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The Academy of
Medical Sciences

BIOSCIENCES FEDERATION



**A Bioscience Sector response to the House of Lords European
Union Committee Inquiry:
Revision of Directive 86/609 on the protection of animals used for
scientific purposes**

1. This document has been prepared as a response to the call for evidence from the House of Lords European Union Committee, Sub-Committee D (Environment and Agriculture). It encompasses the views of a number of organisations, including umbrella organisations, that represent academia, industry, SMEs, charities and other research funders in the United Kingdom, all of which will be directly affected by the revision of the Directive.

Organisations supporting this submission

Association of Medical Research Charities
BioIndustry Association
Biotechnology and Biological Sciences Research Council
Institute of Animal Technology
Laboratory Animals Breeders Association
Medical Research Council
Society of Biology (Biosciences Federation and Institute of Biology until September 1st 2009)
The Academy of Medical Sciences
The Association of the British Pharmaceutical Industry
Understanding Animal Research
Wellcome Trust

Context of this submission

2. The House of Lords Committee will be well aware of the publication of the original Commission proposal in November 2008, and of the plenary vote which finalised the first reading in the European Parliament in May 2009.

3. For the purposes of this submission, we refer to a large extent to the original Commission proposal. Our sector had many serious concerns about that proposal, which are given detailed consideration here. Our organisations published a ‘Declaration of Concern’ in March 2009 about the Commission proposal.¹ As well as problems with the content, the wording throughout the Directive requires significant review for scientific accuracy and internal consistency.

4. However, we also refer at times to the outcome of the European Parliament’s first reading. Our sector engaged in some depth with the debate in the Parliament. We published a ‘Declaration of Support’ for the report of the Agriculture Committee which was put to the plenary for a vote. Despite significant reservations, we supported many of the amendments which were passed by Parliament. However, we pointed out that we retained "strong reservations about some amendments in the Parish Report, which would impact negatively on scientific research that utilises animals. In addition, some of the problems with the original Commission proposal remain. These outstanding issues will need to be addressed in future stages of the revision of this Directive".²

5. We understand that the Commission has so far accepted only a minority of the Parliament’s amendments. It has apparently not supported many of the amendments which would be of most importance to continued biomedical research using animals in Europe.

6. For this reason, the position of the UK Government as it engages in the first reading with the Council of the European Union is of considerable significance.

¹www.understandinganimalresearch.org.uk/policy_issues/european_regulation/uk_bioscience_sector_declaration

²www.understandinganimalresearch.org.uk/policy_issues/european_regulation/declaration_of_support_for_the_parish_report

Executive Summary

1. Objectives of the Directive

7. The bioscience sector recognises the need for Europe-wide legislation concerning the use of animals in research, and we agree that it is timely to update the 1986 Directive. We support the high-level policy objectives outlined in the Home Office consultation on this Directive (of May 2009). These include (in our own wording):

- Harmonisation of EU regulatory requirements
- Promotion of high-quality science and patient benefits
- Promotion of public confidence in humane animal research
- Ensuring high animal welfare standards and the application of the 3Rs (reduction, refinement and replacement).

8. We consider that harmonisation, as well as having potential benefits to animal welfare, is in the UK's economic and scientific interests, in particular in those areas concerning the mobility of personnel, the sharing of projects, and the cost drivers affecting animal supplies. However, we do not believe the draft Directive will adequately fulfil the aim of harmonisation of the market. Indeed some provisions could create greater disparity both within the single market and the global market.

Further information is provided on page 9.

2. International competition

9. We have serious concerns that the draft Directive would undermine UK and European competitiveness. In particular, it would create in many areas a disproportionate workload, excessive cost-burden, and unnecessary restrictions to research, without proportionate benefit to animal welfare. It will make it increasingly difficult for international scientific collaborations with countries outside of the EU.

10. The Commission has stated its intention to reduce the burden and costs of legislation for SMEs and larger companies in order to improve competitiveness, and to continue to strive for the goals laid out in the Lisbon and Gothenburg agendas. In this draft Directive it has failed to carry through that intention.

Further information is provided on page 13.

3. Non-human primates (NHPs)

11. We agree that, as with all animal research, careful ethical evaluation and harm-benefit assessment is required before primate use is authorised. In most EU countries this type of assessment already exists. We disagree with attempts to impose sweeping restrictions or ban NHP use. This could have seriously negative impacts upon the ability of fundamental and applied science to bring much needed medical advances to UK and EU citizens and patients across the world.

12. A blanket requirement for the use of second generation (F2) NHPs (i.e. offspring of animals that have been bred in captivity) would be problematic. Before time lines can be established this would require a feasibility study to assess the impact of such a policy both on animal welfare and on the availability of NHPs to EU researchers.

13. We support the amendments made in Parliament to improve the ability to conduct vital research using NHPs.

Further information is provided on page 16.

4. Extension of the scope

14. A number of the proposed extensions to the scope of the directive are not justified, would significantly increase costs, and present an unworkable administrative burden with no benefit to the welfare of animals. These include the full regulation of all vertebrates humanely killed for their tissues, and the extension of species covered by the Directive to include all embryonic and foetal forms of vertebrates, as well as certain additional classes of invertebrate, including their larval forms. Reliable evidence of sentience has not been scientifically established for most of the animals covered by these extensions.

15. We support those amendments made in the European Parliament to restrict the scope of invertebrate cover, but believe that the scope is still too wide, and not scientifically robust. Other amendments would still represent a major increase in the range of vertebrate studies included under regulation from the existing Directive.

Further information is provided on page 21.

5/6. Authorisations

16. The administrative implementation of the Directive must be clear and well-defined. It is currently confusing and unnecessarily bureaucratic, with potential for unnecessary delays and restrictions to research that would not promote animal welfare or the 3Rs. The Directive does not apply proportionality, in that the degree of control is not adjusted in relation to the potential harm to the animals. The controls need further consideration and amendment.

Further information is provided on page 26.

7. Care and accommodation

17. We support the principle of minimum standards of care and accommodation across Europe (with derogations where necessary, e.g. for farm animal research). The Directive, as currently proposed, is overly prescriptive around cage sizing and environmental requirements. As well as greatly increasing costs for research, some proposals would be actively deleterious to welfare and may compromise the ability of the UK to maintain its animal breeding capabilities.

Further information is provided on page 33.

8. Alternative methods

18. The 3Rs are an intrinsic part of scientific research, not a separate activity. Much of the evidence contributing to the 3Rs has come from research that had other primary aims.

‘Validation’ of the 3Rs is best undertaken through normal scientific processes and not through separate national reference laboratories in every individual Member State. It is unlikely that these could ever contain all the necessary expertise and facilities, and they would be expensive and duplicative.

Further information is provided on page 38.

9. Subsidiarity and legal base

19. The Directive should seek harmonisation across Member States over the principles and outcomes of regulation affecting animal welfare, while permitting flexibility in methods of implementation.

20. The Directive currently lacks proportionality and gives excessive weight to restrictions which would impede research yet have minimal welfare benefit.

Further information is provided on page 41.

Additional areas of concern

Sharing and disclosing data

21. We emphasise the need to adequately balance public interest with the protection of intellectual property rights.

22. Mandatory data-sharing proposals fail to recognise existing initiatives to avoid unnecessary duplication of animal research, the degree of success already achieved, and the technical and legal difficulties involved. They are impractical to implement and would have a detrimental impact on the competitiveness of both industrial and academic research in a globally competitive marketplace, even though there is no evidence that significant welfare benefit would result. The Commission belief that duplication is widespread is not reflected in evidence or in the bioscience sector experience.

Further information is provided on page 44.

Re-use

23. The excessive restrictions imposed by the Commission on the re-use of animals would make it extremely difficult to maintain many research programmes in the EU and, by hindering the application of the 3Rs, would have adverse effects on animal welfare.

24. These concerns were addressed in amendments from the European Parliament.

Classification of severity levels

25. It is very important that severity levels of procedures are properly and precisely defined within the Directive, not least since this is relevant to important judgements elsewhere in the

Directive. Clear bands must appropriately encompass all levels of regulated use, so as to encourage refinement from one band to a lower one.

26. We support the approach taken by the Parliament to initiate the establishment of severity classifications, and welcome the proposal for a Council Working Group to move this forward.

Concluding remarks

27. In summary, health, wealth and social benefits, EU scientific and industrial competitiveness and, importantly, animal welfare, all need to be balanced to ensure the EU adopts a proportionate approach to regulating animal research. The bioscience sector is committed to providing the necessary evidence as well as to working with the UK Government and European institutions to ensure that the revised Directive achieves this balance. The rest of this submission provides a more detailed assessment that we hope will help guide discussion within Government.

Background

28. The UK bioscience sector welcomes this inquiry. We supported the conclusions of an earlier committee - the House of Lords Select Committee on animals in scientific procedures - whose report was published in July 2002. In particular, we agreed with the findings that (i) there is a continued need for animal experiments in applied research, toxicological testing, and in research aimed purely at extending knowledge, (ii) that the UK should strive not for the tightest regulation, but for the best regulation, and (iii) that more consideration could be given to the pursuit of the 3Rs.

29. Both the UK bioscience sector and the Government have responded positively in many ways to the recommendations made by that House of Lords inquiry. We consider the revision of European Directive 86/609 to be an opportunity to further implement and build on those concepts.

30. Research in academia and industry is essential for the acquisition of knowledge and the development of new medicines for medical and veterinary purposes. The use of animals is a small but vital part of that research. Animals are used only when necessary and unavoidable, and where appropriate non-animal methods are unavailable. Both academia and industry have active 3Rs programmes focused on the replacement, refinement, and reduction of the use of animals, and both sectors support and actively collaborate with the UK National Centre for the 3Rs.³

31. We have responded in detail below to the issues raised in the call for evidence, as well as raising some other issues over which we have concerns, or which have arisen in the European Parliament. Whilst we have addressed the issues in much the same order as the call for evidence, we wish to highlight the following as having the most impact on bioscience research in the UK, so that we consider them to be priorities:

- Competitiveness of the EU
- Restrictions on the use and supply of non-human primates
- Restrictions on the re-use of animals
- Sharing of data
- Authorisation of decisions
- Scope of the directive
- Care and accommodation
- Classification of severity levels

³ www.nc3rs.org.uk

Terminology and references

32. We have occasionally used different terminology in different parts of our submission. The Committee can assume that, unless otherwise stated, any reference to:

- The “Committee” refers to the House of Lords Committee.
- The “Directive” or the “proposal” refers to the draft Directive published by the European Commission in November 2008 as a Proposal for a Directive of the European Parliament and of the Council on the protection of animals used for scientific purposes.
- The “Parliament” refers to the European Parliament
- “Parliamentary Amendments” referred to the European Parliament Legislative Resolution of 5 May 2009, first reading.⁴
- The “Commission” refers to the European Commission.
- The “Impact Assessment” refers to the Commission Staff Working Paper titled Impact Assessment.⁵
- The “Prognos Study” refers to the “Study on the impacts of different options for the Revision of the Directive 86/609/EEC on the Protection of Laboratory Animals, Draft summary, Prognos AG”.⁶
- The “Technical Expert Working Group” or “TEWG” refers to the group(s) organised by the Commission to collect scientific and technical background information for the revision.⁷
- The “Expert Internet Consultation” refers to both the process and the results of the Commission “expert questionnaire on the revision of Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes, 16 June - 18 August 2006”.⁸

Additional information

33. Throughout this submission, we have tried to avoid excessive detail. This has sometimes been at the expense of omitting fully referenced background evidence. We are very willing to provide the Committee with additional scientific or policy information on any aspect of this submission, or the draft Directive, on request.

