mean over the six-year period 1995-2000), some 581,884 animals were used in toxicology procedures each year. Rodents made up 83.8%, with primates and dogs representing 0.41% and 0.77% of the total respectively. The use of the latter two species requires special justification under section 5.6 of the ASPA. The numbers of dogs and primates used are shown in Figure 6 and the reasons why they are used in toxicology are summarised in Section 3 of this report.

Figure 6. Numbers of dogs and primates used in toxicology procedures, 1995-2000
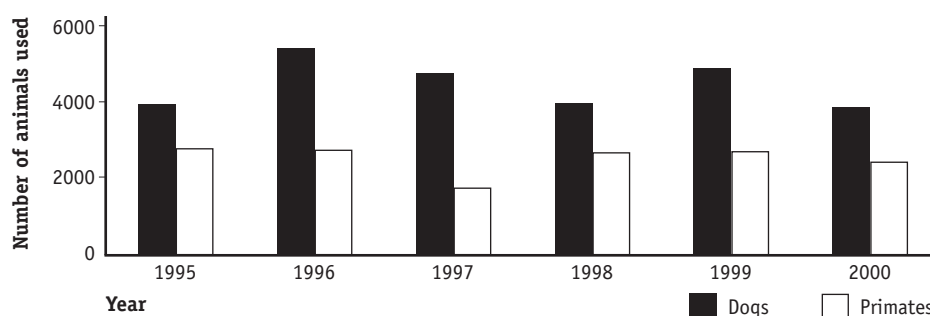
2.3.5 Types of toxicity test

There are eight specific types of toxicity test listed in the HO statistics together with an additional category of 'other tests' for example, safety pharmacology and investigative toxicology. The different tests are shown in Table 5, which also gives the numbers of procedures carried out on each of the individual types of animal used for the year 2000. Primates are used for acute non-lethal, sub-acute non-lethal and sub-acute limit setting tests, subchronic and chronic tests, toxicokinetics and 'other' tests. These are the same categories of tests for which dogs were used in that year.

Table 5: Species used in toxicity testing of pharmaceuticals in Britain, showing numbers of scientific procedures carried out on the different species in the year 2000* (Home Office 2001a)	Type of test	Number of scientific procedures, involving:						
		Rodents	Rabbits	Dogs	Non-human primates	Birds	Fish	Other species
	Acute lethal	47670	-	-	-	-	-	-
	Acute & subacute non-lethal[a]	53354	539	1750	1177	519	2202	357
	Subchronic & chronic (i.e. longer term) tests	14114	330	1162	594	-	-	-
	Carcinogenicity	9662	-	-	-	-	-	-
	Mutagenicity	4867	-	-	-	-	-	-
	Reproductive toxicity	15727	2641	-	-	-	-	-
	Eye and skin tests	2014	268	-	-	-	-	30
	Toxicokinetics	14852	144	356	361	-	133	231
	Other tests	64611	15037	762	392	11289	4960	2586
	TOTAL	226871	18959	4030	2524	11808	7295	3204

a Includes acute non-lethal (27), sub-acute limit setting (454), and sub-acute (696)

* This is only a rough guide to the numbers of animals used, because sometimes more than one procedure is carried out on the same animal. Table taken from Boyd Group (2002)

2.3.6 Level of severity

It is important to know the numbers of primates used in procedures but also crucial to understand the amount of suffering to which they are subjected. The only way to gain a comprehensive understanding of this is to read the project licences and see the research in progress. It is very difficult from the published information to get any sort of feel for what individual animals experience. Projects are classified by the Home Office according to whether their severity is predicted to be mild.

moderate, substantial or unclassified (carried out under terminal anaesthesia). This represents the *overall severity banding* of the project, and the number of projects in force in each category (for all species) is published in the Annual Statistics. The APC Primate Sub-Committee receive a breakdown of the categories of projects specifically involving primates, although this information is not published in the public domain. Table 6 shows the number of projects in each category in the last 5 years.

Table 6: The number of projects involving primates in the UK granted in the last 5 years, according to prospective severity banding	Severity Level	Number of projects				
		1997	1998	1999	2000	2001
	Mild	10	2	6	3	5
	Moderate	15	18	12	13	7
	Substantial	0	0	1	2	0
	Unclassified	0	0	0	2	1
	Total	25	20	19	20	13

The severity banding of the project reflects the overall cumulative suffering to be experienced by each animal (see HO Guidance Notes 5.40 – 5.49 (2000b)), but it is not in itself very informative. More useful in understanding the level of suffering animals are likely to experience, is the classification of the *severity limit* of the individual experimental protocols to which the animals are subjected. An individual project may contain many different protocols at different levels of severity and although the APC will be aware of the protocols in the projects that come before it, this information is not collated and published. (Note, the issue of severity banding is being considered by the Committee as part of its work on the cost/benefit assessment).

All projects for toxicology and general pharmaceutical safety assessment are prospectively banded for severity as mild or moderate. The protocols within these projects are given mild and moderate severity limits, with a small number of protocols carried out on animals under terminal anaesthesia and therefore classed as 'unclassified'.

2.3.7 Summary points

It would be statistically inappropriate to claim unequivocal evidence of 'trends' in primate use within the UK on the basis of the information in the tables and figures above, particularly since the current categories of purposes in the annual statistics have been in use for only six years.

Nonetheless, the overall pattern of use is informative. The main points are summarised below:

- Most of the primates used in scientific procedures are either marmosets and tamarins (38.16%) (note this is mainly the common marmoset, *Callithrix jacchus*) or macaques (59.07%), (mainly long-tailed macaque, *Macaca fascicularis*, and rhesus macaque, *Macaca mulatta*). There has been a move towards these three species and away from prosimians, other New World monkeys, baboons and other Old World monkeys.

- The majority of primates (72.3% of the total over the last six years) are used in toxicology procedures, including for pharmaceutical safety and efficacy assessment. Most of these procedures are carried out to fulfil legislative requirements.

- There is a slight downwards trend in number of marmosets used overall.

- There is no distinct pattern in macaque use over the period of this report.

- In the UK, macaques appear to be the monkeys most commonly used in toxicology procedures - greater numbers of macaques are used in toxicology than marmosets; and a greater percentage of macaque use is for toxicology than is the case for marmoset use.

- No baboons have been used in toxicological procedures for the last five years; and no baboons have been used at all since 1999.

- Slightly more marmosets than macaques are used for procedures other than toxicology.

- The majority of project licences granted in the last 5 years have been in the moderate severity banding.

