

“In a collapsed state”

Imutran xenotransplantation research: a case study of Home Office enforcement of animal experimentation legislation

Uncaged Campaigns' response to Home Office Memorandum “Imutran xenotransplantation research” submitted to Home Affairs Committee in October 2003

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January 2004

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Executive Summary

This report addresses the “Imutran xenotransplantation research” memorandum submitted by the Home Office to the Home Affairs Committee in October 2003.

Background

In April 2003, Uncaged Campaigns, together with its director, Mr Dan Lyons, published over a thousand pages of confidential documents contained in two leaks from Imutran Ltd (spring 2000) and the Home Office (October 2002), together with the report written by Mr Lyons based on those documents. The documents described the conduct and regulation of pig-to-primate organ transplant experiments, conducted at Huntingdon Life Sciences between 1995 and 2000. The report was entitled ‘Diaries of Despair’ in recognition of harrowing clinical observations made by the researchers as hundreds of non-human primates suffered and died following the pig organ transplant procedures.

This publication took place following an extremely difficult two-and-a-half-year legal battle. Imutran (later joined by their parent company, the multinational pharmaceutical corporation Novartis Pharma AG) had applied to the High Court in September 2000 for a permanent and complete injunction suppressing publication of the leaked documents on the grounds of breach of confidentiality and copyright. The claim did not include any accusation of libel on the part of Uncaged and Mr Lyons, despite the strong criticism of Imutran contained in the ‘Diaries of Despair’ report. Significantly, the Home Office declined the opportunity to apply to the court to try to prevent disclosure of its confidential documents.

Uncaged and Mr Lyons successfully argued that the documents revealed breaches of legislation on the part of Imutran, and official misconduct on the part of the Home Office in its implementation of animal research regulations. Therefore, the public interest in revealing such wrongdoing outweighed the claims for commercial confidentiality. Legal aid had been awarded to Mr Lyons following a decision by the Legal Services Commission’s Public Interest Advisory Panel (PIAP). The PIAP judged that the case raised particularly significant matters of public interest, and that the Defendants’ had a good chance of success in the case insofar as the documents demonstrated Home Office misconduct. Imutran and Novartis abandoned their claim and an out-of-court settlement was reached allowing extensive publication of the documents listed by Uncaged as demonstrating the key public interest elements of the case.

While victory in the legal proceedings demonstrated the strength of the evidence of Home Office misconduct, the task of effectively holding the Home Office and Imutran to account for their wrongdoing through an independent inquiry remains. As part of that process, Uncaged supporters lobbied the Home Affairs Committee in the weeks following publication, to encourage the Committee to scrutinise the Home Office's conduct. This is a central constitutional role of the Committee.

The Home Affairs Committee requested a brief memorandum from Mr Lyons outlining the main allegations against the Home Office. Following receipt of this, the Committee wrote to the Home Office on 30 June 2003 with a list of questions regarding its regulation of Imutran's research and the adequacy of its response to the concerns submitted by Uncaged. The Home Office responded in October 2003 by way of a memorandum: "Animals (Scientific Procedures): Imutran xenotransplantation research".

This report is arranged into five sections, corresponding to the five main questions put to the Home Office by the Home Affairs Committee. Sections 1 and 2 discuss the Home Office's assessment of the costs, in terms of the severity of the adverse effects suffered by the animals, and the benefits of Imutran's research. Such an assessment lies at the heart of the regulatory structure for animal experimentation. Section 3 addresses the question of whether the xenotransplantation experiments caused "severe" suffering, which is said to be prohibited. Sections 4 & 5 analyse the adequacy of the format and then the content of the Home Office's main response – a review conducted by the very institution implicated in wrongdoing, the Inspectorate - to the concerns raised by the Diaries of Despair.

Given that the essence of Uncaged's case centres on the Home Office's conduct, it is deeply problematic that the Home Office has been solely responsible for dealing with Uncaged's representations and has consistently prevented independent scrutiny of its actions. As this report explains, when the Home Office response is related to the facts of the case, the formal regulatory structure, checked carefully for internal consistency and compared to other Home Office statements on this matter, it can clearly be seen that it presents a specious case designed specifically to exonerate the Home Office and frustrate adequate review of the operation of the Animals (Scientific Procedures) Act 1986 ('the 1986 Act').

Section 1 – Severity assessments

The Home Affairs Committee asked the Home Office:

“Were any of the experiments which were assessed as of “moderate” severity wrongly classified?”

The vast majority of the primates “sacrificed” in the Imutran research were used in experiments classified at ‘moderate’ severity. The remaining 5%, which involved open chest surgery of an even more invasive nature, were classified at ‘substantial’

Contrary to the Home Office’s case, the answer is a resounding “Yes”. In fact, all of the main xenotransplantation protocols classified as ‘moderate’ were incorrect (paragraphs 1.39, 1.70-1.202). The confidential records for the experiments reveal that primates were “found dead” before they were “sacrificed”. This represents clear-cut, incontrovertible evidence that the procedures were, at least, of ‘substantial’ severity.

Role of severity assessments (paragraphs 1.3-1.11)

Severity assessments of proposed animal experiments play a crucial role in the implementation of the Animals (Scientific Procedures) Act 1986, particularly:

- the operation of the cost-benefit assessment,
- the control and minimisation of animal suffering,
- the level of scrutiny of research applications
- and, to a lesser extent, informed public debate.

Underestimation of severity will inevitably distort the cost-benefit assessment, which is supposed to lie at the heart of the decision-making process, and could potentially result in the illegitimate licensing of animal research. Overestimation of potential benefit will have a similar effect. The question of the costs and benefits of animal research is also a fundamental aspect of the wider public debate about the ethics of animal experimentation.

Nature of the procedures (1.12-1.37)

This section of the report conducts a comparative analysis of the project licences, Home Office statements, the contemporary state of knowledge regarding xenotransplantation and the results of the experiments. This analysis demonstrates that the Home Office’s initial assessment of the severity (and by the same token, the likely benefits) of the Imutran procedures utterly underestimated the known scale of the biological obstacles faced by pig-to-primate organ transplantation, particularly the profound immunological barriers.

The Home Office also relies on purported similarities between the Imutran experiments and clinical practice in its defence of its severity assessments. In fact, the radical nature of the experimental immunosuppressive protocols, the huge differences between the laboratory environment and the hospital environment, and the exceptionally unusual nature of Imutran's cross-species transplant procedures, combine together to make the primate experimental situation profoundly more problematic than the clinical situation. Therefore, the intrinsic severity of the Imutran experiments was much greater than the impression given by the Home Office, and the Home Office appears to be trying to mislead by proposing this fundamentally unreliable analogy.