⁴ <http://www.europarl.europa.eu/sides/getDoc.do?type=TA&reference=P6-TA-2009-0343&language=EN>

⁵ http://ec.europa.eu/environment/chemicals/lab_animals/ia_en.htm

⁶ http://ec.europa.eu/environment/chemicals/lab_animals/ia_en.htm

⁷ http://ec.europa.eu/environment/chemicals/lab_animals/scientific_en.htm

⁸ http://ec.europa.eu/environment/chemicals/lab_animals/questionnaire2.htm

1. Objectives

34. A degree of harmonisation of the rules governing the protection of animals in research is required to avoid distortion of the single market and to harmonise animal welfare standards. Some Member States, such as the UK, have particularly high regulatory requirements for using animals in research. We do not wish to compromise the principles operating in the UK, but to point out the potential or actual economic disadvantages created by regulation that would significantly expand that currently in place in the UK.

35. We do not believe the draft Directive is a proportionate response to the problems caused by the current differences in regulatory regimes. Although it might harmonise some aspects, in others it would further exacerbate the internal market distortions. Importantly it further distorts the global market and would therefore render the EU globally uncompetitive.

36. As the ‘call for evidence’ points out, the Commission has stated two aims for its proposed revision of the 1986 Directive, namely:

- Harmonisation of rules to create a level playing field
- Strengthening the protection of animals used in scientific procedures.

37. In its consultation document of 11 May 2009, the Home Office has broken down these two aims into five high-level policy objectives (p39).⁹ The UK bioscience sector supports these objectives.

38. There is no question that the original 1986 Directive contains ambiguous rules and that it is not uniformly implemented in all Member States. We agree with the Home Office statement that “this has left those with higher standards (such as UK) at a competitive disadvantage”.¹⁰ However added regulation does not of itself necessarily result in more uniform implementation.

Current market distortions

Currently, the most significant variations between Member States which impact adversely on competition (or could do so) are in the following policy areas:

- animal accommodation requirements;
- the rigour of authorisation of procedures;
- training and licensing;
- the development, validation and acceptance of alternative methods.

39. Together, these preclude ready mobility of staff and projects between Member States, and/or cause substantial distortions in the cost base of animal research for different countries.

⁹ www.homeoffice.gov.uk/documents/cons-2009-animals-research/cons-2009-animals-research?view=Binary

¹⁰ 11 May 2009. UK Home Office. Consultation on EU proposals for a new directive on the protection of animals used for scientific purposes.

40. In practice this is a much greater problem for EU members visiting the UK than vice versa. For instance an advanced training course was cancelled in 2008 because EU registrants could not be permitted to undertake the course without advance full training and licensing to UK standards. Despite recent adjustments by the Home Office, it is still much more difficult to have senior colleagues from overseas (including the EU) contribute to studies within the UK than vice versa. This results in a steady drain of certain types of experiments abroad in order to facilitate collaboration at minimum bureaucratic cost.

41. Regulations that apply and/or are applied in the UK but not in other Member States have major financial implications. The combination of higher accommodation requirements in the UK and the drive to “full economic costing” of animal pricing in academia are ever increasing deterrents to research using animals.

Requirements of a revised Directive

42. Greater harmonisation is therefore in the UK’s economic and scientific interests in those areas concerning the mobility of personnel, the sharing of projects, and the cost drivers affecting animal supplies.

43. In any revised Directive it would be in the interests of animal welfare to ensure that the minimum acceptable standards are raised above those currently operating in some Member States, and that they are applied uniformly. This encompasses both animal accommodation and the application of ethical evaluation and harm-benefit analysis to the authorisation of projects.

44. The draft Directive covers the issues that require harmonisation but:

- goes well beyond what is necessary in many areas (e.g. scope and controls over authorisation of procedures); and
- encourages Member States to adopt procedures that would in fact hinder harmonisation (e.g. by determining that training requirements be established by Member States).

45. In general there should be subsidiarity over how the harmonised standards are implemented.

46. Specific problems associated with the draft Commission Proposal, and Amendments from the European Parliament, are illustrated in subsequent sections.

Proportionality

47. We do not accept that the proposed Directive meets the criteria for proportionality which is fundamental to EU law. According to this principle, any action by the Community shall go only as far as is necessary to achieve the objectives of a Treaty, and no further.

48. To justify the proposed Directive, the Commission describes a bleak and negative picture of European bioscience. For example, the Commission Impact Assessment describes numerous economic, animal welfare, scientific and social problems (page 4). We neither recognise nor accept this description. Whilst improvements can always be made, Europe still has a successful and competitive bioscience sector, with higher animal welfare standards than most of the globe, good scientific outcomes, and a high level of public support for well-

conducted animal research. A major risk to this sector, in fact, would be the excessive regulation proposed by the Commission. Such regulation would run counter to the EU ‘Better Regulation’ agenda.¹¹

49. The explanatory memorandum claims that the Commission Proposal “complies with the proportionality principle” (page 13) on the basis that : (i) it harmonises practices whilst leaving scope to Member States to identify the most suitable measures for implementation, and (ii) the benefits of the proposed measures to the internal market as well as to animal welfare outweigh the costs.

50. In our view neither of the above requirements is met because: (i) the Directive is too prescriptive in how practices such as authorisations and care and accommodation requirements are implemented, and (ii) some provisions have very few benefits to the internal market, instead significantly distorting the global market whilst bringing very few animal welfare benefits.

51. Proportionality should also involve an assessment of whether the effects of the measure are disproportionate or excessive in relation to the intended benefits, or whether alternative measures exist which are less restrictive. A careful assessment of the costs and benefits should take place, taking into account the spectrum of potential stakeholders. An example of where the proposal has lacked proportionality is the application of highly bureaucratic administrative measures to regulate microscopic non-sentient invertebrate animals. It has estimated a small financial cost to public bodies, but has considered neither the practicability nor the significant cost to industry, academia, and therefore, the EU market place of such a provision.

52. Specific areas where the requirements could be simplified with little/no impact on animal welfare include:

- Restricting the Scope of the Directive to those areas where there is scientific evidence that it would benefit animal welfare;
- Within the Scope, tailoring the extent of control to be proportionate to the potential harm (welfare deficit) caused by procedures;
- Removal of multiple levels of authorisation;
- Harmonisation of training and mobility of staff between Member States;
- Collection of statistical information.

Impact assessments

53. We would have appreciated the opportunity to consider the full independent impact assessment carried out by Prognos (of which only a draft summary was published).¹² Furthermore, the Commission Impact Assessment does not accord with our own experience and views on the impact or cost of the proposal.

54. The Commission has acknowledged the need to improve its impact assessments, and claims that “in the new impact assessment system, continued attention is given to the analysis

¹¹ http://ec.europa.eu/enterprise/regulation/better_regulation/index_en.htm

¹² http://ec.europa.eu/environment/chemicals/lab_animals/ia_en.htm

of impacts on businesses, in order to ensure a regulatory environment that is conducive to their competitiveness, innovation and growth”.¹³ We do not consider that this has been fulfilled in the Impact Assessment for the proposed Directive. Indeed, the issue of competitiveness detailed on page 62 of the Impact Assessment only considers the current issue of outsourcing of animal procedures from EU countries. It does not consider the impact that the proposed Directive itself would have.

55. The Prognos study appears to be based on little more evidence than that of the information in the 66 questionnaires which it states were returned and analysed, and which by its own admission were "not as complete, detailed and fact-based as expected". There are over 200 certified establishments in the UK alone. Greater effort should have been made to gather evidence, and only then to identify ways to streamline existing regulatory burdens in Member States which the Commission had identified, as well as minimise any additional administrative burden and costs that would result from the Directive. This would be more compatible with the EU better regulation agenda which claims that in “reducing red tape and overbearing bureaucracy, the Commission helps business people and entrepreneurs improve competitiveness.”¹⁴

¹³ http://ec.europa.eu/enterprise/regulation/better_regulation/impact_assessment_en.htm

¹⁴ http://ec.europa.eu/enterprise/regulation/better_regulation/index_en.htm

2. International competition

56. High animal welfare standards are welcomed by the bioscience community, in part because good animal welfare and good science go hand in hand. We believe the EU should be at the forefront of promoting best practice in animal welfare where there is sound scientific evidence of benefit, and would hope this encourages other countries to raise their standards.

57. Our concern is that many of the provisions which purport to increase animal welfare standards merely increase bureaucracy with little or no animal welfare improvement. Such bureaucracy increases costs, thus diminishing international competitiveness. We are already seeing commercial investment increasing faster in countries outside the EU, such as the USA, China and India. Increased costs and bureaucracy are inevitably likely to be contributing factors, even if they are not the only reasons. In UK academia, displacement of animal research even takes place to other Member States where the regulation is less onerous than in the UK.

58. The position of the proposal on this issue is not sufficiently explained. On the one hand, the Impact Assessment identifies that there is a "competitive disadvantage for countries with high animal welfare standards resulting from price differences" (page 4). But at the same time, the Impact Assessment suggests that "outsourcing from the European Community" is not likely to be "due to the stringency of animal welfare legislation" (page 62).

59. While international competitiveness is most obvious in a commercial context, the UK's (and EU's) leading academic role in fundamental and applied bioscience research depends critically on controlling costs and reducing bureaucratic delays. The cutting-edge of bioscience research can move very quickly, and bureaucratic delays can kill the lead held by a research group. This is a significant driver to the export of projects to less regulated countries, whether in the EU or elsewhere.

60. UK academic groups undertaking work requiring non-human primates often collaborate with researchers in other countries where the cost of undertaking such research is less (though there is a requirement for all work supported by the BBSRC, MRC, Wellcome Trust, NC3Rs and Defra that 'when collaborating with other laboratories, or where animal facilities are provided by third parties, researchers and the local ethics committee in the UK should satisfy themselves that welfare standards are consistent with the principles of UK legislation (e.g. the ASPA) and set out in this guidance are applied and maintained').¹⁵ Pushing all such research outside the UK, and indeed outside the EU, would seriously deplete the EU R & D skills base and productivity.

61. Unless adequate harmonisation (of regulations and, more particularly, their implementation) is achieved by the new Directive, this will remain a significant issue. Indeed, it may become worse if more stringent minimum requirements are implemented by some Member States but not others. It is therefore vital that the revised Directive does not exceed levels at which it can and will be implemented uniformly.

62. The primary issues affecting competitiveness in the proposed revised Directive are:

¹⁵ www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC001897

- the increased costs of the regulatory burden (in bureaucracy and animal costs)
- regulatory restrictions limiting research that may be undertaken
- regulatory delays to approvals
- disincentive to staff and institutions of investment in animal-based research in the EU.

63. The first three are addressed more specifically in subsequent sections. The last is more generic, but encompasses all three. Animal-based research is extremely expensive to set up – the facilities are costly and the significant scientific and technical staff involved all need extensive training. Animal costs are high and the rate of generating results usually very low (most obviously compared with many of the robotic systems that are increasingly used in biomedical research). Unless the first three factors are implemented satisfactorily, institutions will not invest in the facilities and staff required. And even if they do, the most able staff will not engage in research that is subject to undue restrictions; they will either stop doing animal-based research, or will do it elsewhere.