CHAPTER 3

THE USE OF PRIMATES IN REGULATORY TOXICOLOGY

The major use of primates in the UK is for pharmaceutical safety and efficacy evaluation, with most procedures being carried out for regulatory purposes. Studies are carried out either in-house by pharmaceutical companies, or are contracted out to contract research organisations (CROs). Most studies for regulatory purposes are carried out in CROs.

There were a number of specific issues that arose during our discussions of this particular area of primate use that we considered to be particularly important in relation to the feasibility of reducing primate use, and therefore of particular relevance to the work of the APC. These are summarised below. The Boyd Group have also discussed these issues in their recent papers on primate use (Boyd Group, 2002) and we would recommend the APC Sub-committee's report and the Boyd Group documents be read in conjunction for a wider appreciation of all the various perspectives.

The major question addressed in this section is how particular animal species are selected for use in pharmaceutical safety studies, and whether the process of species selection does indeed result in the use of primates 'only when it is fully justified' as required by ASPA. The way in which regulatory toxicology studies are licensed under ASPA is then examined, with a view to assessing whether the current system allows an adequate evaluation to be made of the justification for the use of primates in regulatory studies. In addition, questions of study design (particularly the scheduling of rodent and non-rodent studies), the choice of particular primate species, and the re-use of animals are addressed.

3.1 The requirement for tests in two species

The regulatory requirement for the use of animals in pharmaceutical safety evaluation is based on the prevailing majority opinion of toxicologists and regulators that tests on animals are, scientifically, an essential component of the safety assessment process. The regulatory authorities (notably in the USA, EU and Japan) and the regulations they implement, explicitly require testing of pharmacological compounds on a rodent species. There is an additional requirement for testing in a *'non-rodent'* species, on the basis that the known species variation makes reliance on tests in one (rodent) species insufficient for approval of clinical trials in humans. In practice, the second species selected is normally either a dog or a primate, although few regulations actually specify that a primate species should be used.

Thus, for example, Annex I of Directive 2001/83/EC 'on the Community code relating to medicinal products for human use', specifies that acute toxicity studies *"..must be carried out in two or more mammalian species..unless a single species can be justified"*. Significantly, it states that repeated dose toxicity tests *"shall be carried out on two species of mammals one of which must be a non-rodent"*. Toxicokinetic, pharmacokinetic and pharmacodynamic (including safety pharmacology) data are also required, but no comment on species selection is made in the Directive. ICH guidelines (European Agency for the Evaluation of Medicinal Products 1995), which represent the harmonised approach of regulatory authorities in the EU, USA and Japan, include the same requirements as the Directive. The majority of toxicology procedures carried out on primates are part of repeat dose studies (sub-acute limit setting, sub-acute toxicity, sub-chronic and chronic toxicity), but with a substantial number used for toxicokinetics and "other tests" which may include safety pharmacology/pharmacodynamics.

3.1.1 Concerns:

The requirement for a non-rodent as a second species for repeat dose studies seems to have become accepted worldwide. It is a concern that the use of two species has become standard practice for these tests even though there may be cases where a rodent species would be sufficient.

3.2 Selection of a non-rodent species

The Sub-committee considered it was important to ascertain and report on how the second species is selected in practice because the rationale for the selection of a primate should, in theory, provide the specific justification for their use each and every time a safety assessment study uses primates.

The choice of a second, non-rodent, species for pharmaceutical safety testing is currently affected by many factors, some scientific, some practical and some historical (see Broadhead et al 1999). The species traditionally selected is most commonly either the beagle dog or a primate, although mini-pigs or ferrets are sometimes used, and for veterinary drugs, other appropriate "target" species. Species selection is currently being addressed within the pharmaceutical industry (EFPIA and the ABPI) and was the subject of an international conference in 2000, (Selection of Animal Species in Preclinical Safety Testing, organised by the Drug Information Association, Helsingor, Denmark, December 2000). The Home Office, in its Guidance on the Conduct of Regulatory Toxicology and Safety Evaluation Studies (HO, February 2001b) states that *"Scientific considerations should dictate the choice of species for toxicity tests; in particular, the species sensitivity and metabolism and the availability of background data. Practical considerations such as the size of the animal, availability and length of gestation may also have a bearing"* . The ABPI has recently published a "Points to Consider" document on the selection of the non-rodent species developed in conjunction with the Home Office (Smith and Trennery, 2002).

A number of the factors that influence species selection are discussed below:

3.2.1 Scientific considerations

The scientific basis for species selection is summarised by a guideline on repeat dose testing of pharmaceuticals, published by the Committee on Proprietary Medical Products (CPMP) of the EMEA (European Agency for the Evaluation of Medicinal Products 1999): *"Within the usual spectrum of laboratory animals used for toxicity testing, the species should be chosen based on their similarity to humans with regard to pharmacokinetic profile including biotransformation. Exposure to the main human metabolite(s) should be assured. Whenever possible, the selected species should be responsive to the primary pharmacodynamic effect of the substance."*

In some instances, the species of choice may be determined by a prior knowledge of the metabolism and pharmacology of existing, related drugs or by experience gained from tests on different species during the development of a new drug. *In vitro* methods may be used to compare the absorption or metabolism of the candidate drug using microsomal, cell or tissue samples from different species, including humans. Similarly, the presence of the pharmacological target molecules or receptors is often investigated to help select a pharmacologically responsive species.

The dog has generally been the default non-rodent species, except in those cases where physiological and pharmacological homology to humans is of particular importance, or when the dog is considered unsuitable as is the case for NSAIDs and certain drug vehicles such as cremaphor. The HO view is that the dog must be actively de-selected before primate use can be authorised.

Note that recommendation 7 (ii) in the APC's report on regulatory toxicity asked that the HO *"should keep under review the scientific criteria for the*

selection and use of a second species, and in particular dogs and non-human primates" (HO, 1994b). The Home Secretary said in response that he would *"look to the committee (the APC) for regular review of the criteria for the selection and the use of a second species"*(HO, 1996b).

3.2.2 Practical issues

A number of practical considerations also influence species selection. The feasibility of using particular routes of drug administration, ease of collection of body fluids or of making specific physiological measurements, ease of handling, and size in relation to the quantity of drug available for testing, are all taken into account. The availablity of adequate historical (background reference) data for a given species is also a key factor.