Monkey-to-baboon organ transplant experiments (1.42)

Licensing documentation also reveals for the first time that Imutran conducted monkey-to-baboon organ transplant experiments. Although no actual records for the fate of these animals has emerged, a number of relevant factors gives rise to concern about their justifiability on both suffering and potential benefit grounds.

Severity of Imutran procedures

According to the regulations, severity limits are supposed to reflect the potential worst-case scenario in a particular experiment. The Home Office response states that for the Imutran experiments, the Home Office "accepted" Imutran's arguments that the 'moderate' experiments had the potential for merely "local problems" with the transplant, with no potential for systemic adverse effects that would seriously impair the welfare of the animal; in contrast, in the procedures of substantial severity, animals might even die before treatment or euthanasia can be applied. However, an internal Imutran document reveals that the Home Office themselves specifically sought to classify the kidney transplantation experiments – which accounted for most of the xenotransplantation procedures - as merely 'moderate' (1.49).

In direct contradiction to the Home Office's explanation of its assessment of Imutran's research, primates under 'moderate' procedures – including the aforementioned kidney or renal xenograft experiments - were "found dead" before they could be euthanased (1.72, 1.77, 1.86, 1.90). Thus, the severity limit was undoubtedly set incorrectly in respect of these procedures. Other primates under 'moderate' procedures were observed suffering serious impairment of their welfare, often clearly of an acute and systemic nature (as opposed to "local problems", see paragraphs 1.73-1.74, 1.80-1.83, 1.86, 1.91-1.93):

- in a collapsed state
- paralysis,
- stroke,

- “uncoordinated limb spasms”,
- wounds seeping blood and pus for several days,
- vomiting
- diarrhoea
- haemorrhaging
- anaemia
- gangrene
- “in obvious discomfort”,
- “Abdomen swollen and appears fluid filled. Salivating. Very laboured breathing. Extreme difficulty trying to walk”
- weak and unable to stand
- “retching and salivating”
- pneumonia
- shallow and rapid breathing
- “very distressed and having difficulty breathing, mucous membranes blue-grey in colour, animal collapsed.”
- body and limb tremors
- huddled and reluctant to move
- “Appears cold. Extremely pale and weak.”
- grinding teeth
- rolling eyes
- “yellow fluid draining from nostrils”
- bloody discharge and clots from genitalia
- cancer
- “Large abdominal wall abscess”
- “large volume of bloody mucoid faeces”
- “large open wound on right arm, discharging pus”
- “huddled with head between legs”

We defy anyone to examine these verbatim references from the Imutran literature and not be moved by the plight of those primates.

The Home Office’s efforts to undermine the informativeness of the clinical signs and other documentation recording the fate of the animals is shown to be a duplicitous and groundless tactic that raises very serious concerns regarding the Home Office’s commitment to facilitating an informed public debate and its fulfilling its legal and ethical obligation to take into account animal suffering (1.55-1.69).

The potential adverse effects from immunosuppressive drug toxicity were omitted from most of the project licences, even though Imutran acknowledge them in the internal confidential study reports. In the first 'moderate' study conducted by Imutran in 1995, a major cause of primate death was a combination of nausea, gastrointestinal complications involving diarrhoea, anorexia, weakness and general debility as a result of immunosuppressive treatments. This is inconsistent with merely "local problems" with transplants associated by the Home Office with 'moderate' procedures (1.73-1.75). However, subsequent project licences and severity classifications did not even reflect the direct experience gained in this first study, exacerbating concerns that the distorted assessment of the Imutran research was indeed deliberate.

Question 1(a) posed by the Home Affairs Committee asks:

"Are the symptoms of the experiments, as described on pp2-3 of the Uncaged Campaigns memorandum, of the normal degree of severity expected from 'moderate' procedures?"

Although the Home Office tries to claim that the symptoms are just about consistent (rather than 'normal') with 'moderate' severity, the devastating, systemic effects endured by those primates clearly corresponds to the criteria for 'substantial' severity (at the least) rather than the mere 'local problems' said to be associated with 'moderate' severity (1.96-1.97).

Question 1 (b) asks: "How is the classification arrived at?" Clearly, the Home Office's practice has failed to account properly for the potential and actual suffering endured by the Imutran primates. In reality, given the incontrovertible evidence of underestimation and the seemingly deliberate action by the Home Office to categorise procedures as 'moderate', the actual classification appears to be driven by a desire to assist researchers rather than an objective assessment of the likely animal suffering that will occur.

Section 2 – Assessment of benefits

In his note on the cost/benefit assessment, the Chief Inspector himself states that in the assessment, "the 'benefits' relate only to those which might reasonably be expected to arise *directly* from the programme of work for which the licence authorities are sought."¹ (emphasis added) The "essential determinants" of 'benefit' are the "likelihood of success"² and the "utility of

¹ See annex D to Home Office response, paragraph 2.4.

² *ibid.*

the new material”³. The Home Office also “must be satisfied that the procedures are likely to achieve the stated objectives”.⁴ The cost-benefit assessment is supposed to be a process throughout the life of a project licence rather than a one-off event at the beginning.

In 1998, the Home Office responded to concerns about the cost-benefit assessment in the Imutran case by stating that “the main and ultimate benefits of this research can only accrue if xenotransplantation can be used in clinical practice.”

The project licence authorities and other applications reveal that Imutran’s research was formally licensed on the basis that it was likely to achieve the following objectives necessary to commence clinical trials (2.7):

- Prevent hyperacute rejection and elucidate subsequent rejection mechanisms
- Achieve long-term xenograft survival through an effective immunosuppressive protocol
- Assess the ability of the organ to function sufficiently to maintain life of recipient

Question 2(a) of the Committee’s letter to the Home Office asks:

“What results did the Home Office expect, and within what time frame, to justify the suffering to animals involved?”

The Home Office does not appear to have answered this directly. However, compared to the actual licensing documentation and earlier Government statements, the Home Office response gives a fundamentally distorted impression of the objectives and achievements of the Imutran research (2.3-2.10). In actuality, the vast majority of the Imutran research programme over a five year period, involving severe experiments on hundreds of higher primates, was a failed attempt at achieving the second half of objective 1 and, consequently, objectives 2 & 3. Imutran’s research was an overwhelming failure in relation to the conditions upon which it was licensed. Yet the Home Office refused over a five year period to halt the research despite the fact that the potential benefits were not in fact being realised – contrary to public statements from the Home Office regarding how it claims to regulate animal experimentation. The unwillingness of the Home Office to admit this and support independent scrutiny into why its assessment of benefit was so radically flawed is deeply disturbing.