64. We consider that there would be a major welfare cost if research is relocated outside the EU. Because UK regulations are both tighter and more rigorously implemented than in most other Member States, the drive to export research has to date been greater in the UK than elsewhere in the EU (indeed, some of that export is to other Member States). If EU-wide regulation is stricter and fully implemented then the likelihood is that research relocates entirely outside the EU. If standards slip even only somewhat following displacement, those EU countries with the lowest current standards that the Directive is designed to enhance would fall yet further behind the new Directive standards.

65. Particularly strong drivers of displacement are the requirements and associated costs of animal accommodation, which is often of a lower standard outside the EU. Even when EU scientists apply best practice to the procedures they themselves undertake outside the EU, they have little or no control over the accommodation standards in which animals are bred or kept. Displacement is therefore almost bound to have adverse welfare impact on the animals used, and is to be avoided.

66. While the major international pharmaceutical companies are likely to maintain sound standards in their in-house research, wherever undertaken, they are increasingly subcontracting animal work to contract organisations. This is particularly true of biotechnology SMEs which would be unable to undertake much of their research without such organisations. If contract organisations, which operate in a highly competitive global market place, are subjected to uncompetitive costs, they will be forced move from their concentrated base in the UK to more accommodating regimes. This could result in a serious debasement of welfare standards most particularly for the more advanced species (dogs, non-human primates) that are used in much contract research. It would also cause serious economic loss to the UK.

67. There is substantial competition from countries such as China, India and Singapore in developing infrastructure to undertake animal research, which includes not just routine toxicity tests but also R & D. To maintain their competitive edge, the UK and other EU countries need to ensure their brightest and best scientists and industries have sufficient incentive to remain within the EU.

68. Of particular concern in terms of international competitiveness are the amendments passed by the European Parliament on data sharing (Amendments 132, 180, 134, 135, 136, 137). Our sector considers these to be ill-informed, ill-thought out, impossible to implement rigorously, and to have the potential to drive out of the EU most research with any potential intellectual property value.

69. The explanatory memorandum of the Commission proposal claims that "optimum implementation at the national level through the use of identified best practices will provide ample opportunity to reduce unnecessary red-tape and administrative costs". Unfortunately, in many cases the provisions proposed will do exactly the opposite. For example, making mandatory methods of appropriate (humane) killing and cage sizes will increase the cost of research, and hinder the application of best practice without proportionate animal welfare benefits. For example, it does not allow yet-to-be-developed refinements or superior methods of humane killing and housing regimes to be incorporated into the respective Annex or introduced into practice. By creating rigid and complex systems of authorisations and other permissions, the draft Directive fails to reflect the good practice that exists currently in many member states (such as the use of notifications where harms to animals are minimal).

70. These examples illustrate the disincentives which would be created by the proposed Directive to retaining animal based research within the EU.

3. Restrictions to research on non-human primates

(Article 8, Article 10, Article 50 and Amendments No 56, 57, 58, 59, 60, and 61)

71. Around 12 million animals are used each year in scientific procedures in the EU. Of these, around 10,000 (less than 0.1%) are non-human primates (NHPs). By comparison, the US uses three times the number of NHPs in relation to total animal procedures.

72. 'NHPs'¹⁶ include:

- Great Apes, such as chimpanzees and gorillas; (Great Apes have not been used for medical research in any EU country since 2000).
- New world monkeys such as marmosets and squirrel monkeys; and
- Old world monkeys such as macaques.

Impact of limitation of NHP use

73. We agree with the statement in the draft Directive that use of non-human primates is of highest concern to the public. Although there is evidence of this from surveys, the public remains supportive of research including the use of NHPs when appropriate and proportionate controls are in place. The proposed restrictions to the use of NHPs on the basis of their phylogenetic relation to humans are disproportionate and potentially detrimental. The revised Directive should recognise the positive contribution that the use of NHP has made to the fundamental knowledge which has led to treatments for humans and animals.

74. Limiting the use of NHPs to 'life threatening or debilitating clinical conditions' as per Article 8 (1) (a) would have the effect of:

- Restricting fundamental research into structure, function and malfunction of humans and other animals, including studies in immunology, anatomy, physiology (including reproductive health), microbiology and neuroscience. Such research is crucial to further development of therapeutics for human and animal health.
- Limiting R & D investment in health related-sectors;¹⁷ and thereby impairing EU competitiveness.
- Slowing innovation and impeding vaccine and drug development and commercial collaboration.

75. We are concerned that this proposed restriction has never appeared in the documents or deliberations of the Technical Expert Working Groups, the Internet Consultation or the impact assessments for the Directive.

76. The Commission Impact Assessment claims, in relation to the use of NHPs in scientific procedures, that it is "controversial whether their high sensitivity and awareness makes them a good scientific model under the current breeding, housing and care conditions" (page 50).

¹⁶ Reference in this document to NHPs refers to new and old world monkeys only.

¹⁷ Olsen J., Baker M., Freund T., di Luca M., Mendlewicz J., Ragen I., Westphal M., 'Consensus document on European brain research' Journal of Neurology, Neurosurgery and Psychiatry (2006) 77 (supplement 1) notes that Europe's young neuroscientists are taking up posts in the USA and staying there.

77. We are concerned that there is no evidence to support this claim that current care and accommodation requirements adversely affect their efficacy as a scientific model. It is contrary to the views of leading researchers and institutions across the world. The reports of the Weatherall Committee¹⁸ and the Scientific Steering Committee (SSC)¹⁹, were already in the public domain at that time, but were not cited by the Commission.

78. Furthermore, the Commission made their proposals for restricting the use of NHPs after requesting an assessment from the Scientific Committee on Health and Environmental Risks (SCHER), but before the report was published. This report²⁰ found that at present there are no valid alternatives which would allow for a discontinuation in the use of NHPs. Both the SCHER Report and the UK Weatherall Report clearly detail the disease areas in which the use of NHPs have made a major contribution to therapeutic outputs and where continued use is deemed to be necessary. Neither suggests that current accommodation and care standards impede this vital contribution.

79. We believe the amendments introduced by the European Parliament report (Amendments 56 and 57) adequately addresses our concerns regarding use by lifting the restrictions on the use of NHPs. It should therefore be supported.

Areas of research which may be curtailed due to the proposed restrictions

80. The provisions in Article 8(1) (a) have the potential to prohibit certain lines of research which are essential in developing fundamental areas of knowledge into human and animal health. The inability to undertake such fundamental research in the EU will erode the scientific knowledge-base and drive R & D investment out of the EU.

81. Some examples of fundamental research which may be curtailed by the current draft of the Directive include research on:

- memory systems in the primate brain (to potentially assist memory disorders)
- decision-making and social valuation (to be applied to neurological illnesses such as autism, depression and obsessive compulsive disorder)
- attention (to help understand disorders such as Alzheimer's disease or attention deficit hyperactivity)
- neurostimulation (to help develop techniques to improve the recovery of limb function following injury to the brain or spinal cord)
- vision (to help understand and treat visual disorders)
- reproduction (to help understand and treat early miscarriage, endometriosis, polycystic ovary syndrome and problems with menstrual cycles).

82. Limiting the use of NHPs in the EU will certainly drive researchers to non-EU countries such as the USA and Asia. We have already seen trends within industry to move research using NHPs out of the UK due to the high costs of supply, transportation and previously to gain protection from animal extremism as well as to limit bureaucracy. We

¹⁸ www.acmedsci.ac.uk/images/project/nhpdwnl.pdf

¹⁹ "The need for non-human primates in biomedical research" by The Scientific Steering Committee (SSC), April 2002

²⁰ http://ec.europa.eu/environment/chemicals/lab_animals/pdf/scher_o_110.pdf

would not wish to see a further erosion of the research-base due to restrictions in NHP use. In the public sector, academics are noting that young researchers in neuroscience are ‘taking up posts in the USA and staying there’.²¹ Movement of young researchers out of the UK and out of the EU will have a significant impact on the UK’s research base.

Ban on use of great apes (Article 8 (2) and Safeguard Clause (Article 50))

83. Article 8(2) bans the use of great apes in procedures, subject to the safeguard clause in Article 50. Great apes have not been used in research in Europe since 2000 or in the UK since 1998. This is not cause however for an outright legislative ban, and therefore we strongly argue that the safeguard clause be retained. An outright ban should logically and ethically mean that any vaccines developed using great apes should also be banned in Europe. For example, vaccines for Hepatitis C are being developed in chimpanzees, as that is the only other species, aside from humans, which develops a Hepatitis C infection. It is essential that we keep our options open to use great apes if the need arises, especially as we see the development of new variants of disease and new global pandemic threats.

Animals bred for use in procedures (Article 10)

84. The draft Directive requires that non-human primates must be second generation bred in captivity (F2) to be able to be used in research and in Annex III sets out a timetable for breeding up of F2 animals for use in research. The rationale for this provision is to end the use of wild-caught primates for breeding purposes.

85. No research has been carried out, however, as to:

- whether this proposal will have any real impact in reducing the taking of animals in the wild;
- the achievability of the proposal within the designated timeframe;
- the animal welfare impact for the F1 animals that would need to be culled, and the impact of increased breeding pressure on stock females;
- the impact of significant in-breeding to achieve the targets;
- whether there would in practice be the real welfare gains that appear to be assumed.

86. The Commission’s Impact Assessment casts considerable doubt on its own proposal. The Impact Assessment points out that "for macaques, the shortest possible transitional period would be about seven years from now but it is very unclear when breeding colonies could achieve self-sustainability in practice" (page 50).

87. The assessment continues to point out numerous problems and uncertainties with the proposal. For example, it acknowledges that "a particular problem arises from the fact that it has turned out to be difficult for several species to establish self-sustaining breeding colonies" (page 22). In addition, the Commission acknowledges that “breeders would in the short run easily be able to sell the same amount of F1 animals to countries outside the European Community than they currently export to the European Community. Such a supply shift could only be prevented by a global move to use only F2+ animals”. The Commission recognises that “the impacts on science and competitiveness would be highly negative”.

²¹ Olsen J., Baker M., Freund T., di Luca M., Mendlewicz J., Ragen I., Westphal M., ‘Consensus document on European brain research’ *Journal of Neurology, Neurosurgery and Psychiatry* (2006) 77 (supplement 1)

88. Contrary to the above position, the Commission goes on to propose in the Impact Assessment that "a reasonable transitional period of seven years for the transition to F2+" for macaques (page 52).

89. This provision will have an immediate short-term impact on the availability of such animals for academic, government, EU and industrial research programmes in Europe - albeit with some exceptions, since F2+ macaques are available for academic research in the UK (at some considerable cost). Owing to the limited number of breeders and the significant demand from countries such as the USA which do not have such restrictions, it is likely that breeders will favour other countries first. This will consequently compromise supplies to the EU and hence the competitiveness of European-based research.

90. The requirement to use F2 animals will necessitate a greater than 100% increase in the number of animals kept in captivity for breeding purposes. Again, this appears to have animal welfare implications which are contradictory to the intended aim.

91. The availability of first and second generation purpose-bred macaques is already such that breeders and suppliers can currently only just cope with the demand from the global scientific community. Macaques (*cynomolgus* and *rhesus*) are the more frequently used species of NHPs in toxicology tests to assess the safety of new drugs in neurological disease models such as Parkinson's, and in infectious disease, malaria and the production of vaccines.