Note, it was suggested to the Sub-committee that, in some cases, CROs may choose primates simply because they have them available - some do maintain small groups of primates for individual clients - or because they have greater in-house expertise with these species. This suggestion was vigorously denied by the pharmaceutical industry on the grounds that decisions to use primates were made according to scientific rationale and the cost of these animals made it uneconomic to use them unless they were absolutely essential. They point out that since primates are ordered for a specific study or group of studies, and not as an unassigned batch for stock purposes, a surplus of animals is unlikely to arise. It is also common practice to avoid ordering a surplus of animals by ensuring quality at source before despatch. For a large study, for example 24 animals, it would be usual to obtain an additional male and female for the selection process. The additional two animals would then be used for a preliminary or sighting study where the entry criteria on to study can be wider. The conflicting statements about the basis for selecting a primate are discussed further in section 3.2.3 but more information is needed to provide a conclusive answer.

3.2.3 Regulatory influences

The power wielded by regulators, and particularly those of the US Food and Drug Administration (FDA), who are both the most demanding and the keyholders to the single largest market, is considerable. This is alarming given that there is a lack of transparency in their function – it is extremely hard to ascertain exactly how they operate. There is also a concern about the consistency between individual regulators and national regulatory bodies.

In practice, the real, perceived or anticipated requirements of regulators are an extremely important factor in species selection, although good practice with respect to ethical and animal welfare issues are also important concerns. The pharmaceutical industry (and others) now operate in a global market, and will wish to provide data that is acceptable to regulatory authorities in many countries. The studies carried out are likely to be designed to satisfy the most demanding regulator worldwide. However, except in rare circumstances, in no country (including the USA), do the *regulations themselves* (as opposed to the *regulatory authorities*) explicitly require the use of primates as the non-rodent mammal: i.e. there is no *mandatory* requirement to use a primate (see Broadhead et al, 1999, for a summary of regulatory requirements relating to dogs and other non-rodent species). Nevertheless, there is a concern that the requirement for, and use of, primates (or dogs for that matter) may have become more a matter of convention than a deliberate choice based on the principles of species selection discussed above. This matter needs to be explored further.

Regulators are generally reluctant to dictate the data they require prior to submission – they state in public that they expect "good data" without necessarily saying what this is. This presumably reflects their belief that the company developing a new chemical product has more background information on the substance, and is therefore

better placed to design an appropriate testing strategy (within broad guidelines). No doubt regulators also wish to maintain their position as independent assessors of the data, rather than having an intimate involvement in study design. For example, the right to reject data as inappropriate or inadequate, perhaps in the light of new information or public concerns, might be compromised if the study design had been dictated by the regulators themselves. There are additional considerations relating to legal liability for possible adverse effects, and where the ultimate responsibility for this lies. There is also the question of whether it is the regulators who set the actual requirements or their scientific advisors.

Thus, it appears that at an international level, continuation of the 'convention' of primate use is at least in part dictated by the pharmaceutical industry's reluctance to risk being forced to repeat studies at a regulator's insistence, if data from a species other than a primate are rejected. Moreover, even though regulators themselves may be much more concerned with the adequacy of a species' biochemical cross-reactivity with humans (and thus willing to accept data from animals other than primates as a second species), the industry's *perception* is that there can be variation between individual regulators, even within the same agency, and that the regulators' view of the adequacy of data may change with time, even during the development of a single compound.

The pharmaceutical industry globally is operating in a highly competitive environment (as are CROs) and commercial pressures may make companies unwilling to take the risk of using an animal other than a primate, or to waste time trying to establish individual regulators' preferences. Most CROs in the UK say that they will question client demands where these seem inappropriate, but the use of a primate is less likely to cost the industry time and money (and possibly other animals) in the long run, even where it is believed that another animal

model, or presumably a non-animal alternative, would be more appropriate.

However, we understand that the current strategy of European Pharmas is to avoid the use of the primate unless absolutely essential. Before embarking on a testing programme, particularly if primates or mini pigs are to be used, it is not unusual for a company to obtain the views of the regulatory agency before commencing work.

It has also been suggested that increasing fear of litigation (especially in the USA) on the part of both industry and the regulators may be influencing their approach to safety evaluation. The greater similarity of primates to humans is perceived to make their use a more effective legal safeguard, reinforcing the preference for a primate model.

3.2.4 Ethical concerns

The desire to avoid the use of primates in research and testing, on ethical grounds has found expression in both EU and UK legislation:

Directive 86/609 on the protection of experimental animals, Article 7. para 3 states that: *"When an experiment has to be performed, the choice of species shall be carefully considered and, where necessary, explained to the authority. In a choice between experiments, those which use the minimum number of animals, involve animals with the lowest degree of neurophysiological sensitivity, cause the least pain, suffering, distress or lasting harm and which are most likely to provide satisfactory results shall be selected."* (EC, 1986)

The ASPA states in section 5.6 that: *The Secretary of State shall not grant a project licence authorising the use of cats, dogs, primates or equidae unless he is satisfied that animals of no other species are suitable for the purposes of the programme to be specified in the licence or that it is not practicable to obtain animals of any other species that are suitable for those purposes.*

There is thus an obligation in law to base species selection for pharmaceutical safety testing on the presumption that primates will only be used when no other species would be suitable for assessing the safety of the particular medicinal product under examination.

3.2.5 Conclusions:

The mechanism by which particular species are selected for use in pharmaceutical safety studies is a key concern because it provides, or should provide, the basis for the justification for using primates in those cases where they are selected. The question is whether the mechanisms for choosing mammalian species for testing each individual pharmaceutical are adequate, appropriate, correctly applied or even in existence in some places.

We recognise that some of the concerns raised in section 3.2 are difficult to substantiate or refute. Nevertheless, we believe that these concerns are important and should be investigated further (see recommendation 1). Given that the goal is to assess the safety of a compound prior to clinical trials, the following questions must be asked:

- **is a non-rodent species *always* necessary *scientifically* to provide the information that is required to protect the safety of human volunteers?**
- **is species selection unduly influenced by anticipated regulatory preferences, tradition, or economic considerations?**
- **are the investigations used to underpin the scientific selection criteria sufficiently extensive in terms of methodology and range of species considered?**
- **is every attempt made to select the most appropriate species for every compound in every case?**
- **is sufficient consideration always given to the legal obligation to ensure that a primate is the only suitable species?**

It is difficult to determine who has responsibility and who *should have* responsibility for defining the data that are required for the safety assessment of pharmaceuticals. The way the current system works is very complex, and is difficult to understand and interpret for anyone not closely involved with it. Key concerns are that:

- **there is a lack of consistency and predictability in regulators' demands that may result in the use of primates as a precaution rather than as a scientific necessity;**
- **the inter-relationship between, and various roles and responsibilities of, national and international regulators, pharmaceutical companies, CROs and the HO as the animal procedure licencing authority are complex and not at all clear;**
- **commercial pressures limit challenge to perceived and real regulatory requirements.**

3.3 Choice of a particular primate species

Where primates are used, anthropoid primates tend to be the species selected (see Smith et al., 2001 for a review of this issue). Macaques are the most common primates used in regulatory toxicity testing (see section 2.3.2.). However, it is considered that scientifically there is little to choose between New and Old World monkeys in terms of metabolic similarity to humans, although this does depend on the compound being evaluated. Small-bodied New World species like marmosets are cheaper to purchase and to house, are quicker to breed, require smaller drug doses, and are considered acceptable models now that a good knowledge-base exists for them (Smith et al., 2001). Marmosets are also relatively easy to acquire given that the UK can more or less meet the current demand with animals bred in this country. It is possible therefore that the use of marmosets for regulatory toxicology may increase, with a concomitant decline in the demand for macaques.
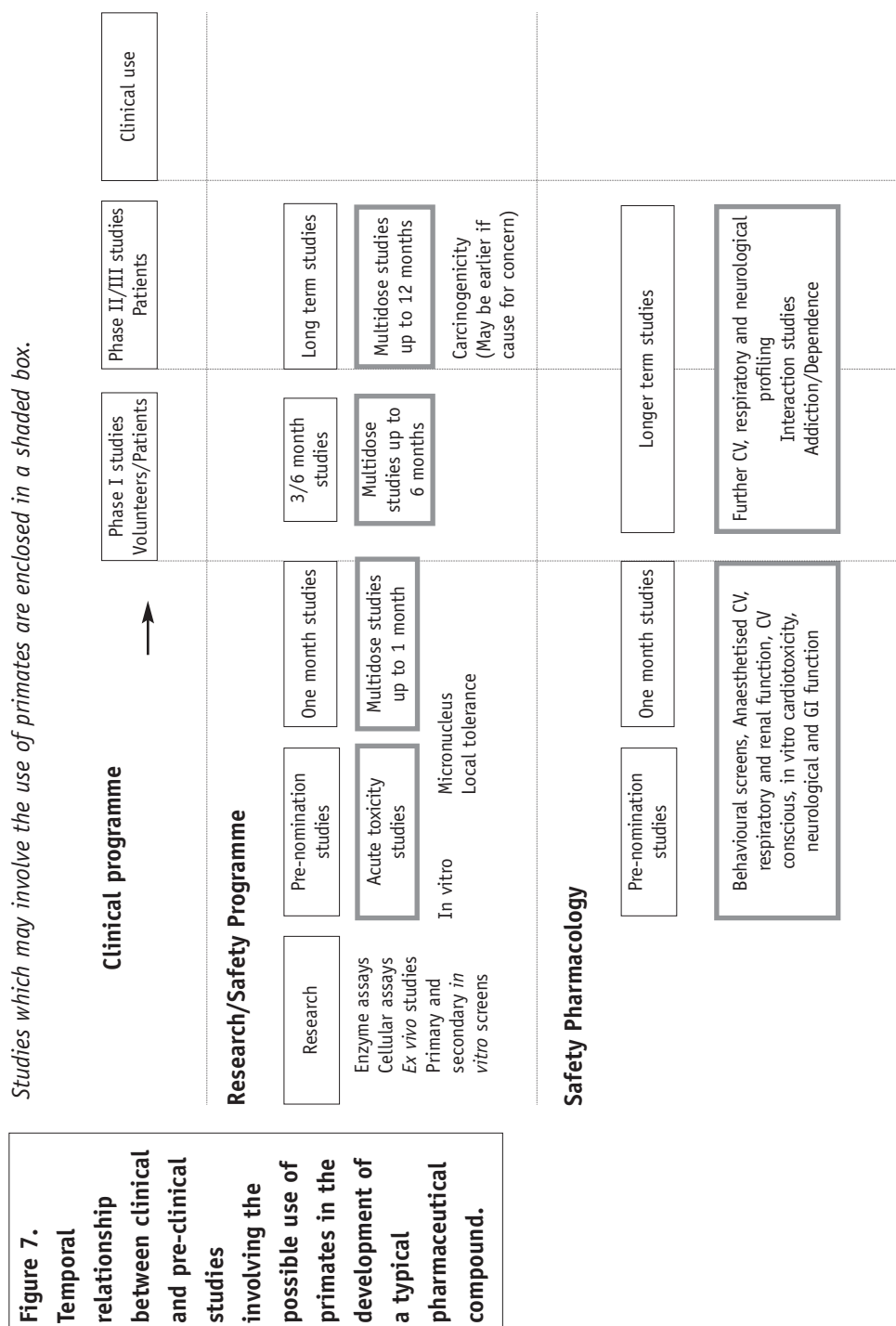
There is a perception that marmosets are less stressed than macaques by life in a laboratory environment.

The Boyd Group evaluated this perception by systematically comparing the consequences for animal welfare of the supply and use of marmosets and macaques in scientific procedures. The Boyd Group concluded that: *"the choice between marmosets and macaques was not always straightforward on welfare grounds, and needs to be considered case-by-case (depending, in particular, on the scientific procedures involved)".* We agree.

3.4 Study design and timing

The timing of the various pre-clinical stages was also identified in our discussions as a matter of concern. The way that primate studies fit into the general pattern of pre-clinical safety studies is shown in figure 7.

Figure 7. Temporal relationship between clinical and pre-clinical studies involving the possible use of primates in the development of a typical pharmaceutical compound.

Studies which may involve the use of primates are enclosed in a shaded box.

Commercial pressure to move to clinical trials in humans as soon as possible is even now increasing the pressure on companies to overlap the pre-clinical phases of their research in order to save time. For example, to speed progress to Phase I clinical trials, there is pressure to conduct the one-month studies on rodents and the selected non-rodent species at the same time, rather than wait for the results of the rodent tests. In extreme cases, all repeat dose studies might be initiated at once. However, if studies overlap and a compound fails due to toxicity that was detectable in rodents then some primates will have been wasted. This is a matter of serious concern and is in direct conflict with how we would expect ASPA to operate. In order to prevent wasteage of these animals, all phases of drug development up to and including chronic studies in rodents should be completed before a product is tested on a primate. The pressure to shorten the time to clinical trials can only be expected to increase, and serious consideration needs to be given to what the sequence of successive phases should be. It is important to ensure that commercial pressures do not compromise the principle of minimising primate use in the design of pre-clinical studies.