When all the factors regarding the likely marginal utility of Imutran’s primate experiments are considered, we submit that, in answer to question 2 posed by the Committee, the likely failure of Imutran’s research should have been clear at the initial assessment stage or, at the very least,

³ *ibid.*, para 5.23.

⁴ Hansard, Written Answers for 28 June 2000, Mike O’Brien, 125262 “Xenotransplantation”.

shortly into the programme (say by end of 1996 at latest) when it was confirmed that effective, yet tolerable immunosuppression was unattainable. But the key concern we have regarding the Home Office is that they did not scrutinise Imutran's application with sufficient rigour or conviction to address this question adequately and fulfil their duties under the 1986 Act (2.16-2.31).

In their recent response, the Home Office's description of how the Imutran research programme came to an end cannot be reconciled with the version published by the Home Office during the legal proceedings between Uncaged and Imutran/Novartis (and Imutran's pleadings to the High Court) (2.32-2.42). Originally, the Home Office claimed that Imutran voluntarily implemented a moratorium on their research in mid-1999 and subsequently handed back their project licence authorities to the Home Office. Now, the Home Office is claiming that Imutran were forced by the Home Office to cease their research. Either the Home Office has attempted to prejudice the court proceedings in Imutran's favour, or the current statements exaggerate the rigour of the Home Office's approach to regulation.

Section 3 – Severe Suffering?

The lack of correspondence to the human clinical situation, by the Home Office's own case, suggests that the severity of the procedures should have been classified as having the potential for 'severe pain and distress' which would have outlawed the procedures under any circumstances. The actual records for the dying animals support this conclusion.

Section 4 – Format of Government Response

Cost/benefit assessment

The decision made by Home Office to ignore the fundamental question raised by the Diaries of Despair report - the adequacy of the cost-benefit assessment – was made prior to any proper consideration by the Home Office, and was an entirely defensive and tactical decision with no relation to the facts of the case. A letter from a Home Office minister a week after Uncaged's submission of the Diaries of Despair report indicates that the general approach of the Home Office had already been determined and at a meeting five weeks later to discuss the Home Office approach, the minister had not read the report and was not in a position to discuss any of the facts of the case.

Substantial severity

Only a very small proportion of Imutran's xenotransplantation procedures (5%), unavoidably involving particularly invasive surgery, was classified as of 'substantial' severity. Even in this instance, the Home Office description of its assessment of these procedures does not correspond to the licensing documentation, which in turn still failed to consider the full range and intensity of the adverse effects actually suffered by the animals.

Furthermore, the Home Office account does not appear to provide a discernible difference between "substantial" severity and "severe" pain, the latter being prohibited.

"Rubber-stamping" of application

Imutran's confidential documentation reveals how the Inspectorate reviewed Imutran's licence application ahead of an important APC meeting to consider the application, a meeting that was described by Imutran's personal Inspector as a 'rubber-stamping' affair on several occasions. The same Inspector helped review the deaths of monkeys in transit from the Philippines behind a mutually-understood veil of anonymity. The Inspector and Imutran agreed that the transport crates had actually broken minimum size and ventilation rules, yet this crucial feature of the deaths was omitted from later official reports of the incident.

The documentation, together with the strong evidence of a biased cost-benefit assessment, indicates a collusive relationship between Inspector and applicant whereby authority to conduct animal research is facilitated rather than a matter of neutral and objective scrutiny.

Analysis of the evidence surrounding an Imutran application that took several months to approve reveals that rather than it being a result of vigorous scrutiny by the Home Office, the lengthy consideration appears to have been driven largely by the Animal Procedures Committee's (APC) explicit concern at Imutran's "cavalier" attitude to the regulatory system and Imutran's performance of xenotransplantation experiments on wild-caught baboons in direct violation of the APC's recommendations which had been accepted by the Home Office.

APC by-pass

The decision by the Home Office to exclude the APC from an inquiry into Imutran's research flew squarely in the face of an unequivocal policy announcement following concerns expressed by the APC over a previous biased Inspectorate report.

The APC wrote three times to Home Office ministers requesting an explanation for the Home Office decision, but did not receive a satisfactory reply. A majority of the Committee's members thought that it was unreasonable for the Home Office to mount a merely 'routine review' into Imutran's compliance with the Animals (Scientific Procedures) Act 1986 ('ASPA').

Huntingdon Life Sciences

The Chief Inspector's compliance review dealt with a small number of admitted mistakes that were, in fact, relevant to HLS's fulfilment of its Certificate of Designation. However, the Chief Inspector's review fails to mention HLS once and gives the false impression that the mistakes were the responsibility of Imutran.

Furthermore, the manifold breaches of severity limits that occurred during Imutran's research also implicate HLS staff for failing to carry out their animal care duties. Once again, no action has been taken.

Section 5 - Content of the Chief Inspector's compliance review

"Unauthorised experiments hidden"

Correspondence between Imutran and the Home Office reveals that Imutran experimented on baboons in direct contradiction to the conditions of the APC's recommendation to approve an Imutran application. The reason why this was not considered an infringement was that trust had been extended to Imutran and thus licence documentation had not been amended to reflect the advice of the APC. The Chief Inspector's review makes no mention whatsoever of Imutran's conduct, even though the APC felt it constituted a betrayal of trust and demonstrated a cavalier attitude to the regulatory system. These omissions indicate a lack of openness on the part of the Home Office and an indulgent and biased attitude towards Imutran.

"Distorted cost-benefit assessment"

The Home Office claims that it licensed Imutran's research merely on the basis of "new scientific insights" that might be gained, and irrespective of any actual benefits gained in terms of achieving progress to fulfil the conditions for the commencement of clinical trials.

In fact, this Home Office assertion contradicts:

- (a) Stated policy on the determination of benefits in the cost-benefit assessment, which requires that the likelihood of success and the utility of the product being developed are the essential determinants of benefit. The Home Office must, apparently, be satisfied that the specific licensed research is likely to achieve its objectives.
- (b) The actual Imutran applications and project licence authorities. These form the official legal basis for the licensing of Imutran's research, and repeatedly included unsound claims of progress in the research and explicit objectives that involved achieving startling breakthroughs allowing the commencement of clinical trials.
- (c) Earlier Government statements justifying its licensing of Imutran's research, which referred to the main and ultimate objective of clinical use of pig organs.

"Horrific procedures ignored"

The CI's review failed to discuss and respond to the clear breaches of the 'moderate' severity limit.

Broader policy observations

Although the Imutran case study provides a unique insight into the animal experimentation and how it is regulated, concerns regarding the attitude of the Home Office Inspectorate go back many years.