92. There are a number of ongoing pilot projects evaluating the impact of self-sustaining colonies and inbreeding. Some of these pilots show significant impact on fertility rates and other physiological parameters. These need to be properly completed to better assess the impact of an F2 requirement both on animal welfare and on research.

93. We therefore support the amendment (Amendment 60) from the European Parliament which provides that an animal welfare assessment and feasibility evaluation of implementation of the F2 requirements should take place five years after entry into force of the Directive.

Release of NHPs from controls

94. Parliamentary amendment (80) would preclude release of NHPs. Such a blanket ban would, for instance, prevent the disbanding of healthy animals in a breeding colony to zoos or other non-research institutions, outcomes which are contrary to 3Rs policies. Decisions on release should be based on individual assessment, with veterinary input, not on such sweeping rules.

NHPs as endangered species

95. Whilst this has not been a prominent part of the debate since the publication of the draft Directive, it is worth mentioning that antivivisection groups frequently imply that the use of NHPs in research is contributing to potential extinction.

96. This is not the case. None of the species of monkey commonly used in research is endangered. Indeed, in some countries these monkeys are considered as pests and are routinely shot or captured due to the damage caused by excessive numbers.

97. The issue of endangered species was properly addressed in the Commission Impact Assessment, which stated that there is "no indication that this is really a problem for those species used in large numbers for research." More generically it states that "Research plays an insignificant role for biodiversity in comparison to the destruction of habitats, e.g. of tropical forests, that should be urgently addressed via conservation policies" (page 39).

4. Extension of the Scope

(Article 2, Annex I, Amendments No.28, 30, 31, 34, 150, 151, 152)

Overview

98. The extension of the scope of the proposed Directive is not justified. It would bring large areas of research that were previously not regulated under bureaucratic control without any tangible animal welfare benefits. This would impede scientific research and markedly restrict our ability to compete internationally in areas of considerable commercial and scientific importance.

99. Whilst it is acknowledged that there is currently a significant disparity between Member States as to the extent of protection by regulation, the sweeping extension of scope of the draft Directive is likely to exacerbate the disparities between the internal EU market and the global market.

100. We believe that the economic burden on national authorising establishments, research institutes, and the commercial sector, estimated conservatively by the Commission in five Member States to cost between €6.6 million and €10 million per year, far outweigh any animal welfare benefit this provision might bring.

101. The provisions would impact negatively on UK scientific research, education, the development of aquaculture-related or other biotechnologies and environmental studies.

Pain, suffering distress or lasting harm

102. In addition to the general provisions on scope in Article 2, the draft Directive defines a 'procedure' as any use of an animal for experimental or other scientific purposes, with known or unknown outcome, which "may" cause the animal pain, suffering distress or lasting harm.

103. Our organisations consider that use of the word "may" in the definition of a procedure is seriously problematic, because there is always a remote possibility that anything done to an animal "may" cause pain, suffering, distress and lasting harm even when it is neither likely nor intended to do so. This has caused difficulties for the interpretation of the A(SP)A in the UK. We support those amendments passed by the Parliament which substitute "is likely to" or "is expected to" for "may" (Amendments 28 and 42). However, Amendment 34 (definition of procedure) is problematic (i) because it uses "may" rather than "expected" or "likely", and (ii) because it uses "may or may not". This Amendment would therefore bring within the scope the use of any animal used for any scientific study, even when there is no harm inflicted and even when the animal is not sentient. This would cover animals humanely killed for their tissue, all animals used in observational studies and all immature invertebrates. In practice this would not be possible to manage, and is clearly inconsistent with Amendment 33 which excludes practices that do not cause pain, suffering, distress or lasting harm.

Vertebrates bred for organs and tissue

104. The Directive and Parliamentary amendments are inconsistent as to the inclusion of animals killed humanely for their tissues. The claim by the Commission in the Expert Internet Consultation that "the extension of the scope to cover animals bred for the primary purpose of

their tissues and organs would significantly improve the welfare of the animals involved" is not supported by evidence, and was not supported by the Technical Expert Working Group.

105. Extension of the scope to all such animals would cause a major increase in regulatory burden with no animal welfare benefit. Indeed it may adversely affect welfare in that raising the level of bureaucracy and cost around using isolated organs and tissue removes an incentive to use them instead of using living animals. It therefore runs counter to the entire 3Rs agenda. The assumption from the Commission that "only a small number of companies will specialise in providing these services thus keeping additional administrative costs low" does not appear to have supporting evidence.

106. The Technical Expert Working Group for Scope agreed that the primary concern with such animals should be their welfare, and that this could in practice be promoted by ensuring that the authorisation of premises automatically meant that all animals of protected species contained therein were covered by the scope of the Directive with regard to housing and husbandry conditions, education and training of staff etc. Moreover allowable means for humane killing are also covered by the Directive.

107. The implication of this is consistent with our view, namely that animals bred for organs and tissues should fall under the general provisions of the Directive, but should not be classified as procedures or require specific authorisation for humane killing. We consider the situation to be improved by the Parliamentary Amendment 28, but this will require confirmation from the Council.

Routine procedures

108. The Technical Expert Working Group for Scope agreed that routine procedures, such as marking and any management or clinical veterinary duties carried out for the day-to-day well-being of the animals should be excluded. We support this conclusion. It would be particularly helpful if in Article 2.4 (b) the identification of the genetic status of animals was recognised as the routine husbandry procedure that it is.

Immature forms of vertebrates

109. Including all embryonic and foetal forms as from the last third of their development is arbitrary, since sentience has not been established for all of them. For example, the Technical Expert Working Group for Scope considered that they "were not in a position to form a scientific opinion as to when a rodent fetus or new-born may be capable of suffering, although suggested the final 20% of pregnancy may be appropriate for rodent and poultry species".

110. A particular issue would be the cover of embryonated hens' eggs for vaccine production and quality assessment (for some production processes), where more than a million eggs a day are used to fulfil the demand for flu vaccine supply and flu pandemic preparedness.

111. An amendment from the European Parliament (Amendment 30) has restricted the "independently feeding larval forms and embryonic or foetal forms" to species of mammal as from the last third of their normal development. This is helpful, although the wording will need further clarification, since mammals do not have independently feeding larval forms.

112. The European Parliament amendment would now exclude fish embryos, which are used as alternatives to higher animal species. We support this, since including them in the scope would subject them to administrative procedures listed in the Directive, and discourage further research on alternative methods using these immature non-sentient forms. Our view is consistent with that of the Technical Expert Working Group for Scope, which noted "significant difficulties with including these forms in such a way that all provisions of the Directive apply, in particular the impracticality of making an accurate count".

113. The issue of the development stage at which there is sufficient anatomical development to permit sentience, and therefore to warrant inclusion in the controls, requires a better scientific analysis.

Invertebrates

114. There is no clear scientific rationale as to why the scope should be extended to selected invertebrates (cyclostomes, cephalopods and decapods). The report of the Scientific Committee of the European Food Standards Agency (EFSA) does not provide robust scientific evidence to support such an extension. Extensive studies have not produced scientific evidence that decapods perceive pain and might 'suffer' during scientific procedures.

115. There may be a tentative case for extending EU regulation to certain adult cephalopods, such as octopus (Superorder Octopodiformes), squid and cuttlefish (Superorder Decapodiformes). There is some evidence these animals may experience pain and suffering resulting from having well developed senses and complex nervous systems. The only invertebrate covered by the UK legislation is *Octopus vulgaris*. This conclusion would be consistent with the findings of the Technical Expert Working Group which found that "insufficient evidence is available at the present time to consider the inclusion of any invertebrate species other than of cephalopods".

116. Including other invertebrates, together with immature forms, has no scientific basis and would result in regulation covering potentially enormous numbers, given the density of immature planktonic forms in every sample of seawater. Certainly the Commission has provided little robust scientific evidence as to why such a provision is proportionate or necessary.

117. We consider that European Parliament amendments 151 and 152 (which remove cyclostomes and reduce the species of decapod crustaceans to infraorders Brachyura and Astacidea) to be an improvement. However, the decapods Brachyura and Astacidea, which cover lobsters, crabs and crayfish, constitute the majority of decapods used in academic research and research into aquaculture. In addition, immature forms are still covered. As a result, the regulatory burdens would in practice be little altered by the European Parliament amendment.

118. Extending the scope of the Directive to cover whole classes of invertebrates may also have the unintended consequence of undermining the incentive to use them as animal models in place of vertebrates; decapods are increasingly used as replacements for higher order animals as part of the 3Rs agenda.

119. Crustacea are common, cheap, abundant, the adults are relatively large, and they are easy to keep and handle. Their physiology makes them ideal for educational studies in

behaviour and physiology. There is no justification, but much disadvantage, to banning such use for secondary education. It will also have an impact on in-vivo skills training at undergraduate and postgraduate levels. Decapods are regularly used in such training; imposing a regulatory cost for using such animals is likely to lead to the EU being a less attractive place to undertake such training. The ABPI has recently reported on the shortage of in-vivo skills in the UK and the need to ensure that live animal work is supported.²² The Bioscience Innovation Growth Team Review and Refresh of Bioscience 2015 also proposes that in-vivo skills be included in the Strategically Important and Vulnerable Subjects list.

120. Decapods are ecologically sensitive and their biology therefore of great scientific interest in addressing environmental concerns (pollution and effects of climate change).

121. Decapods are commercially very important. Studies of decapod crustacea for the aquaculture industry could disappear very quickly to countries in the Far East where the UK faces intense commercial competition. The increased cost and bureaucracy in research would diminish the UK's competitive edge in industries such as the bio-discovery of useful biotechnologies and natural products.

122. Taking the above into account, we believe that decapods, cyclostomes and immature forms of all invertebrates should be removed completely from the scope of the Directive. The impact of including them in the legislation would be grossly disproportionate to any tangible welfare benefit achieved.

Problems of implementing the proposed legislation on invertebrates

123. It would be very difficult to apply the requirements of the Directive to invertebrates in the following areas:

- Assessment of 'severity' level, since this is based on experience of pain for which there is very little scientific evidence in such species;
- Methods of humane killing, since there are no known methods of rapid, pharmacologically-validated euthanasia that could be specified for decapods. It is unclear if any of the reagents currently used to 'anaesthetise' invertebrates have any analgesic benefit.
- Inclusion of larval (but nonetheless 'free-feeding' stages) would pose questions over legal controls over sampling seawater, assessing plankton distribution, and even whether feeding plankton to experimental fish would be a regulated procedure.
- Only specialists could identify the species of immature forms, which can be microscopic. Even without species identification, counting the huge numbers would be an insurmountable obstacle.
- Supply and breeding, since decapods are obtained from fishing by-catches, collected directly from the wild or purchased from commercial growers. There are no dedicated breeding establishments and none are likely to be set up as viable businesses.
- The sheer diversity of species and lifestyles within the invertebrate orders would require regulations to be drawn up almost on a species by species basis.

²² www.abpi.org.uk/Details.asp?ProductID=325

- Few staff currently have the required knowledge of crustacean biology to enable them to assess potential welfare issues (even if they exist) or implement the legislation. Training would be costly and time-consuming. The only people available to provide any training would be the scientists proposing to do the work.