It was suggested that the competitive, commercial environment in which safety assessment is done and the concomitant speed of response required by CROs may also create problems with respect to the actual design of regulatory and other studies. CROs are often constrained to a tight timescale when making bids for contracts, and although most say they will question client demands where these seem inappropriate, they are unlikely to have the luxury of time to engage in lengthy discussions with either their clients or regulators, or to develop innovative experimental designs. This inevitably means that new studies are simply slotted into standard designs.

Those cases that require the use of primates are typically the repeat dose studies of 1, 6, and 12

months duration. Designs of such studies have been harmonised by ICH and there is little scope or reason to deviate from these unless previous work has indicated a need to do so. Group sizes are minimal considering the limitation of background pathology data.

The point at which there is most scope for innovative design is when a primate is used to elucidate a specific issue. In such cases we have been advised that extensive dialogue usually ensues between the CRO, the regulator and the toxicologist, in order to achieve the best possible outcome.

3.4.1 Concerns:

We have identified the following two concerns which we consider merit further investigation, but there are conflicting views as to whether these reflect the current situation. Both points nevertheless require further discussion:

- **Primates may be wasted if the temporal pattern and design of pre-clinical studies is influenced more by commercial pressure than by the need to minimise primate use.**

- **Commercial pressures may limit the time available to seek alternative approaches or study designs for individual contracts and substances tested.**

3.5 Alternatives to primate use in regulatory toxicology

This report does not attempt to do justice to the subject of replacement alternatives and to the work that has already been done either to directly replace animals (specifically primates), or to reduce or avoid their use. The pharmaceutical industry has clearly been responsible for significant contributions in these areas. Thoughtful experimental design and the harmonisation of guidelines undertaken by bodies such as the ICH have also been extremely important and the APC endorses and encourages further work in this area.

In toxicology, primates are used in repeat dose toxicity tests, in pharmacokinetics and in safety pharmacology studies (see Table 6). Non-animal methods are under development in most of these areas, but further work is urgently needed. For example in pharmacokinetics, highly sensitive analytical methods increasingly permit safe, ethical, microdose studies in healthy human volunteers at an early stage of drug development prior to phase I clinical trials. Such studies, using nuclear magnetic resonance spectroscopy, accelerator mass spectrometry, positron emission tomography (PET) and other techniques, provide human pharmacokinetic data such as drug bioavailability, distribution to and elimination from different target tissues, the identity and level of drug metabolites and plasma clearance. Useful information can be gained even at doses well below the pharmacologically active level (Saleem et al., 2001; Turteltaub and Vogel, 2000; Young et al., 2001).

Increasingly, it is becoming possible to identify and measure in human volunteers early markers of potential drug effects at the biochemical level. Such biomarkers can allow assessment of likely efficacy or toxicity, at a time point and a drug dose far in advance of and below actual toxic thresholds. In particular, nuclear magnetic resonance spectroscopy is being developed in a new field known as metabonomics. Small changes in a range of normal metabolites in intermediate biochemical pathways are detected, providing a 'fingerprint' of potential drug effects on energy metabolism, liver or kidney function, to take three examples (references Shockcor et al., 1996; Shockcor et al., 2000)

Human data of this kind can assist the early selection of leading drug candidates, so that inappropriate compounds are eliminated before they are further tested in animals. They also permit the identification of the most relevant species for whatever subsequent toxicity and pharmacokinetic tests are later conducted in animals, thus minimising wastage of animals. Early human data

could also identify cases where the use of a second animal species, such as primates or dogs, would be unnecessary or inappropriate.

3.5.1 Concerns

The approaches described above are being followed because they offer advantages for drug development. They also have the potential to replace some primates in regulatory toxicology. However, resources are needed to move the technologies from the research phase to the stage where they can be routinely used.

3.6 Licensing of Regulatory Toxicology procedures under ASPA

Because much regulatory (and other) toxicology comprises standard repetitive protocols, and because CROs bid for contracts in a relatively short timescale, the HO licencing policy has been to award very large "generic" project licences to contract laboratories and pharmaceutical companies carrying out such work. This practice is described in the HO Guidance on the Conduct of Regulatory Toxicology and Safety Evaluation Studies (HO 2001b) in the following terms: *"Individual Project Licence applications are drafted to cover specific, coherent categories of test materials (e.g. chemicals, pharmaceuticals, biocides etc.) and to identify the likely range of specific test requirements."* Such licences may each, therefore, include a large number of different protocols and procedures for standard types of toxicity test. The severity limits and species used for each protocol will be defined, but the actual substances to be tested will not be specified other than in generic terms. Despite this, the current administration of these licences is viewed by industry as cumbersome with respect to the length of time it can take to process the initial licence application and subsequent amendments, and the constraints that this imposes on CROs competing for contracts. The commonly expressed belief is that the level of 'bureaucracy' may result in research/testing contracts going (or being awarded) overseas.

The concept of generic licences is criticised on the grounds that it makes harm-benefit decisions under ASPA difficult. Under ASPA, the benefits of using primates in regulatory toxicity testing is viewed in terms of *"the need for regulatory authorities to have sufficient information to assess risks to which humans, animals, plants or the environment are exposed when the test substances are produced, transported or used"*. The benefit is not assessed in terms of the utility of the substances themselves (Home Office 1998b, p.56, paragraph 5.24; and Home Office 2001b, paragraph 1.3) but only in relation to the objective of ensuring that products and ingredients can be manufactured and used safely. There is no requirement to include consideration of the nature and strength of the likely benefits of, or need for, the substances themselves. On these grounds, project licences may permit the use of animals in testing a wide range of different kinds of substance, defined only in general terms in the licence.

In contrast, when animals are used in the development of new products and ingredients, *"the utility of the new materials is one of the main determinants of benefit"* and *"In the case of new medicines, this may be deemed to be high"* (Home Office 1998b, p. 56, paragraph 5.23). In some cases, substances undergoing regulatory toxicity testing will have been developed under another project licence, and thus their potential benefits will already have been considered under the terms of ASPA. However, in other cases (for example, where foreign clients bring substances to UK CROs), development of the substances will not have involved the use of animals under ASPA and, therefore, the potential benefits of the new materials will not have been considered under the terms of the Act. In such cases, there is no legal requirement that these benefits be included as part of the justification for using primates in testing. (See Boyd Group document for a fuller discussion of the question of benefit of the products tested.)