In 1962, following regular petitioning by the RSPCA, the Home Secretary set up a committee under Sir Stanley Littlewood to consider the regulation of animal experimentation. The subsequent Littlewood Report commented, in an otherwise generally conservative document, that the Home Office was not 'concerned to assess the potential value of proposed research or the results of past research' but was only concerned to make sure the right certificates were being applied for.⁵

The Animals (Scientific Procedures) Act 1986 replaced the 1876 Cruelty to Animals Act. The fundamental advance contained in the 1986 Act was the requirement for a cost-benefit assessment, although the pro-animal research lobby did attempt to block this measure. This measure could be seen as a half-way house between a complete prohibition on the infliction of

⁵ Reported at Garner, R, (1998) Political Animals: Animal Protection Politics in Britain and the United States, Macmillan: 178.

pain – the position of the RSPCA for example – and no restriction on the suffering that can be inflicted – a position realised by the granting of a certificate under the 1876 legislation. However, the Home Office Inspectorate remained in place, and is heavily biased towards animal research, with 81% of Inspectors having a background in animal research. There is a perception that, despite the introduction of the 1986 Act, the regulation of animal experimentation has not evolved to reflect the key elements of the new legislation, in particular the cost-benefit assessment. The Imutran case study appears to confirm that situation.

More recently, the House of Lords Select Committee has conducted an inquiry into the use of animals in scientific procedures in the UK, and reported in July 2002. Although Mr Lyons gave evidence at an informal meeting to the Committee, Imutran refused to alter the terms of the injunction, as it then stood, to allow submission of the documentation to the Committee to aid it in its deliberations.

In the context of, once again, a broadly conservative report, the key conclusion of the Committee was “that changes are needed in the institutional arrangements, in the information which is made available, and in the attitudes shown by all concerned, from the specialist to the public.”

At paragraph 5.7, the Committee stated:

“Belief in the impartiality of the Inspectorate has been undermined by allegations such as those made by Uncaged Campaigns concerning Imutran, a company which undertook research into xenotransplantation. The Home Office, despite promising in November 2000 that members of the APC would participate in any investigations into allegations of malpractice, did not invite the APC to participate in the investigation into Imutran. Indeed, no formal investigation took place, only a routine review of compliance issues by the Inspectorate.⁶ The actions of the Inspectorate, which were criticised by Uncaged, were also not subject to scrutiny by an external body.”

The Committee goes on to criticise the Inspectorate for its review of the implementation of the recently introduced Ethical Review Process (ERP) which is supposed to take place at animal research establishments:

“We consider this review to be flawed on many counts... shortcomings are blamed on local implementation while the Home Office and Inspectorate exonerate themselves entirely.”
(paragraph 5.11)

They go on:

“Both these matters, the independence of the inspection process and the independence of policy review, centre on the monitoring of the Inspectorate... We recommend that the Inspectorate should be subject to periodic review, by a body other than the Inspectorate itself.” (paragraphs 5.12-5.13)

On the subject of the APC, the Committee found that

“it has no executive authority and no clear lines of accountability. It is a committee looking for a role. We consider that it should take a more active role in monitoring the work of the Inspectorate... We recommend that the secretariat of the Animal Procedures Committee should be strengthened and more clearly separated from the Home Office regulators.”

We believe that these observations are pertinent to the Imutran case and provide a reasonable starting point for possible improvements in the operation of the 1986 Act. Institutional structures must be improved to ensure better accountability and balance in the scrutiny of animal research proposals. Openness is a key element of this. The House of Lords Committee also made recommendations on this matter:

“We consider the current levels of secrecy surrounding animal experiments to be excessive... From the evidence we have received, we consider that there should be a presumption in favour of information being publicly available... We recommend that Section 24 (the confidentiality clause) should be repealed.”

Unfortunately, the Home Office response to the House of Lords Committee has been less than constructive. When the House of Lords debated the report on 17th October 2003, there was “near unanimity of the relative feebleness of the Government’s initial response” [L Smith, concluding remarks]. Words used in the debate included “complacent, timid and... conservative” [B. Warnock]; “patronising and complacent” [L Lucas]; “negative and complacent” [L Smith, opening remarks].

There is undoubtedly a broad consensus, including many of those not opposed to animal experimentation in principle, that the current implementation of the 1986 Act is biased and unsatisfactory in many respects. The Imutran case provides unique evidence which confirm that consensus view.

⁶ At a footnote to the text here in the HoL report, it states ‘Robert McCracken, a member of the APC, was unhappy with this review: “the concerns raised... were not allayed by the brief, routine report by the Inspectorate.” (Q.804)’

Note on references

- Documents prefixed 'ND' are those leaked from the Home Office in October 2002. They are accessible at: <http://www.xenodiaries.org/newdocs.pdf>
- Documents prefixed 'WCB', 'CY' and 'hlsapp' were those photocopies included in the original leak from Imutran Ltd in spring 2000 and are accessible at: <http://www.xenodiaries.org/docs.pdf>
- The leaked reports and clinical signs for the Imutran studies (e.g. ITN25, IAN009, etc.) can be found at: <http://www.xenodiaries.org/studies.pdf>
- A redacted form of the original Diaries of Despair report can be viewed at: <http://www.xenodiaries.org/report.pdf>
- The Home Office Chief Inspector's June 2001 Compliance Review is at: <http://www.homeoffice.gov.uk/docs/imutranreport.pdf>
- The Home Office response to letter of the Home Affairs Committee of June 2003 (and to which this report responds) can be found at: <http://www.homeoffice.gov.uk/docs2/horesponseimutranjun2003.html>
- The RSPCA's report on this matter can be found via: <http://www.rspca.org.uk/servlet/ContentServer?pagename=RSPCA/News/NewsArchive&articleid=1024472942660&newsmode=normal&marker=91>

1. 'Moderate' severity classification

1.1 In response to the Home Affairs Committee's (HAC) question: '**1. Were any of the experiments which were classified as of "moderate severity" wrongly classified?**', the Home Office (HO) replies 'No', and proceeds to attempt to validate this position, particularly at paragraphs 21 to 36. This section demonstrates how, by the HO's own criteria, their denial of misclassification is wholly unsustainable.

1.2 Initially, we would like to make some contextual and explanatory points regarding the roles played by severity assessments and the status of xenotransplantation research to assist the HAC's consideration of the HO's regulation of Imutran's research and its response to the HAC's questions. We will then cite several instances of primates "found dead", in a collapsed state or unequivocally suffering a serious impairment of their welfare under 'moderate' procedures. This evidence will provide straightforward, unequivocal evidence of HO misconduct in both the setting and enforcement of severity limits, and also the HO responses to allegations and questions on this matter (including the response to the HAC).