Death as a lasting harm

124. An amendment was tabled in the European Parliament to include death as falling within the definition of lasting harm. It was not passed, but could reappear at second reading.

125. Our organisations oppose the inclusion of death as falling within the scope of a “procedure” (under the term “lasting harm”). This could result in numerous appeals of decisions which apply a severity classification and conduct a harm-benefit assessment. In particular it would prove exceptionally difficult to determine what degree of harm should be given to death itself, given the fact that the overwhelming majority of animals used in scientific research are bred for the purpose, and are humanely killed at the end of the procedure in any case (in order to analyse their tissues).

126. We note that our view is consistent with a High Court ruling in 2008 in the UK which rejected the inclusion of death as a lasting harm under the UK A(SP)A.²³ We can provide a more detailed note to the Committee on our rationale if requested. The lesson from the High Court experience is that it would be much more satisfactory for the Directive to be explicit in excluding humane killing from being a regulated procedure.

²³ http://scienceandresearch.homeoffice.gov.uk/animal-research/publications-and-reference/publications/09pcd-holders-circulars-2008/06june2008/PCD_Circular_June_2008.pdf?view=Binary. The BUAV argued that the death of an animal is simply that it is no longer living, as distinct from any suffering preceding death should be considered in the cost benefit assessment of a project licence application as an adverse effect, but the court ruled against the BUAV.

5/6. Authorisation of Decisions

(Articles 20-43)

Principle

127. In accordance with general regulatory principles, the extent of control should be proportional to the potential harm caused by the procedures and therefore the potential welfare gains of regulation. The level of bureaucracy and burden of costs should be minimised when the harms to animals are least. This would allow the competent authority to concentrate efforts on maximising application of the 3Rs, and improving animal welfare for project licences that involve moderate or substantial pain, suffering, distress or lasting harm. The role of the competent authority should not detract from the importance of other safeguards elsewhere in the system, including ethical review, harm/benefit assessment, application of the 3Rs, humane endpoints etc.

Commission proposal

128. The Commission proposal is one of comprehensive mandatory authorisations. There are some benefits to authorisation, namely that it gives a centralised process which facilitates a consistent application of control procedures. It may reassure the public in that a further level of control is applied, and be more appropriate for smaller establishments that do not possess the ability to conduct robust processes because of limited internal expertise. It passes the final accountability to the competent authority in cases of dispute.

129. The explanatory memorandum in the Commission proposal points out that *“stakeholders supported the approach to ensure a flexible mechanism that allows implementation to be determined at a national level”*.

130. The reality is that the Commission has proposed complex and multiple levels of authorisation and review prior to and during the conduct of research. This will not automatically improve the implementation of the 3Rs; indeed it may have a negative welfare impact by hindering the flexibility to rapidly adopt new techniques which would advance animal welfare.

Complexity of authorisation process

131. The complexity of the levels of authorisation and review currently proposed illustrated in the diagram below.

1. The applicant must submit details to a competent authority for ethical evaluation, on which apparently no time limit is placed. The ethical evaluation must involve extremely detailed assessment as set out in Article 37, with no less than 15 areas of information to submit. The results of the ethical evaluation are presumably returned to the applicant for revision.
2. The establishment must keep records of the ethical evaluation (from the competent authority), to submit back to the competent authority on request.
3. The user establishment must then submit the modified application to a (probably different) competent authority for project authorisation, together with the project proposal and details of the 10 further areas of information required as set out in Annex VII.
4. The establishment must keep records (from the competent authority), in order to submit back to that competent authority upon request.
5. There are additional requirements for retrospective assessment to be determined during the ethical evaluation. The non-technical project summary must then be updated with the results of the retrospective assessment.

Timing of decision-making

136. The Commission Impact Assessment highlights that “member state authorities seem to have relatively unclear standards for the timing of these procedures and often also the criteria for decision-making seem from the applicant's point of view open to interpretation” (page 16).

137. We welcome, in principle, deadlines for authorisations. However, we believe such deadlines should also cover the ethical evaluation, which could be open-ended (depending on how the competent authorities are designated) and could cause substantial delays.

138. It is unclear why the proposal has separated these two processes, since it stated in its Expert Internet Consultation that “it is important to note that terms authorisation and ethical evaluation are interlinked. This is especially important when discussing delays due to authorisation... It is not possible to separate the two in a meaningful manner and in a way that would be applicable throughout the EU. Therefore the stated delays due to authorisation are considered to cover also delays due to ethical evaluation”. We would support this analysis.

139. Although the proposal has reduced the problem of different interpretations of what is required for decision-making, this is at the cost of a system which is overly prescriptive, complex, and at times self-contradictory and confusing.

The possibility of notifications

140. The proposal is for a rigid system of authorisations of all projects, together with an ethical evaluation process to which it is not clear that time limits apply. The proposal does not take into consideration sufficiently the additional financial costs of such a highly controlled system, and has not adequately assessed the potential delays to research which could result. The Commission appears not to have assessed whether notifications could have

been applied in some cases, even though they are occasionally used in some Member States where animal welfare standards are high.²⁵

141. A notification process allows rapid progression of projects or amendments where harms to the animals are minimal and ethical evaluation at a local level has been favourable. The competent authority still has the opportunity to intervene and/or conduct retrospective audit if any issues deemed to be of concern arise. It also allows prompt implementation of refinements to procedures which can be identified during studies. It allows both the competent authority and the establishment to focus effort on those projects and procedures involving greater pain, suffering, distress or lasting harm.

An alternative approach

142. The Commission has consistently emphasised the need for flexible implementation of the Directive at the level of the Member State. In our view, this should include the ability for countries to use notifications where appropriate, and also to allow ethical evaluation at the institutional level in certain cases. Hence different mechanisms can apply in different Member States, as long as there are safeguards to ensure projects have been properly justified, ethically evaluated and all safeguards applied.

143. One possible approach would be for the internal permanent ethical review body (PERB) of an institution (which is capable of being designated as a competent authority for ethical evaluation under the Commission proposal) to conduct an initial ethical review in order to assign a severity classification to the proposed procedures. If these are only classified as mild, the PERB could continue to conduct a full ethical evaluation including harm/benefit assessment.

144. Projects containing only mild procedures where the ethical evaluation was favourable could then be notified in advance to the competent authority for authorisations, together with details of the ethical evaluation and notice of the intended start date. There must be sufficient time for the competent authority to intervene, and a mechanism to flag up issues which might be of concern (for example, use of an unusually large number of a species of high sensitivity). Authorisation by the competent authority could be given retrospectively, or could be deemed to be given after a certain time period allowed ('Tell & Do after a preset interval').

145. This approach would be consistent with the findings of the Technical Expert Working Group. They noted that "in some countries the green light of the registered ethical review committee is at the same time the authorisation of the project", and considered that "without the green light of the ethical review committee no authorisation will be granted".

146. Projects containing moderate or substantial procedures and all those involving NHPs must be submitted to the competent authority for authorisation. The competent authority could conduct a full ethical evaluation and confirm whether a 'favourable' assessment was correct. Applying a principle of proportionality, a decision of the competent authority should be available within 30 days for moderate procedures or 60 days for severe procedures or those using NHPs. A longer period may be appropriate for exceptionally complex projects ('Submit & Wait for authorisation').

²⁵ For example the German Animal Welfare Act allows notifications for the use of invertebrates. Article 8a (1) states that "Any person intending to conduct experiments on cephalopods or decapods shall notify the planned experiment to the competent authority at least two weeks before the experiment begins".

Amendments to Projects

147. Amendments to mild or moderate project licences that do not increase the severity limit should be notified in advance to the competent authority with no time limit before implementation ('Tell & Do'). Amendments that involve an increase in severity limit, substantial procedures or those in NHPs should be submitted, together with the outcome of the PERB's ethical assessment, to the competent authority for authorisation. This is consistent with the Technical Expert Working Group's proposal that "a local ethics committee could approve minor changes on a fast-track basis and refer major changes to the national competent authority".

Additional parts of the authorisation process

148. The Prognos study states that "retrospective analysis has the potential to verify which types of animal tests have really been useful for the progress of science and which have been rather unreliable" (page 17). This is only of limited truth:

- Looking at single projects in isolation shortly after completion can have benefits for the 3Rs, but will not be particularly useful in determining scientific value given that the benefits of fundamental research can take a decade or more to become apparent
- Systematic reviews may be of value but depend on a substantial body of research, not single studies
- The assessment of the value of scientific research is, and should always be, an intrinsic part of the scientific process. It should come about through publication of results and subsequent assessment of a body of properly peer-reviewed scientific papers.
- For regulatory studies the majority of work is conducted to meet internationally agreed requirements. It will not be reasonable or appropriate to interpret the outcome of a single project and its impact on the overall scientific approach.

149. The Commission has itself acknowledged the potential problems with retrospective analysis which it identified in its preliminary analysis. The expert Internet consultation states that "preliminary results indicate that introduction of retrospective analysis of all projects would however lead to a high increase in costs in the short and medium term while it is yet uncertain if the objectives of learning from mistakes and achieving more accurate data collection on severity and benefits are met" (page 26).

150. Annual review of projects (Article 26) should be restricted to projects that are classified as "severe", as should retrospective review, as now proposed by the European Parliament.

Harmonisation of training

151. The Commission draft proposes that Member States be left to determine training requirements (Article 20). However, there are already clear differences in training and licensing requirements between Member States. This hinders ready mobility of staff and projects between Member States, and thereby incurs significant bureaucratic costs. Unless the new Directive specifically ensures that training requirements are unified and uniformly recognised across the EU, unnecessary bureaucratic obstacles will remain.

Collection of statistical information

152. Retrospective reporting of severity is agreed to be desirable but (as several groups internationally have found) surprisingly difficult to achieve in a manner that is meaningful, efficient and consistent. Making it mandatory, while leaving it to Member States to decide how it will operate, will result in further major disparities between Member States in terms of both the bureaucratic load and the comparability of data. If such a requirement is to be introduced, it needs to be designed to be effective and efficient and be operated consistently across Member States.

153. The enhanced scope of the Directive will greatly increase recording and reporting requirements, as described elsewhere.

Restrictions on procedures

154. The draft Directive and/or Parliament's amendments impose a series of restrictions on the research that may be undertaken within the EU. Several would have a serious impact on the ability of the EU to maintain its world-leading science base.

155. We do not consider these restrictions to be well justified. They are an example of how the Directive is in general overly-prescriptive, excessively detailed, and too complex.

156. Examples include:

- Restricting or preventing use of non-human primates (NHPs) in fundamental research. See section 3 on NHPs on page 16.
- Preventing procedures classified as 'severe' if more than 'transient'. Neither word is currently defined adequately. This restriction could preclude research into the most debilitating or serious human and animal diseases, such as arthritis or toxaeemias. Rather than an outright ban, the approach should be to ensure a rigorous ethical review incorporating a harm:benefit analysis that ensures that serious adverse impact is only authorised when the likely benefit warrants it. A reference point in human medicine would be appropriate here: the procedures to be undertaken would be no worse than those suffered by human patients and would almost always be far shorter lasting (e.g. about two weeks for arthritis studies in rodents compared to decades for the disease in humans).
- Prevention of some types of 'reuse' (Article 16). If taken according to the wording of the Commission draft, this would prevent procedures such as the implantation of telemetry devices followed by recording data from them. Just such techniques foster the 3Rs by generating more and better data from fewer animals, and therefore should be encouraged rather than restricted. The Parliament amendments (No.s 72, 73, 74, 75) adequately address this problem, and should therefore be supported.
- Restrictions on research undertaken outside research institutions (Article 21). The draft is inconsistent but there is a strong potential for there to be serious restrictions on the use of animals that are not purpose bred (which would for instance restrict environmental studies) or the use of non-approved accommodation (which would prevent research on farm animal welfare under commercial conditions). The wording would appear to derive from a blinkered view that all animal research is for medical research, which is to ignore research for veterinary, farm animal or environmental studies.