Furthermore, project licence holders have responsibility for justifying species choice to the Home Office - the HO Guidance on the Conduct of Regulatory Toxicology and Safety Evaluation Studies makes a number of points about the selection of species, two of which are of particular relevance here:

"The applicant should summarise how the second species will in practice be selected" (para 6.5)

"Specific justification is required for the use of cats, dogs, equidae and non-human primates". (para 6.6)

These points, taken together with the general principles of the guidance, should surely mean that the licence applicant must have a clear strategy for species selection, which must be applied to each substance that is tested under the project licence, and that in granting the licence, the HO Inspectorate must be satisfied that the proposed strategy will provide a valid justification for the use of a particular species, for any substance that might be tested under the licence. However, it is difficult to understand how generic licences can allow scientifically sound and ethically acceptable strategies for test design and species selection to be developed that will be applicable to a wide range of test substances, since, in practice, project licences are not required to justify the species choice in advance for *each substance* tested.

The amount of pain and suffering that occurs with generic licences is also difficult to monitor because of the unspecified primate use, as is the amount of effort made in practice to identify alternatives.

None of this accords well with the fact that the use of primates under ASPA (section 5.6) requires special justification. Clearly, it is important to balance the speed of response to a request for a new study with the need to properly review all individual uses of primates. The APC is convinced that a mechanism could be developed to allow the fast-track review of individual 'projects' within the

framework of a generic licence, but at the same time enable tighter control and monitoring of primate use, thus going some way to allaying public fears that these licenses are wholly open-ended.

This issue was discussed by the APC during preparation of the Committee's report on regulatory toxicology in 1993. One of the recommendations submitted to the Home Secretary at that time read: *"for toxicology project licence applications proposing the use of old world non-human primates (e.g. macaques and baboons) in procedures of greater than mild severity, the justification for using such primates should be set out clearly in the application on a study by study basis"* (HO 1994b). The Home Secretary rejected this advice on the grounds that it would impose too great a burden on both the inspectorate and industry. It was proposed instead that retrospective reporting should be required in all such cases to monitor the specific case by case justifications for regulatory toxicity tests. In March 1996, a letter outlining this proposal was sent to all holders of project licences authorising toxicology procedures of more than mild severity in Old World primates. The APC received no feed-back on how the proposed system worked, and as far as the Sub-Committee can ascertain, this was because there were difficulties in deciding precisely what information needed to be collected, how it should be reported and subsequently interpreted.

Our understanding of the original proposal was that each study would simply require a specific justification for the use of Old World monkeys and that this might require at most a page or two. What the APC envisaged at the time was a simple reporting mechanism to the local inspector, who would be able to grant or withhold approval to proceed under the terms of the existing licence if the study was deemed acceptable, without the need to refer the case to higher authority within the Home Office or to the Secretary of State. The situation has now changed with the introduction of local Ethical Review Processes (ERPs). Some ERPs

carry out *prospective* reviews for the individual substances tested. This accords with the Chief Inspector's suggestion in setting out the general principles of the ERP that prospective case by case review would be a useful function of individual ERPs. Another issue is that, at present, project licensees estimate the maximum number of animals they are likely to need throughout the life of the licence. The numbers used each year are reported back to the HO for inclusion in the annual statistics but there is no provision for the HO to cross check actual against predicted numbers used, or review how many animals actually suffered more than mild effects. This information is important in order to monitor primate use more comprehensively.

Clearly the concept of prospective review would more closely meet the APC's original proposal and we believe it is timely to review the current situation in the light of the development of the ERP to determine whether there is a system in place that is effective in meeting the APC's original concerns. However, the aim of any such system should not only be to achieve better advance oversight of procedures which account for large numbers of primates, but also to acquire details of the numbers of primates used in, and the severity of, the different kinds of procedures.

3.6.1 Concerns:

Regulatory toxicology studies are carried out under 'generic' licences which do not require justification for primate use for each substance tested. A key concern is whether this system allows for adequate assessment of the harms, benefits and justification for primate use, and for monitoring primate use.

The APC is unclear as to whether the retrospective reporting system proposed in 1996 had any added value with respect to addressing these concerns. Local ERPs may now be undertaking prospective review on a study by study basis. This is closer to the APC's original

proposal. However, it is not clear what happens in practice, and whether ERPs review actual as opposed to predicted numbers used and severity levels reached by individual animals. Further discussion on this point, particularly with CROs would be useful.

3.7 Re-use under ASPA

The re-use of animals under ASPA is not generally permitted except in certain defined circumstances (see paras 5.55-5.66 of the HO Guidance notes on the operation of the ASPA [HO 2000b]). This is to avoid the accumulated harms that would occur to individual animals if they were subjected to more than one procedure.

Most toxicological studies require post-mortems on each animal so re-use would not be possible even if authorised under ASPA. There is however scope for re-use of animals in other types of study. At present, this is relatively limited in the UK, mainly because clients are concerned about confidentiality (if full details of the previous use has to be disclosed to the subsequent client) as well as the risk of confounded data. A solution to the confidentiality issue may be to encourage sponsors to maintain their own dedicated groups of primates at CROs and some companies have done this. However, this would have to take into account the effects of long term confinement of the animals as well as the re-use itself.

The issue of confounded data may indeed be a problem in some areas, but not in others. For example, metabolite studies can and often do involve multiple use of animals, since techniques now exist to separate out the individual effects of different components

The issue of re-use is an ongoing topic of discussion amongst groups such as the Laboratory Animal Veterinary Association who have recently published new guidance (LAVA, 2001). Re-use of primates could allow for a reduction in the total

numbers of animals used overall. This is clearly desirable. However, this could result in increased harm for the individual animals concerned, because of the accumulative effect of multiple usage. These two factors – reduced numbers versus increased costs to the individuals concerned – need to be carefully evaluated and weighed. The HO Inspectorate do not allow re-use of an animal unless s/he has returned to a 'baseline' position and there are no long term effects in terms of pain or other adverse effects of procedures. Their view is that reducing the numbers of animals used overall does not justify causing a significant increase in the cost for the individual animals involved. We agree with this principle, but believe the balance should be reviewed case by case. For primates, particularly Old World species, the additional costs of not re-using them are high because of adverse effects associated with their sourcing, transport and acclimitisation to a laboratory environment.

3.7.1 Concerns:

Reduction in the numbers of primates used in pharmaceutical safety assessment is a desirable goal and it might be possible to achieve this by re-using more animals. However, it is important that the advantages of such action are carefully weighed against any detrimental effects for the individual animals concerned.