Role of severity assessments in implementation of regulations

1.3 It is interesting to note that in response to criticisms of the HO's assessment and enforcement of severity limits and bands, the HO belittles the role of these tools in implementing the Animals (Scientific Procedures) Act 1986 ('the 1986 Act').⁷ However, although categorisations of severity naturally have to be determined on the basis of the information in the project licence (which, by law, must not be deliberately or recklessly false), on paper - at least - severity limits and bands play a crucial role in assessing and controlling animal experimentation.

1.4 Severity limits are set for each of the separate procedures (or 'protocols') that make up the project licence. This limit is supposed to set a crucial condition on the project licence to *control animal pain and suffering*. The head of the relevant section of the project licence states: "This information is essential for the determination of the severity limit of the procedure which must be observed as a condition of this project licence and of the licences of participating personal licensees."⁸ Exceeding the severity limit is a potential breach of the project licence, an

⁷ See for example, paragraph 4.7 of Annex C, part of a HO response to a critical report on brain experiments on primates, and more subtly at para 16-17 of HO response.

⁸ See document ND1.27.

infringement of the law and could result in the revocation of the licence (see paras 5.43-5.46 of Annex B to HO memo).

1.5 The severity band is allocated to the project and it is this that is used to represent “the ‘cost’ to be taken into consideration when applying the cost/benefit assessment” (para 5.7 of HO memo Annex D), which is the crucial assessment to decide whether research should be permitted at all. At paragraphs 18-19 of their response, the HO explain that, according to stated policy, the severity band, while being “determined by the average animal used” during the intended project, reflects the “actual suffering likely to be caused as a result” of each protocol that makes up the proposed project. Thus, while the allocation of an overall severity band contains a greater element of judgement than severity limit classifications, if the potential suffering caused by a protocol, represented by the severity limit, is underestimated, then logically this will distort determination of overall severity and hence the cost-benefit assessment.

1.6 In addition, under standard condition 8 for project licences, the project licence-holder must promptly notify the Home Secretary if a severity limit has been, or is likely to be breached. The most recent HO Guidance indicates that this is so that the cost/benefit assessment can be re-examined.⁹ Thus, in the context of the Imutran case, the breaching of the moderate severity limits (which, as we shall explain below, occurred on numerous occasions) significantly undermines the adequacy of the HO’s cost-benefit assessment.

1.7 In our discussion of severity assessments, we will focus on those assessments as expressed in severity limits, with the understanding that those discussions will help determine the validity of the wider cost-benefit assessment. Severity limits also play additional, crucial roles in the operation of the regulatory system.

1.8 The HO memo’s lengthy discussions at paras 21-26 and the discussion in the HO Guidance on the Operation of the 1986 Act¹⁰ appear to confirm an important role for severity limits. In any event, the evidence for HO misconduct is overwhelming whether one relies on

- the allocated severity limits combined with the HO’s description of how these are determined (see paragraph 23 of HO response), and/or
- the actual information in the project licences

⁹ Paragraph 5.44.

¹⁰ See Annexes A & B of HO Response. Section 21(1) of the 1986 Act states: “The Secretary of State shall publish information to serve as guidance with respect to the manner in which he proposes to exercise his power to grant licences and certificates under this Act and with respect to the conditions which he proposes to include in such licences as certificates.”

1.9 The Imutran case study is highly unusual because the actual project licences have been leaked and published following our public interest legal victory, therefore providing a unique opportunity to conduct a detailed, evidence-based assessment of the adequacy of the assessment and monitoring of severity.

1.10 Particularly in the case of primate experiments, the severity limits allocated to procedures also *affects the level of scrutiny* received by the application. Proposals to conduct procedures of ‘substantial’ severity on primates are considered by the Animal Procedures Committee (APC),¹¹ whereas ‘moderate’ severity procedures are not usually examined by the APC.

Role of severity assessments in informing public debate

1.11 In addition to the regulatory role played by both severity limits and bands, they also play a role in informing the public about animal research and the levels of suffering involved. Apart from leaks and undercover investigations, the only information available to the public that gives any indication of the levels of suffering experienced by animals is to be found in the breakdown of project licences into severity bands, published by the Home Office in the annual “Statistics of Scientific Procedures on Living Animals”.¹² Thus, severity bands currently perform a relatively important, if highly limited and unverifiable, role in informing the public debate about animal research. Any underestimations in the severity band assessment will thus mislead the public about the extent of suffering and hence the acceptability of animal research.

The status of xenotransplantation

1.12 The state of knowledge regarding the immunological (and other) obstacles to viable pig-to-primate organ transplants is an important consideration in an examination of the general adequacy of the Home Office’s initial assessments of

1. the likely suffering to be experienced by primates subjected to pig organ transplant experiments (‘costs’), and
2. the likelihood of achieving success in those experiments to permit the commencement of human trials of the procedure (‘benefits’¹³).

¹¹ Report of the Animal Procedures Committee for 1999, HC 630, p.4, paragraph 26.

¹² See, for example, p.83 in the statistics for 2002.

¹³ This aspect will be examined in detail at section 2.

1.13 Close examination of the HO 'Guidance' on the operation of the 1986 Act reveals that breaches of severity limits are permitted "if an animal has suffered more than authorised either unexpectedly or for extraneous reasons", although if that does occur then "steps must be taken to alleviate the suffering at once."¹⁴ This regulation itself is a source of concern as it appears to reward researchers for ignorance of or disregard for the possible adverse effects and suffering caused by the experiments by providing this potential defence for breaching the severity limit. In order to ascertain whether adverse effects, particularly at the beginning of a research project, are really 'unexpected' or 'extraneous', one needs to examine the state of knowledge about proposed procedures. This would also be relevant to determining whether an offence has taken place under section 23 of the 1986 Act, which deals with the furnishing of "false information" in order to obtain a licence. If a likely adverse effect of a procedure is not admitted in the project licence, then this potentially constitutes a criminal offence.

1.14 A *New Scientist* article published in June 1994¹⁵ provides an informative overview of the status of xenotransplantation, nine months *prior* to the commencement of the first study described in the leaked Imutran documentation, ITN3 (see below under "Heterotopic abdominal cardiac xenografting in cynomolgus monkeys").

Immunosuppression

1.15 The *New Scientist* article describes how the genetic engineering of pigs had prevented the first immunological attack – 'hyperacute rejection' - suffered by pig organs when transplanted into distantly related species, i.e. primates.¹⁶ However, in discussion of the subsequent rejection mechanisms to be overcome in the development of pig organ transplants, the author notes that while in human-to-human transplants the immune response is suppressed with drugs, "with pig organs, those responses could turn out to be much stronger."