- Restrictions on release from the controls. Article 19 includes "animals used or intended to be used in procedures", and Amendment 80 excludes NHPs from release. It is entirely right that such release should be controlled, and be subject to veterinary approval. But it is important to avoid wording that has unintended consequences. For instance, it would be absurd to prevent release back to the wild of wild animals caught in environmental studies. It would be similarly foolish to block the release of a monkey colony that was no longer required for research. Both these instances would currently require culling of the animals or the entire colony if no longer needed for research.

7. Care and Accommodation

(Article 32 and Annex IV)

157. The principle of minimum standards of care and accommodation for laboratory animals across Europe is desirable.

158. The draft Directive sets out mandatory standards for care and accommodation in Annex IV. This incorporates elements of the guidelines from Council of Europe ETS 123 Appendix A. The dates given when the guidelines would become mandatory are January 2012 or January 2017 depending on species. These are fixed dates, regardless of when the Directive is actually passed and then implemented in member states.

159. It is of note that the Commission has already approved ETS 123 as a recommendation “on guidelines for the accommodation and care of animals used for experimental and other scientific purposes (2007/526/EC - 18 June 2007)” and states that “Member States should pay regard to the guidelines set out in the Annex to this Recommendation”.

160. There is no consistent approach to the status of these guidelines. They are referred to originally in the Impact Assessment as “standards” (page 11), but subsequently as “guidelines” (page 18).

161. Considerable expertise was involved from both scientific and animal welfare organisations over a number of years to develop the ‘good practice guidelines’ for ETS 123. The expert groups submitted background information to support their proposals, based on scientific evidence and practical experience, and these are particularly valuable in the general sections which sets out the performance standards required for animal welfare. However, specifications for cage sizes are engineering standards, for which specific scientific evidence does not exist.

162. There are significant concerns in many sectors across the EU that this proposal is overly prescriptive and lacks proportionality, given the significant costs and uncertain welfare benefits, particularly for rodent species. The Commission has estimated that only about 20% of establishments in Europe have implemented ETS 123. Those complying could be smaller establishments where the standards were easiest to implement, and/or those with the greatest capital expenditure programmes, such as in the commercial sector.

163. A similar figure for compliance is specified by the Commission in its analysis of the data from the Prognos study in 2006 (page 48) as a “preliminary finding” and therefore cannot be relied upon, given the diversity of respondents and non-respondents to the survey. In fact, the sampling through the survey was likely to be biased towards those users who were more likely to be in full compliance, and did not take account of the fact that, where animals are not bred in-house, a small number of breeders supply the overwhelming majority of animals to user establishments.

164. It is a credible proposition that large laboratory animal species such as dogs and non-human primates need better housing and husbandry practices than they currently have in many EU member states. However, for rodents, a greater degree of flexibility in space allowances is adequate for stock animals, especially given the long-standing experience with

current UK provisions. Good animal welfare can often be achieved by means other than increasing cage size, such as by environmental enrichment.

165. The standards now proposed in Annex IV for space allocation for stock rodents significantly exceed the enforced UK standards set out in the UK Codes of Practice. These provide animal welfare to the high standards demanded by the Home Office, even though they do not meet the exact specifications of ETS 123.

166. Several Articles (especially 32), probably unintentionally, would restrict the ability to undertake research on farm animals and on wildlife. It is essential that scientific research for the welfare of farm animals, and for ecological protection and wildlife or conservation purposes, can be carried out under conditions representative of those on the farm or in the wild or elsewhere. For example, the space allowance under which broiler chickens are kept on a farm is far less than that detailed in the draft Directive.

The situation in the UK

167. A strict and detailed Code of Practice has existed in the UK from 1986 with stocking density requirements less than those proposed in the revised Appendix A of ETS 123. The UK stock holding floor space allowances have never been cited as being inadequate or directly leading to compromises in animal welfare.

168. The UK's strict regulatory inspection regime to date has included the breeding facilities for all species within its scope, and the UK has been continuously self-sufficient in breeding and supplying standard stock animals. This significant experience of the use of research animals, combined with a strict inspection and monitoring regime, has not been considered in the Commission Impact Assessment despite providing significant practical evidence supporting appropriate standards in animal welfare.

169. Currently, as ETS 123 is guidance, the Home Office is able to provide derogation for research that involves animals covered by the legislation but where the ETS standards are either not necessary for welfare or where they are not appropriate for scientific reasons.

Alternative solutions

170. A preferable solution would be for the recitals to refer to Appendix A as preferred guidelines. Minimum standards in Annex IV could then be based on established criteria to strike a balance between animal welfare and cost.

171. An alternative proposal is that Appendix A should be neither a minimum requirement, nor a non-mandatory guideline. Rather, it should be the formal basis on which national authorities inspect and implement, with the ability to apply discretion and derogations, as well as scientific judgement.

172. In view of the issue concerning agricultural research, we therefore propose that the requirement that 'all animals should be provided with accommodation, an environment, at least some freedom of movement, food, water and care which are appropriate to their health and well-being' (Article 32) should apply only to animals held within licensed establishments. For studies of commercial husbandry or management, animals should, where there is scientific justification, be allowed to be kept at the space allowance typical of standard husbandry. Equivalent derogations need to apply to environmental studies.

Background

173. Appendix A of ETS 123 was developed as a guideline, probably aspirational, not to be mandated as a minimum standard. It was always recognized that if it was to be transposed into a new Directive, it would remain guidance, in a similar manner to the status of Annex II in the current Directive. This reflects in part that there were aspects of ETS123 (e.g. the very expensive relative humidity requirements) that did not gain universal acceptance across the expert group.

174. It was always intended that the UK Home Office would ratify ETS 123 and this it did within one year, but derogating the space allowances for stock animals specified in Appendix A to those currently used and defined in existing Codes of Practice. ETS 123 was to be appended to A(SP)A as a Code of Practice, not as law.

175. If Annexes in a Directive cannot be guidelines, then more appropriate, realistic and considered minimum standards need to be adopted.

176. We have concerns over the Commission process for developing these provisions. The Commission relied upon its expert Internet consultation, but this involved only a single option being put forward -- that elements of the revised Appendix A become minimum standards. No other options were suggested for the consultation, and no review of the suitability of ETS 123 as mandatory standards was carried out. This approach contravenes the Commission's own guidelines on impact assessments and consultations, which states that they should identify “alternative policy options and their likely positive and negative impacts”.²⁶

177. The overwhelming majority of respondents who gave comments to the Commission Expert Internet Consultation were opposed to Appendix A becoming minimum standards.

178. The Commission suggested that the adaptation of the revised guidelines would permanently increase daily housing costs for rodents by approximately €0.02 per animal. No evidence was given to support this. Comments from the consultation overwhelmingly assessed this to be a very large underestimate.

179. The Commission Impact Assessment suggests that currently “3% of the animal studies performed in all 25 Member States yield unreliable results due to inconsistent or unsuitable housing and care conditions” and that this would not happen if the revised ETS 123 standards had been mandatory. It then assumes the annual benefits in all (the then 25) Member States would be in the range of €90 million.

180. There was no evidence presented that 3% of animal studies yield unreliable results, nor that this is in some way linked to a failure to abide by ETS 123 standards. This appears to be based on an assumption that welfare standards are poor just because the ETS 123 has not been applied, although no evidence is supplied to support the assumption.

Flawed transposition

181. The statement by the Commission that the proposal to make elements of Appendix A mandatory would “*bring the Directive in line with current scientific and technical*

²⁶ http://ec.europa.eu/enterprise/regulation/better_regulation/impact_assessment_en.htm

knowledge” cannot be substantiated. The expert working group report from the ETS 123 states “*exact numeric values for minimum cage sizes and heights as well as for maximum stocking densities can never be scientifically evaluated and proved*” (Process of determining recommendations by the expert group”, Section II.1.1, rabbit and rodent report).

182. Much of the advice in Appendix A is aimed at encouraging good practice, with advisory qualifications. It is therefore regrettable that the Commission proposal has omitted much of the text of Appendix A, which contains the principles to be applied and the performance standards to be implemented. In fact, omission of such text could result in poor animal welfare. For example, requiring social housing without qualifications could result in injuries to male rabbits, some male strains of mice and male hamsters through their natural competitive behaviours. There is no provision for exemptions to group housing for scientific reasons e.g. for metabolism studies or for surgically prepared animals that need to recuperate in isolation.

183. The Commission acknowledges in its Impact Assessment that “many of the general provisions and recommendations of the revised guidelines for health, transport, quarantine, acclimatisation, isolation, watering, feeding, cleaning, records and identification are already in place in many establishments, as these are integral parts of good scientific/laboratory practice to obtain reliable and reproducible scientific results”.

184. Annex IV in the Commission proposal incorporated much of the Revised Appendix A, but with some significant and concerning changes. The basis of reasoning for these changes has not been made clear. In some cases they would undermine animal welfare, in others they would interfere unnecessarily with legitimate research. Furthermore, the provisions do not cover breeding/weaning practices, nutritional and health issues, as well as environmental conditions and some relevant species-specific information.

185. For example, there has been an inadvertent transcription of text from the existing Directive which could lead to a 50% reduction in space allowances for laboratory dogs during procedures, and the temperatures specified for some amphibian and reptile species could result in their death. This serves to emphasize the potential dangers to welfare of the Directive incorporating legally-binding details of a technical nature.

Impact of the Commission proposal

186. The Commission appears not to have considered the economic and indirect welfare consequences of the proposed requirements.

187. Transition to the stocking densities in Annex IV, mandated by Article 32, would require massive capital investment in some establishments and sectors. It is not simply a matter of buying new cages and equipment. In some cases, lower stocking densities would reduce the capacity of existing space, and require new buildings to be constructed. This transition has to be carried out without jeopardising the research activity.

188. The total investment required for commercial laboratory animal breeders of common specifications of rodent species and rabbits in the UK could be substantial - equivalent to the total capital spend of the relevant businesses in Europe for several years (according to the calculations of the largest animal breeders in Europe²⁷) meaning there would be enormous

²⁷ As referred to in the submission to this inquiry from the Laboratory Animal Breeders Association

pressure on budgets at a time when there are already global constraints on access to capital. The total capital investment across Europe for additional space and replacement equipment could exceed €100M which is very large in comparison with the size of the businesses that must support it.

189. Capital costs to the much larger number of universities and public research institutions would likewise be substantial.

190. Much of the pharmaceutical and contract research sector has anticipated the need to move to Appendix A standards already. However, within the public and academic sector, capital planning cycles can be prolonged. The time lag between planning, building and commissioning new facilities is very significant. A transitional time period of at least five years, and preferably 10, would be necessary to comply with the new annex.