The APC would like to hear whether opportunities for re-use and the advantages and disadvantages of this are always fully explored.

CHAPTER 4
FUTURE USE OF PRIMATES

Since so much of current primate use is for the development and testing of pharmaceuticals, it is clear that the numbers of primates used in the future will be closely linked to developments in the pharmaceutical industry. From our discussions with members of the ABPI it became clear that although there is some suggestion of a decline in the *total* number of primates used in the UK since 1994, it would be unwise to assume that this will continue into the future. There is no reason to believe that pharmaceutical development as a whole will decrease, and in addition new developments in, for example, the neurosciences and in human genome research, may change the nature of the products developed such that the demand for primates as models in basic research, and in drug development and safety assessment, may actually increase over the next decade or so for reasons described below. The development of biotechnology derived products and molecules more specifically targeted at human receptors (e.g. clinical antibodies, DNA- and protein-derived products) is another factor that is likely to have an impact on primate use since animals that are phylogenetically more distant from humans may not be considered suitable for efficacy and safety studies for such products.

The increased longevity of human populations is likely to make the degenerative diseases of old age increasingly more intrusive in both social, human welfare, and economic terms, thereby making the development of solutions to these problems as pressing as the current concerns with "lifestyle" diseases such as heart disease and cancer. The pharmaceutical industry's view is that its future lies in developing entirely new classes of neuroactive drugs to combat the increasingly important neurological diseases of old age. Such drugs are likely to be biochemically very different from those that have been the focus of pharmacological interest hitherto, because much of the work on new classes of neuroactive drugs is likely to focus on those that act on very specific neurological systems. The existence and availability of an effective non-human model with similar neuroanatomical and biochemical properties to humans, both for basic research in the neurosciences and subsequent pharmaceutical development, is considered by the pharmaceutical industry to be paramount to the success of this endeavour.

The need for an effective model is likely to operate at three levels with respect to: (i) cognitive function and behaviour; (ii) gross anatomy and neuroanatomy; (iii) cell and tissue structure and function including receptor specificity and antigenicity. Anthropoid primates are the only species that share with humans the advanced frontal lobe brain functions that are most commonly involved in many neuro-degenerative diseases. Furthermore, the specificity and antigenicity of some of the potential products may be so restricted that only anthropoid primates (i.e. monkeys and apes) would provide useful models for their development and testing. It is industry's view that this may well mean that primates will become the *only* species, rather than merely the *preferred* option, both for fundamental research into these conditions and for the regulatory toxicology associated with product development. The UK has considerable expertise in using primates in neuroscience research and in drug development thus making it likely that, in the first instance, much of this work will naturally gravitate towards the UK. Indeed the UK Government together with the Wellcome Trust has agreed to the funding for a new international neuroscience centre in Cambridge. These developments are a cause of concern insofar as they may increase primate use.

A further concern that we have identified is that the emphasis on the need for homology with human biological systems may lead to pressure for using great apes (in particular, chimpanzees) precisely because of their greater genetic, neuroanatomical and cognitive similarity to humans. The use of great apes is currently banned in some countries in Europe (UK, Eire) and New Zealand has also recently instigated a ban. However, small numbers of chimpanzees are still being used in the Netherlands for hepatitis research, although the Dutch Minister of Education, Culture and Science stated in 2001 that research on these animals must end. Chimpanzees are used for hepatitis C, HIV and schistosomiasis research in research programmes funded by the EU Commission. Such programmes are usually part of multidisciplinary, many partnered research projects so although UK researchers may not actually use chimpanzees themselves they may be party to research programmes which incorporate experimental data obtained from these animals.

If it is considered that chimpanzees are required in the future, then given the UK ban on chimpanzee use, UK-based pharmaceutical companies might move their research and development activities elsewhere. Drugs whose development may have involved the use of primates that could not have been used here, may then be imported and used in the UK. Similarly, results from multinational research programmes involving chimpanzees may be used as part of collaborative and/or interdisciplinary research programmes. This process effectively undermines the intent of any ban on experiments on great apes. (Note that similar problems might occur with the ban on use of wild-caught primates.) Alternatively, economic and political expediency might lead to pressure to revoke the ban currently in force within the UK.

This is, of course, at present only speculation, but the ban on chimpanzee use was invoked because it was considered morally unacceptable to confine them in laboratories and use them in scientific

procedures, and the Sub-committee believes that it would be unacceptable to reverse or make any exceptions to this decision.

4.1 Concerns:

If the predictions above are realised and the demand to use primates increases, then this clearly creates a conflict with regard to the APC's stated goals of *"minimising, and eventually eliminating primate use and suffering"*. **Any renewed demand to use the chimpanzee as a model would conflict with the existing ban on chimpanzee use.**

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS: THE WAY FORWARD

The drive to produce pharmaceuticals for human benefit, and the associated primate use that this currently entails, clearly creates a conflict with the desire to minimise and eliminate the use of primates in experiments.   If the predictions of an increased demand for primate use are realised then this conflict becomes more intense. The Sub-committee believes it is extremely important to recognise this conflict, and *absolutely essential* to more determinedly and actively seek ways of resolving it. However, it must be recognised that this is a global issue, which needs to be tackled on an international basis.

If, as seems likely, the vast majority of primate use continues to be in the development and safety assessment of pharmaceuticals, then it is clear that this is where the focus needs to be if major reductions in use are to be achieved. We recognise that progress has already been made in this respect. However, we believe that significant in-roads could still be made in reducing the numbers of primates used in toxicology if there was sufficient international commitment to this goal. It is essential to establish such a commitment, together with a mechanism that will ensure that primates are only used when the objective of ensuring the safety of human subjects cannot be achieved by any other means. In such cases, every effort should be made to ensure that safety evaluation programmes are designed to minimise the numbers of primates used, reduce suffering, and eliminate the possibility of wastage of animals. It will also be of paramount importance to develop convincing arguments to persuade national regulators (and their scientific and political advisors) that primates are not an essential part of the sequence of regulatory testing for all medicinal products.

5.1 Recommendations

Taking the issues forward

Recommendation 1

We recommend that the Home Secretary convene 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.

Development of alternatives

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 the international regulatory arena as a high priority goal, which requires immediate and dedicated attention. A coherent appropriately resourced stategy must be developed to achieve this goal.

Species selection and associated issues

Recommendation 3

We believe it is essential to instigate a detailed examination of regulatory policies on species selection in toxicity testing (requiring regulators to justify their need for primate data). This should incorporate the points and questions identified in Section 3.2 and 3.3.