¹⁴ Guidance on the Operation of the Animals (Scientific Procedures) Act 1986, published 1990, para 4.19. This Guidance was in operation at the time of the Imutran experiments, and has since been superseded by the Guidance published in 2000 and produced by the HO at Annexes A & B. The two Guidances are essentially the same in respect to the setting and enforcement of severity limits.

¹⁵ D.Concar, "The organ factory of the future?", *New Scientist*, 18 June 1994, pp.24-29.

¹⁶ Note that this already accounts for the first three of the six 'benefits' that the Home Office claim that Imutran achieved in their research (para 38 of their response and also see section 2 below for discussion).

1.16 Published papers discussing xenotransplantation in 1994 include the following observations:

- “Nothing is known about the phenomena following successfully suppressed hyperacute xenogeneic rejection (HXR).” C. Hammer, “Xenotransplantation and its future,” *Forensic Sci Int.* 1994 Dec 16;69(3):259-68.
- “Because of the genetic disparity between these two species, routine immunosuppression will probably not suffice for the long-term survival of pig to primate xenografts.” Sachs DH, “The pig as a potential xenograft donor”, *Vet Immunol Immunopathol.* 1994 Oct;43(1-3):185-91.

1.17 These observations are relevant to the quality of the original severity assessments carried out by the licence applicants (Imutran) and the Home Office Inspectorate. Given the intrinsically radical nature of cross-species transplant experiments between distantly-related species, the unknown nature of the rejection mechanisms post-hyperacute rejection, and the prediction of a more intense immune response compared to established clinical practice, it should be expected that adverse effects due to immunosuppressive drug toxicity would be taken account of in determining the likely severity of the experiments. Furthermore, the Home Office should have predicted the occurrence of drug toxicity from the immunosuppressive regimes that Imutran proposed to administer to the primates.

1.18 However, even in its most recent response, the HO gives an inconsistent description of its assessment of the potential suffering or adverse effects caused by drug toxicity. At the first bullet point of paragraph 23, the HO’s description of its ‘moderate’ severity assessment, which corresponds to the first four Imutran protocols discussed at paragraphs 1.70-1.87 below (‘Heterotopic abdominal xenografting in cynomolgus monkeys’, ‘Pancreatic islet xenografting’, ‘Heterotopic cervical cardiac xenotransplantation’ and ‘Heterotopic abdominal heart xenografting in baboons’), does not acknowledge the potential for drug toxicity, thereby downplaying the number and severity of potential symptoms caused by the procedures:

“The Inspectorate’s assessment was that the surgical procedures and post-operative care are similar to those used in human clinical practice and other established research contexts. Failure or rejection of the rejected organ should not (in those cases where the animal’s own organs remained in place) seriously impair the welfare of the animals, rather it would cause local problems and not interfere with the normal working of the animals’ own organ.”

1.19 While in respect of the renal xenotransplantation procedures, once again there is no reference to adverse effects caused by drug toxicity, with the focus being on the suffering caused by gradual renal failure caused by rejection of the organ.¹⁷

1.20 In contrast, at paragraph 35 of the HO response, “the immunosuppressive regimen” is listed as a welfare ‘cost’ that it claims was considered, although the discussion seems to underplay the frequency and severity of immunosuppressive side-effects and fails to reflect Imutran’s inability to suppress xenograft rejection without causing toxic side-effects. Thus the actual study documentation reveals that “the *best possible* provision for the welfare of the animals and the viability of the transplanted organ” (as the HO puts it, emphasis added) was, even if it is a true reflection of the immunosuppressive regimens, in fact quite poor given the intrinsic problems faced in this situation.¹⁸

1.21 In any case, the potential for adverse effects from immunosuppressive drugs was not included in the actual project licence authorities for PPL80/848¹⁹, which, according to the HO, are supposed “to convey the detailed information essential to the cost component of the regulatory cost/benefit assessment or to define the welfare and scientific endpoints to be applied if and when licence authorities are granted.”²⁰ Similarly, the heading of the relevant section of the project licence includes the following standard statement:

“This information is essential for the determination of the severity limit of the procedure which must be observed as a condition of this project licence and of the licences of participating personal licensees.”²¹

1.22 Therefore, the sporadic HO references to immunosuppressive drug toxicity as a source of suffering in the recent response seem to be little more than a retrospective attempt to give the impression that a proper assessment of severity was conducted.

1.23 The strength and appropriateness of the immunosuppression used by Imutran in their primate experiments was discussed at some length at a meeting of the Xenotransplantation SubCommittee of the US Government’s Food and Drug Administration (FDAXS).²² The meeting took place on 4 June 1999 and involved the world’s leading xenotransplantation researchers,

¹⁷ Paragraph 23, second bullet point.

¹⁸ See below at paragraphs 1.70-1.101 for discussion of the actual suffering caused by these procedures.

¹⁹ See documents ND1.33-1.36, ND1.38-1.39, ND1.56, ND1.42.

²⁰ HO response, para 17.

²¹ See document ND1.27.

²² Referred to at <http://www.fda.gov/cber/xap/trans.htm>

including Imutran. Transplant surgeon and researcher Dr Robert Michler noted that even in the case of the longest survivors in the Imutran experiments:²³

“the particular doses are not particularly those which we would find acceptable for human transplantation... The doses you have referred to in the documents are doses that would induce hypertension, certainly induce renal dysfunction if not renal failure in patients...”²⁴

1.24 Later at the meeting, Dr David Cooper expanded on this theme:

“The other thing that has worried me, as I mentioned this morning, is that if you have got animals that are still showing signs of rejection, but at the same time are getting lymphoproliferative disease, lymphomas, tumors developing, it means that they are getting quite heavy immunosuppressions, you are not controlling the rejection, but you are still seeing the serious effects of that immunosuppression.”²⁵

1.25 Following the initial leak from Imutran, Uncaged submitted the confidential documents to the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA). At the next Open Meeting of the Authority in February 2001, UKXIRA’s expert immunologist, Professor Herb Sewell, made the following comments on Imutran’s primate research:

“If there was to be any move towards clinical trials, and there could be some way of containing rejection, that would have to be with immunosuppressive drugs – at that time that was the dominant thought – but those drug regimens should be of a level that would be seen as acceptable and sensible if one was to extrapolate to the clinical situation. In animal models systems people can sometimes use very extreme protocols, and that in itself is a matter that needs ethical debate. But many of those protocols really bear no resemblance to reality in moving to man...”