191. All these factors could put great strain on capital budgets and substantially increase the cost of breeding many of the species and strains of animals used in biomedical research. This would be likely to lead to:

- disruption to animal supplies and research activities during the required building programmes;
- the significant additional costs of production being at some point passed on to users.
- increased animal costs adding to regulatory costs in harming EU competitiveness;
- research operations involving large numbers of animals moving out of the EU;
- animal breeding being moved to areas either within or outside the EU with lower labour costs and/or capital requirements;
- adverse welfare implications from the resulting increased transport distances and housing under conditions not controlled by the EU;
- undermining the security of supply because of limited portals of entry.

192. It is therefore far from clear that the proposed housing standards would result in the welfare gains envisaged, yet the direct and indirect economic costs would be great.

8. Alternative Methods (and the 3Rs)

(Article 46)

193. The ‘3Rs’

- Replace the use of animals wherever possible;
- Reduce the number of animals needed to achieve the objectives;
- Refine methods to cause animals the least possible distress.

194. Statistics collected by the Home Office show that the number of scientific procedures involving animals in 2007 in the UK was just over three million. This is significantly less than 25 years ago, although the numbers fluctuate from year to year. Yet, over the same period, the number of new medicines under development in the UK increased substantially, and remains high.

195. This reflects the fact that significant parts of the research process, which in the past required the use of many animals, now need comparatively few. This is in turn thanks to advances in science that have progressively yielded ‘alternatives’ that, once validated scientifically, can replace the use of animals. From a political and welfare perspective it is important to appreciate that such improvements arise from a larger body of R&D and have to date resulted primarily as spin-offs from research that was not directed *prima facie* at the 3Rs – e.g. computer modelling, *in silico* assays, magnetic resonance imaging.

196. Scientists in academia and industry communicate extensively and collaborate to improve research methods and share best scientific practice. All researchers use alternative methods wherever possible – to do otherwise is not only illegal (in the UK) and unethical, but also far too expensive. While alternatives should be used where available and appropriate, they should not be mandated where there is no international acceptance, since animal studies would still be required outside the EU.

197. In the UK, the requirement to consider alternatives is assessed formally in the ethical review and harm:benefit analyses that are legally required before a licence to proceed is granted. The UK Home Office states that "use of animals in scientific procedures will not be licensed if alternative non-animal techniques are available".²⁸ We support moves in the draft Directive that would introduce EU-wide ethical review, provided that it is undertaken as efficiently as possible.

198. It remains the case, however, that some use of animals is essential in the development of clinical therapies. Where farm animal welfare, veterinary or environmental research is concerned, animal-free research would be impossible, as the final stage of such research inevitably requires animal trials of the species in question. Total replacement of animals in research is therefore not a feasible prospect.

199. Where animal use remains essential to scientific and clinical progress, the 3Rs are accepted as the basic principles for working towards minimising the adverse impact of those procedures that need to be undertaken. In that regard it is notable that good scientists are

²⁸ <http://scienceandresearch.homeoffice.gov.uk/animal-research/animal-testing-faqs/>

committed to good animal welfare since they recognise that good welfare is essential for good science.

200. The UK bioscience sector funds and works closely with the National Centre for the 3Rs on active programmes to support the 3Rs in research and embed them in daily practice. The NC3Rs in turn funds 3Rs research in the best research laboratories. This is a highly effective and efficient model that should be adopted across the EU.

201. However, developing alternatives to the use of animals in medicines research is a long and difficult process. At the moment, there is often a point in the process where there are barriers that computers and in vitro methods cannot yet help to cross. As our biological, medical and technological knowledge grows, we look forward to a time when animal research will become progressively less central to the development of human therapies. As this is not imminent, the priority remains to develop safe and effective medicines and other therapies involving considered and compassionate use of animals.

202. Recent examples of advances in 3Rs made by UK scientists in academia and industry, and relevant to medicines development, were showcased to members of the European Parliament in February 2009, and include:

- Developing gene expression analysis techniques for screening compounds;
- Adopting a 'weight of evidence' approach – uses fewer animals per dose-tolerance study;
- Use of radio-telemetry devices (remote sensor implants) - 95% reduction in number of dogs in 2005 in research to develop a bronchodilator agent for asthma;
- Review of information required by regulators in conventional acute toxicology testing. Potential to reduce use by several thousands per year (cross-industry collaboration), currently in consideration by regulators.

203. Importantly, the most productive environment for generating 3R improvements and new alternatives is in active research laboratories, not in some standalone 3Rs laboratory centre, which was proposed in the draft Directive. While an EU-wide organisation could certainly help validate newly developed alternatives/improvements, and push for acceptance by regulatory authorities, it does not make sense to duplicate this in each member state.

204. The proposals for National Reference Laboratories are unnecessary and infeasible and would not be effective at developing alternative methods. They would divert research funding away from research which might not only develop alternatives, but further benefit biomedical discoveries.

205. Once validated, implementation is brought about by a combination of reduced costs (a strong incentive in both industry and academia), a flexible regulatory framework (which is difficult to implement given the global nature of medicine development, registration and use) and a 3Rs culture embedded in the day-to-day work of scientists, who in general would prefer not to use animals in studies targeted at human benefit. Across the EU this culture should be supported by effective but efficient ethical review and regulation over the use of animals in research.

206. The Commission claims in its Impact Assessment that "increased uptake of alternative methods will boost EU industry". There is no evidence to support this claim, which is

frequently made by antivivisection groups. Researchers will wish to use the best method available in every case. As outlined above, there is already every incentive for industry to both develop and use alternative methods.

9. Subsidiarity and legal base

207. The UK bioscience sector does not claim to be in a specialist position to comment on the legalities of introducing EU legislation.

208. The Commission explains that the following broad options have been considered (explanatory memorandum page 8):

- Deregulation;
- Maintaining status quo;
- Strengthening the current legislation;
- Voluntary agreements as an alternative to legislation.

209. The UK bioscience sector accepts that strengthening the current EU legislation is a valid choice for some aspects of the Directive, such as minimum standards of animal welfare, which should apply uniformly across Europe. However, the approach of the proposed Directive appears to have been to collate all existing regulation and apply the most stringent level of regulation in each case. A more balanced approach would have been to identify and strengthen appropriate parts of the regulatory framework, whilst not adding legislation to cover aspects where animal welfare benefits would be virtually non-existent (such as designating as protected potentially billions of non-sentient microscopic crustacea).

210. Other examples where there is no welfare cost include humane killing of animals and non-recovery experiments performed entirely under anaesthesia. It is entirely unnecessary to incur the full weight of the proposed controls in these areas.

211. The Commission has acknowledged the possibility that Member States could “streamline” regulatory controls and so “contribute to simplification” (Impact Assessment page 11). But the complexity of the proposals allows virtually no opportunity for this to happen.

212. As a result, we are concerned that the Commission approach is excessively stringent. The Commission does not appear to have taken into account the risks of excessive regulation to the competitive position of Europe in the long-term.

Subsidiarity

213. If the advantages of harmonisation are accepted, as proposed in Section 1 (‘Objectives’), then subsidiarity must be seen in relation to harmonisation.

214. We understand that EU law (as well as an amendment passed by the Parliament) permits Member States to implement more stringent conditions than those laid down in a Directive. We see the merits of this, but are also mindful of the ease with which the important benefits of harmonisation may be eroded.

215. In that light, the UK bioscience sector advocates harmonisation of those outcomes that (i) support the single market, and (ii) benefit animal welfare (assuming always that the benefits are based on scientific evidence). However, we would wish to see subsidiarity over the procedures by which those outcomes are achieved.

216. Importantly, one of the outcomes of the single market should be mobility of staff and projects. This is not incorporated into the draft articles, although stated in the preamble.

217. In particular, our sector feels it is not appropriate for the EU to determine:

- the structure of national committees responsible for the various authorisations;
- the structure and operation of pan-EU bodies to which Member States would be subservient;
- the controls over data-sharing.

Legal Base

218. We are of the opinion that Article 95 of the Treaty of Rome is not properly fulfilled by the draft Directive. The Directive does not adequately guarantee harmonisation across the internal market for breeding, supplying and use of animals.

219. For the provisions in the draft Directive relating to animal welfare, the Commission is relying on the principles set out by the protocol on protection and welfare of animals annexed to the Amsterdam Treaty. This proposal recognises that animals (vertebrates in this context) are sentient beings, and requires that “in formulating and implementing the Community's agriculture, transport, internal market and research policies, the Community and the Member States shall pay full regard to the welfare requirements of animals...”.

220. A number of measures proposed by the Commission involve restrictions such that certain types of research cannot be carried out at all. For example, the Commission proposes a ban on the use of non-human primates unless linked to life-threatening or debilitating disorders. In such cases where research is disallowed, the Commission appears to be arguing that animal welfare considerations override research policies. It is not clear that this is the intention of the protocol on protection and welfare of animals.

Legal status of annexes

221. One legal issue that is of significant concern is the status of annexes to the Directive. We understand from the Commission that, unlike the previous Directive, annexes to the new Directive will necessarily be mandatory and may not act as guidance. Absolute clarification of this issue is vital before the wording of the various annexes is discussed further and approved.

222. This is of greatest significance to Annex IV on accommodation standards. The content of this annex is based on, but does not accurately reflect, the Council of Europe Convention ETS123 for the protection of vertebrate animals used for experimental and other purposes.²⁹ This document was agreed by its expert committee subject to it being advisory only and not mandatory.

²⁹ <http://conventions.coe.int/Treaty/en/Treaties/Html/123.htm>

223. Moreover, the evidence on which ET123 was based is already at least 5 years old. It is essential that the wording of any mandatory annex is such as to permit new scientific evidence to be incorporated.

Sharing of Data

(Article 44, Amendment No.132, 134, 135, 136, 137, 180)

224. The UK bioscience sector strongly supports the overall concept of sharing non-confidential data to avoid duplication of procedures. Data should be (and are) reviewed, and new studies planned, on the basis of what is already known. Facilitating access to publicly-available data is a key priority.

225. Additional regulation on data-sharing could be used to generate some valuable additional exchanges of information with benefit to animal welfare, and to research progress. However, the proposals for mandatory data sharing as proposed by Parliamentary amendments are likely to disproportionately increase costs with little animal welfare benefit, and have a major adverse impact on the protection of intellectual property rights. This could threaten both the viability of pharmaceutical research in the EU and the competitiveness of academic institutions.

226. Regulation must be based on an understanding that there are many different types of animal research. A legal requirement for the same type of data sharing across all sectors is simply impracticable, and the cost of ensuring that all relevant data are easily accessible (as well as the difficulty in defining what is relevant) would be a significant burden on research institutions, funders of research and for administrative agencies required to oversee that the required process had been followed. The Commission proposal, amended by the Parliament, intends to reflect legislation applied to the chemical industry (under REACH) across all sectors. This proposal has severe limitations:

- REACH is applied to chemicals which will have common usage but not to those covered by intellectual property protection;
- Academic research depends upon publications but the timing of disclosure is critical for correct interpretation and application, as well as for the protection of intellectual property;
- There appears to be confusion as to the amount of duplication involving animal work that actually occurs.

227. Our concerns are consistent with those of the Technical Expert Working Group, which noted that "any system for sharing data that required assessing the 'value' of studies, particularly those early in the R&D process, would be highly problematic and effectively make a system unworkable. It is unclear also how any requirement could extend to studies carried out in non-EU countries, thus placing EU industry in an uncompetitive situation" (page 14)

Duplication and validation

228. It is important to distinguish between the undesirable duplication of animal experiments and the validation of data from animal studies. Reproducibility of results is a necessary part of the scientific process as published data may later be found to be inaccurate or irreproducible. Blocking the ability to replicate critical observations would seriously restrict scientific progress. It is however right to prevent or limit duplication unless there is a scientific justification for doing so.