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.

The aim must be to introduce a harmonised, consistent, scientifically justified policy for species selection both nationally and internationally. This might take the form of policy statements, guidelines and/or international agreements. The use of primate models for non-medical (i.e. agricultural, industrial, food safety) products should be actively discouraged.

British regulatory bodies (the Department of Health, the Medicines Control Agency, the Veterinary Medicines Directorate, the Health and Safety Executive, the Department of Trade and Industry, the Pesticides Safety Directorate, and the Department of the Environment Transport and the Regions) have already agreed a set of principles on animal welfare in the assessment of safety and risk (see Appendix 1). This includes a commitment to *"seek to influence international harmonisation initiatives to ensure that policies and practices take full account of the ethical duty to protect the welfare and minimise the numbers of animals used in safety assessments"*. We understand that the Home Office has input into meetings where these bodies discuss animal welfare principles.

Recommendation 4

The HO 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.

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.

The ready availability of human tissue is crucial for encouraging the use of *in vitro* methods to select appropriate species for safety evaluation of pharmaceuticals. It is also vital to encourage and support the development and use of alternative methods of wider applicability in research that currently involves primate use.

There has always been a serious shortage of human tissue for research. However demand is increasing, while recent revelations about the removal of children's organs without parents' permission has damaged public confidence in tissue and organ donation. The provision of human cells and tissue for research needs a clear regulatory framework to restore public confidence and should operate on a non-profit basis.

Recommendation 6

The availability of animal tissues for comparative *in vitro* studies should be improved and we urge the pharmaceutical industry, the HO and ERPs to promote in-house tissue sharing and further promote tissue banks.

It should not be necessary to kill healthy animals just for their tissues. We recognise that many companies do try to encourage maximum useage of animal tissues but we believe such options could be further explored.

Recommendation 7

The use of highly sensitive analytical methods to provide human pharmocokinetic 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 ultra-low dose studies in human volunteers should be encouraged.

Increasing technological sophistication is beginning to make the pre-phase I use of *in vivo* human studies, using Microdoses with volunteers, a practical proposition. Since studies on humans offer the opportunity to collect data that are both more appropriate and more reliable, we should give serious consideration to actively encouraging the use of Microdose *in vivo* studies with human volunteers. Such studies, early in drug development, would help to inform the process of species selection and could reduce wasteage of animals in testing drugs that would fail in Phase I clinical trials.

Validity and necessity

Recommendation 8

The use of primates in the safety assessment of pharmaceuticals can clearly only be justified under current UK legislation if the data obtained are both valid (relevant for humans) and necessary in order for a safety assessment to be made. 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.

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.

The collation of existing data on a variety of species, including man, would allow decisions to be made in a transparent manner about the *need* for the use of primates on scientific grounds i.e. to identify cases where primates (or individual species of primate) are the *only* suitable model for humans. Sharing comparative data from primate and other species (including humans) could be done through a neutral third party (such as the Centre for Medicines Research).

The need to protect commercially sensitive information is recognised, but this could be protected by using a codename for companies' products and, the identity of the participating companies need not be revealed. Regulatory authorities also hold comparative historical data which could be treated likewise. The Government has already proposed a data sharing concordat for relevant departments and greater transparency regarding the concordat itself would be a start.

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.

Using such an approach to assess the appropriate duration of chronic tests in non-rodent species, the EU, Japanese and US authorities were able to reduce the previous maximum required multidose study duration from 12- to 9-months. A similar study on the predictivity of the primate tests for human safety could establish the value or otherwise of such tests

Existing primate and clinical data presently in the files of companies and regulatory authorities could be shared through a neutral third party. The data-sharing concordat for government departments may provide a framework by which regulatory data could be contributed. The Association of British Pharmaceutical Industry or the Centre for Medicines Research would be a body to approach for gaining the co-operation of the drug industry in such a study. A possible source of funding might be the Home Office budget for Three Rs research, which is administered through the Animal Procedures Committee. Additional funding may be also required and the pharmaceutical industry may be willing partners.

Regulatory toxicology and the ASPA

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 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.

We believe that each study should require a specific *prospective* justification for the use of both Old and New World primate species. The aim must be to achieve better advance oversight of procedures which account for large numbers of these animals. A prospective review should include consideration of whether the mechanism of species selection encompasses a thorough evaluation and assessment of existing information on similar substances, structural activity relationships, the results of in vitro tests, and the need for the product.

The role of the ERP is particularly important in this respect and we understand that some individual ERPs are reviewing studies in this way. We would be interested to hear feed-back on how this system is working.

Recommendation 12

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

This would provide better oversight of projects requiring large numbers of primates and should help identify areas for reduction and refinement.

Recommendation 13

The design and sequence of pre-clinical safety studies needs to be reviewed. We ask the HO 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.

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 HO in conjunction with project licence holders and ERPs, taking into account all of the advantages and disadvantages for individual animals.

Finally:

We appreciate that it can be argued that some of these recommendations reflect existing practice. However, this is not sufficiently widely appreciated - or widely applied from a worldwide global perspective - and there should be greater efforts made to make this explicit in codes of good practice and in appropriate documents, reports and publications. Licence application forms and the ethical review process, for example, rarely show clear evidence that significant effort has been devoted to evaluating the necessity for using a primate model in specific instances. We recognise that in some cases implementation of these recommendations will simply be a matter of targeted education aimed at changing an existing culture, but that a change in legislation, or regulations, will be essential in other cases.

It is claimed that the excessive bureaucracy (real or perceived) of the existing licencing system, combined with any further restrictions on use of animals may have the consequence of driving pharmaceutical research and testing currently undertaken in the UK, overseas where welfare

standards may be much lower. We would regard this as unfortunate, but equally would be unhappy with this argument being used uncritically to reduce the level of control or maintain what is thought by others to be an unsatisfactory status quo.

CHAPTER 6

ADDENDUM

The Home Office Statistics for the year 2001 were published just after this report had been agreed for publication and the figures are not therefore incorporated into the full text.   In summary, the general pattern of use was similar to previous years. The total number of primates used was 3,342. This is 391 animals more than in the year 2000.

There was a similar proportion of macaques and marmosets used as in previous years– 2,219 macaques and 1,123 marmosets and tamarins; and the split between the total used for toxicology (61.9%) and non-toxicology (38.1%) was also similar.

The only difference to note is the change in marmoset use. In the year 2000, 616 animals were used in toxicology and 444 in non-toxicology. In 2001, the figures were 252 and 871 respectively.

CHAPTER 7

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