The best survival data has come from consortia involving Imutran – they’ve shown for instance that the pig-to-baboon model in a very limited number of animals that we can get survival up to 39 days but with some significant co-morbidity. In their kidney transplant model they get longer survival – some of the animals up to 70 days plus, but again the suppressive regimen which involve a cocktail of at least three potent

²³ Involving kidney xenotransplantation.

²⁴ <http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3517t2b.pdf> , p2, lines 10-16. (P.102 of whole transcript, which is split into three pdf documents on the website.)

²⁵ <http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3517t2b.pdf>, p30, lines 14-21. Dr Cooper is referring to kidney xenotransplantation study IAN013, conducted by Imutran in Spring 1998 under PPL80/848, with a ‘moderate’ severity limit and banding.

immunosuppressives plus splenectomy²⁶ I would suggest would not be acceptable for human management. There is ongoing problems about animal welfare and that should always be kept as part of the calculus when one is looking at the way forward...”

1.26 In summary, significant systemic primate suffering as a result of failed immunosuppressive drug regimens that were not analogous to clinical practice was a predictable outcome of the Imutran primate experiments. Yet this cause of suffering did not form part of Imutran and the HO’s statutory consideration of ‘costs’ to animals in the licensing process. Some of the actual effects of these procedures are related below under the discussions of the various Imutran protocols.²⁷

“A very uncommon operation”

1.27 The HO’s description of its assessment of the severity of the Imutran procedures appears to suggest broadly that the xenotransplantation experiments were relatively conventional procedures:

“The Inspectorate’s assessment was [in the case of heterotopic organ transplants] that the surgical procedures and post-operative care are similar to those used in human clinical practice and other established research contexts.”²⁸

1.28 This characterisation seriously underestimates the highly experimental and radically novel nature of cross-species organ transplantation procedures. The lack of progress achieved in xenotransplantation research in the last eight years is a retrospective testament to its speculative character. But, before and early in Imutran’s research programme, the towering obstacles to xenotransplantation were noted. The Kennedy Report, commissioned by the Secretary of State for Health in 1995 following Imutran’s claims of imminent clinical trials of pig hearts,²⁹ remarked:

²⁶ Splenectomy = removal of the spleen.

²⁷ See below at paragraphs 1.70-1.101.

²⁸ HO response, para 23, first bullet.

²⁹ See, for example, “Pig-to-human heart transplant ‘breakthrough’ stirs debate over timing of trials”, Nature, Vol 377, 21 September 1995: 185-186. “Pig-to-human heart transplant slated to begin in 1996”, Nature Medicine, Vol 1, No.10, October 1995: 987.

“to describe xenotransplantation as a frontier in medical science is to invite a raised eyebrow from the world-weary and to risk relegating it to the status of this season’s fashion... Perhaps, this is one area where the word frontier is not hyperbole.”³⁰

1.29 While a recently published review of xenotransplantation makes a general observation:

“A chain is only as strong as its weakest link; this is also true for xenogeneic immunology, physiology, and pharmacology. The phylogenic distance between man and pig comprises 180 million years. This tremendous distance has to be bridged by new and still unknown methods to outwit evolution.”³¹

1.30 In addition to the radical nature of xenotransplantation, there are a number of specific factors relevant to the assessment of severity that confirm that the Imutran experiments were far from analogous to “human clinical practice”, contrary to the HO claims. One of the key considerations at the June 1999 FDAXS meeting was the extent to which the primate experiments were analogous to the clinical situation, and some illuminating insights came out of the discussion. In his presentation, Dr David Cooper noted that:

“...it is very difficult to manage baboons in the [laboratory] environment. They are prone to infections, and so on. You do not have any of the ability to look after that you have to look after a patient in an intensive care unit or in the hospital surroundings.”³²

1.31 The American researcher Dr Christopher MacGregor commented:

“... there is a huge difference in the practical management of a non-human primate receiving a xenotransplant compared to a human.”³³

1.32 Dr Steve Woodle, a consultant to the FDAXS, observed:

“... you can’t take care of an animal in a laboratory setting the way you can a human... you are in the Stone Age with an animal in a laboratory.”³⁴

³⁰ “Animal Tissue into Humans: a report by the Advisory Group on the Ethics of Xenotransplantation” (Department of Health: 1996) from ‘Chairman’s Foreword’, p.vii .’

³¹ Hammer C. “Xenotransplantation: the good, the bad, and the ugly or how far are we to clinical application?” *Transplant Proc.* 2003 May;35(3):1256-7.

³² <http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3517t2a.pdf> , pp.25-26, lines 21-1.

³³ <http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3517t2a.pdf> , p.125, lines 11-13.

³⁴ <http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3517t2b.pdf> , pp42-43, lines 22-4. (Pp. 142-1433 of whole transcript, which is split into three pdf documents on the website.)

1.33 As we have seen, the vast majority of the Imutran research involved ‘heterotopic’ xenotransplants – transplants of organs into unnatural positions. Dr Robert Michler, a transplant surgeon and animal researcher, reminded the FDAXS meeting that in the human sphere, such a procedure was “a very uncommon operation.”³⁵ Emphasising the acute novelty of the procedure in the Imutran context, Dr Michler later told the meeting:

“doing a heterotopic transplant in an animal model is an entirely different operation than doing it in a human. The connections are different. So, there is no parallel there, very little parallel there.”³⁶

1.34 In the circumstances, and also bearing in mind the toxicity of the immunosuppressive regimens used by Imutran, it is bewildering that the HO Inspectorate should consider (or claim that it considered) solid organ xenotransplantation experiments as analogous to conventional transplantation. Yet the adequate operation of the regulatory system requires that the HO makes reasonable and well-informed judgments on the likely costs and benefits of animal research. From the very beginning, the HO appears to have failed to grasp, or turned a blind eye to, the extreme nature of the research it was licensing.

1.35 The HO response puts great store on purported similarities between primate experimentation and clinical practice in its denial of the occurrence of ‘severe’ suffering in the Imutran research.³⁷ For example, at paragraph 57, the HO claims:

“The quality of the clinical management of the animals, as attested to by the full records, is considered to have been such that good provision was made to minimise the resulting suffering, and to have kept it within the bounds of that which is encountered in human clinical practice – this was sufficient for the suffering that did occur to be accommodated within the allocated severity limits and bands.”

1.36 In fact, the fundamental unreliability of the research/clinical practice analogy undermines the HO assessment and characterisation of the levels of suffering experienced by the primates.

1.37 One additional, important difference between the treatment of the Imutran primates and the human sphere is the frequency of monitoring, particularly during the 13 hour overnight period. The RSPCA noted in their report on the Imutran research:

“In the study reports it states that recipient animals were closely monitored for the first 24 hours post transplant and thereafter checked regularly throughout the working day...