229. There is however no evidence of widespread unnecessary duplication. “Avoidance of unnecessary duplication of procedures” is already part of Annex VII (list of information requirements for applications for the project authorisation in Article 36) which implies the need to check for existing data. Agencies that fund research always expect to be assured that the proposal is new and does not simply repeat previous studies unless there are particularly good scientific reasons to do so.

230. Similar compounds are sometimes studied in the development of new medicines, but this should not be confused with duplication. Even slight modifications and variations to chemical structure can have huge impacts on safety and efficacy for patients, and can result in a product with a different mode of action or safety profile and therefore new or better treatment for a disease. For example, subtly different chemical changes to the dopamine structure can lead to the compound either being a useful drug to treat Parkinson’s disease, or causing serious side-effects. Similarly, ketamine isomers can be either an anaesthetic or hallucinogen. In another example, the histamine H₂-receptor antagonists, cimetidine and ranitidine, act in the same way and seem quite similar. Yet cimetidine is sometimes unusable because of adverse side-effects, and hence the development and animal testing of ranitidine represented a significant advance for some patients.

Transparency

231. We support the proposal for the provision of a lay summary of work outlined in the project licence (generated by the applicant) to be made publicly available. A similar scheme already operates in the UK with the disclosure of abstracts on the Home Office website for most project licences.

232. The benefits of public disclosure of animal research data must however be balanced against researchers’ rights to privacy and the protection of personal data. It is paramount to ensure both the safety of staff and premises, and the integrity of intellectual property.

Proposals in the Directive

233. Under Article 44 of the original Commission proposal, Member States are required to ensure the sharing of data generated by procedures. Regulatory testing was excluded, and the proposal was subject to the safeguarding of confidential information.

234. Under the revisions from the European Parliament, the exclusion for regulatory testing and the safeguard for confidential information were removed. The new text included sharing of data generated by procedures which took place in the European Union prior to the Directive coming into force. An additional obligation is for anyone seeking to rely on data owned by another to contribute, where appropriate, towards the cost of producing such data.

235. These amendments from the European Parliament appear to be based on data-sharing requirements applied to chemical and pesticide legislation. However, in that case, data are from very standardised toxicology studies of off-patent chemicals. Pesticides are often reformulations or combinations of older chemicals, and if new chemical entities were developed, these would not be subject to the requirement for toxicology data sharing. It is also key to understand that the purpose of toxicity testing in the pesticides sector is mainly to generate data for hazard assessment, deriving permitted daily exposures to control occupational hazard.

236. The situation for pharmaceutical/biotechnology research is significantly different. Pharmaceutical research is rarely duplicated, with much R&D effort focused on developing new molecular entities. Where different companies may be working on the same established entity, well-developed processes for the registration of generics avoid the recreation of existing data. In the pharmaceutical sector, toxicity testing is undertaken to assess risk prior to administration in humans. This is a different purpose from the pesticides sector, and data-sharing measures appropriate for pesticides are not directly applicable to the pharmaceutical sector. Furthermore the majority of animals used in the pharmaceutical sector are not involved in toxicity testing but in discovery and developing new areas of biology that may allow pharmaceutical intervention leading to disease benefit.

The commercial perspective

237. Bringing a new medicine to market is the result of usually over 10 years developmental work, at an average cost of €800 million per medicine. The cost and risk are borne by the pharmaceutical industry. This leaves limited years to recoup the cost of development before the expiry of patent terms.

238. Protecting intellectual property (IP) is critical to ensure that a company does not lose the product of its original research and development. For this reason, IP-sensitive or commercial information must be carefully excluded from disclosure. In addition, there are legal restrictions on publishing data on a patented molecule. To require such confidential research data to be shared would seriously compromise the commercial viability of the pharmaceutical industry in Europe.

239. Academic institutions will similarly need to protect IP prior to publication, and such data include those submitted in grant applications. Maintaining confidentiality in this area is essential in maintaining Europe's scientific and commercial competitiveness.

Regulatory research

240. Toxicity testing is required by law as part of the licensing process of a new medicine. It is carried out on novel, patented compounds, which by definition ensures there is no duplication. This type of research follows strict and uniform protocols. Any Member State should accept the validity of regulatory toxicity testing carried out in another. A well-developed generic medicines procedure ensures that data do not need to be recreated for existing molecular entities.

241. Industry and the regulatory agencies worldwide are already actively engaged in data-sharing initiatives, one of whose intentions is to reduce, refine and replace the use of animal toxicity tests. These initiatives include those intended to qualify novel biomarkers for disease, to better understand toxicological assessment and data interpretation, and to develop novel computer based processes. Among the many shared efforts are:

- ILSI HESI - Health and Environmental Sciences Institute
- Critical Path Institute - Predictive Safety Testing Consortium
- Innovative Medicines Initiative (Europe)
- ECVAM Consortium on In Vitro Models for Drug Induced Liver Injury

- Registry of Industrial Toxicology Animal Data (RITA)
- Extractables and Leachables Safety Information Exchange (ELSIE) consortium
- EFPIA³⁰/RSPCA/FRAME³¹, Excipients³² Database Consortium

242. An example of these is the EFPIA/RSPCA/FRAME Excipients Database Consortium. This is a cross-pharmaceutical industry consortium formed under the auspices of the EFPIA Safety Working Group in collaboration with the RSPCA and FRAME. It contains 10 member companies and database host (LHASA) and its purpose is to build a common database of toxicity information on commonly used excipients with the overall aim of decreasing the potential for new or additional toxicology testing, thereby reducing or eliminating animal use and refining future studies.

243. This will enable pharmaceutical companies to use new excipients with minimal needs for toxicity testing versus needing full toxicology programmes.

Basic and applied research

244. The very nature of basic and much applied research means that almost all projects and protocols are different. The desire to share data is very strong – all scientists want to see their work published, and they also exchange information at conferences. Indeed the UK Research Councils all have policies on data-sharing;³³ it is strongly encouraged, unless there are overriding IP considerations. However, it may be difficult to know at what stage data are to be published in a scientific journal, and their prior release in any form can jeopardise both scientific publication in high-level journals and the retention of intellectual property rights. The relevance of data from long-term programmes of research can take years to ascertain.

245. Fortunately there are already initiatives of networks and collaborations to encourage and facilitate sharing of data, and reduce any unnecessary duplication of animal procedures.

246. A pan-European database called ELIXIR³⁴ has recently been established to improve the sharing of biological data. Other initiatives such as EUCOM, NORCOM and KOMP are international collaborations that share knock-out mouse lines, reducing the number of genetically-modified animals produced internationally. Sharing the details of the mouse genome has resulted in far less duplication than might have happened otherwise.

247. These examples might suggest that this approach should be expanded across many areas of research, but the practicalities mean that this is not immediately feasible. In general, progress has been fastest and most successful for large, consistent and well-defined areas of research, such as genetics research in rodents. Many other areas of research are too diverse or fragmented to permit such gains, even with the high level of collaboration that is required.

³⁰ EFPIA: European Federation of Pharmaceutical Industries and Associations. See Lhasa Ltd: A not-for-profit company specialising in toxicology, metabolism and data-sharing software. See www.lhasalimited.org

³¹ FRAME: Fund for the Replacement of Animals in Medical Experiments

³² Excipient: an inactive compound used to bulk out or support the active medicine

³³ See eg: www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/Datasharinginitiative/index.htm

³⁴ <http://www.elixir-europe.org/page.php?page=home>

248. Funders already require that applicants proposing to use animals will have undertaken due diligence in reviewing the existing literature in the field, and demonstrating that their proposed research does not repeat previous studies. There is no reason why funders would support studies that have already been undertaken and published. Each application must scientifically and ethically justify the use of animals, including why the procedure is necessary to further a certain field of knowledge.

249. In the UK, researchers must also address how they have considered refinement, replacement and reduction in their study design. Such information is reviewed by peer reviewers, funding committees, ethical review panels and the Home Office.

250. Forcing research institutions to share provisional data is not a proven methodology for advances in animal welfare or science. Instead, it would increase bureaucracy and divert time and resources away from the important quest to understand human and animal diseases.

Databases

251. Databases are often put forward as a way to collect and disseminate information on animal experiments, including information on procedures and welfare issues. The intention is to avoid duplication or repetition of research, and generate information to assist in progressing the 3Rs. However, the extraordinary complexity of such a venture means there is a long way to go before any meaningful attempt can be made on a European central data repository. A central database was rejected for possible inclusion in the Commission proposal.

252. There are some examples in biomedical science of centralised informatics activities that have been successful, for example ENSEMBL, which provides a central portal for a variety of annotations of genome sequences.

253. But these existing databases draw together datasets that are relatively well-defined and consistent in their format. By comparison, data on the outcomes of animal experimentation in institutions across Europe will be highly diverse, primarily because the scientific questions being addressed, and therefore the protocols followed, are also highly diverse. We know, for example, that the outcome of a procedure on a genetically-modified mouse will depend upon a number of factors including:

- the precise procedure that is used (the standard operating procedure, SOP) which may vary across institutes;
- the precise mutant allele generated in the genetically-modified mice;
- the environmental conditions in the animal house, including the type of environmental enrichment in the cage, the diet and the bedding materials used.

254. All these factors will impinge upon the phenotype measured and the welfare outcomes. In essence, describing phenotype and welfare in an animal is complex, and must include genotype, phenotype, SOP and animal house environment. Whilst this can at times result in confusing variation, it can also throw up important differences that illuminate the underlying questions. For this reason it would be scientifically highly retrograde to attempt to standardise protocols in an attempt to get data to fit into any such database.

255. Standardised descriptions or vocabularies for phenotyping procedures and environmental conditions would have to be implemented across Europe if we are to have meaningful database entries in any central data repository. We would need to agree on the parameters and language to apply to the complex data sets, and on the standards that would need to be adopted.

256. There may appear merit in making available ‘negative’ or ‘null’ results. However, a mandatory data-sharing scheme, for example requiring researchers to publish negative data on a website, is unlikely to be successful. Even if it could be made to work, the data would not be accessible to researchers unless they already knew about them. One possible avenue to tackle this problem is a move to open-source publishing, with funding agencies insisting on research results being put into the public domain, when there is no risk to IP. This area is currently developing rapidly. However, there remains the essential problem with negative data of knowing whether it represents a true biological result or a technical failure to carry out the experiments in the manner that would have generated a positive result instead. The implication is that the database would need to include all technical details as well as the result – a daunting and impracticable task.

257. At the present time, developing the procedures for documentation and data acquisition would be an enormous task. Just to run a centralised database would require a huge institute with a vast budget. Experience from similarly complex ventures in other fields suggests it might well not succeed.

Conclusion

258. In summary, we strongly support the principle of sharing of data, where the data structure is appropriate, where the access to data is appropriately controlled, and where doing so is clearly linked to animal welfare benefits and/or good science. There are many successful initiatives already in operation, and we welcome more such plans where they are rationally conceived. We believe, however, that the Directive should encourage progress in this area, rather than mandate it -- because of the immense difficulties outlined above of applying this practice across all areas.