³⁵ <http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3517t2a.pdf> , p.40, line 8.

³⁶ <http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3517t2b.pdf> , p.97, lines 21-24.

³⁷ In answer to question 3a of the HAC, at paragraphs 51 to 59.

Some animals were found dead in the morning, presumably having died overnight, or were found dead in the afternoon. The Chief Inspector's report (para 5.13) states that: 'Records confirm that both veterinary and medical staff provided 24-hour-a-day clinical cover.' It is difficult to understand how, if this was the case, animals could be just 'found dead' in the morning."³⁸

Severity limits for the various Imutran xenotransplantation procedures

1.38 Here we outline which severity limits were allocated to the various xenotransplantation procedures performed by Imutran. The HO response refers to three project licences issued to Imutran.³⁹ In fact, the vast majority of the research described in the two leaks of documentation was licensed under the first project licence, PPL 80/848, which ran from 1994 to 1999. There are no records for any procedures being carried out under PPL 80/1223 (pig-to-primate heart xenotransplantation, 1998-2000), while a relatively small number of pig-to-primate kidney transplants appear to have been conducted under PPL 80/1366 (1999-2000).

1.39 This list sets out how many primates were subjected to the various xenotransplantation procedures licensed under PPL 80/848 and the severity limit allocated to them:

- Heterotopic abdominal cardiac xenografting in cynomolgus monkeys. 65 monkeys, Moderate severity limit. (A further 24 monkeys were used in this type of procedure in an early 'developmental' study, ITN2⁴⁰, but no study report has emerged.)
- Pancreatic islet xenografting. 37 monkeys. Moderate severity limit.
- Heterotopic cervical cardiac xenotransplantation. 6 baboons. Moderate severity limit.
- Heterotopic abdominal heart xenografting in baboons. 27 baboons. Moderate severity limit.
- Heterotopic renal xenografting. Approx 300 monkeys. Moderate severity limit.

1.40 In addition, 16 baboons were killed in "orthotopic cardiac xenotransplantation" procedures, involving the replacement of the primates' own hearts with a pig heart. These were the only procedures to be given a 'substantial' severity limit.

1.41 Therefore, more than 95% of the Imutran xenograft procedures were 'heterotopic' transplants that were classified as, *at worst*⁴¹, of 'moderate' severity.

³⁸ RSPCA Report: Non-Human Primates in Xenotransplantation Research in the UK, June 2002: 42.

³⁹ At paragraph 1.

⁴⁰ See Document ND9.1.

1.42 Early in the research programme, monkeys and baboons were also used by Imutran in ‘moderate’ severity monkey-to-baboon organ transplant (*‘concordant xenografts’*) experiments under PPL80/848. These experiments licensed the use of 50 monkeys and 50 baboons per year to try to develop primate organs for use in infants with heart defects, though the research path appears to have been abandoned following concerns about the safety and ethics of using primate organs, particularly in young infants as detailed in the HO licence. Some licensing documentation in relation to these experiments emerged in the October 2002 leak from the HO⁴², but no study reports or other information has emerged to describe exactly what happened to the animals during those experiments. These are controversial procedures and both Imutran and the Home Office have been very coy indeed about discussing them. The first time that Uncaged became aware of the occurrence of such experiments was in October 2002 due to the Home Office leak. In the absence of disclosed documentation, it is difficult to ascertain the levels of suffering experienced during these procedures. However, the highly speculative and lethal nature of the experiments, the involvement of primates as both sources and recipients of organs, the use of the ‘cervical’ model (transplanting the organ into the neck) and the consequences of the remainder of Imutran’s research programme are all factors which raise serious concerns about such procedures.

Home Office determination of severity limits

1.43 Paragraph 4.8 of the relevant Guidance on the operation of the 1986 Act explains:
“Such an assessment should reflect the maximum severity expected to be experienced by any animal. It should not take into account the numbers of animals which might experience the maximum severity or the proportion of the animal’s lifetime for which it might experience severe effects.”

1.44 In other words, even if it were possible that a single animal could experience ‘substantial’ or ‘severe’ pain or distress for more than an instant, the severity limit should reflect that worst-case scenario.

1.45 In paragraph 23 of its response, the Home Office provides its story of how the various xenotransplantation procedures were assessed. This is a crucial passage of the Home Office’s response:

⁴¹ See, for example, paragraph 18 of HO response.

⁴² See ND1.6-1.9, 1.20-1.26, 2.1-2.3.

“a moderate severity limit would be appropriate in the case of heterotopic organ transplants, where the recipient animal’s own organ would remain in situ and continue to function... Failure or rejection of the rejected organ should not seriously impair the welfare of the animals, rather it would *cause local problems and not interfere with the normal working of the animals’ own organ.*

“a substantial severity limit would be appropriate in the case [where]... some animals might *die before appropriate clinical investigation and management, or euthanasia, could be applied.*”

(Emphases added)

1.46 At paragraph 24, the HO claims “The Inspectorate tested and challenged these arguments”, although no evidence is cited of any thorough, detached scrutiny. The HO provides no specific examples of a difference of opinion between Imutran and the HO in its assessment of severity. On the contrary, the discussions at paragraph 23 indicate a high degree of agreement between the Inspectors and Imutran. At paragraph 25 the HO admits that the arguments “were eventually accepted.”

1.47 It is important to understand that the final project licence becomes the legal basis upon which the research is licensed, and HO Inspectors work closely with applicants in the drawing up of the licences. This is expressed by the HO in the following terms:

“A considerable proportion of Inspectorate resources is devoted to ensuring that project licence applications cannot be further refined.”⁴³

1.48 The concern is that, to be more accurate, the Inspectorate works hard to ensure that project licence applicants are successful rather than acting as neutral and objective scrutineers.

1.49 Furthermore, the Imutran documentation indicates an indulgent attitude from the HO towards Imutran rather than a “challenging” one. As the first Uncaged memorandum notes, a confidential document provides a glimpse of the collusion between Imutran and the Home Office to ‘fix’ the system in their favour: “Sandoz [Imutran’s parent company at the time] have suggested kidney transplants, the Home Office will attempt to get these classified as moderate procedures.”⁴⁴ We note that the HO did not reply to this specific piece of worrying evidence.

1.50 Paragraph 26 of the HO response is also misleading. It claims:

⁴³ See Note on Cost/benefit assessment by the Chief Inspector, at annex D to the HO response, para 4.5.

⁴⁴ See document CY14.1 .

“This analysis of the appropriateness of the severity limits and severity bands imposed was also discussed, and endorsed as sound, when the Animal Procedures Committee considered the Imutran applications. Paragraph 32 of the APC Report for 1999 records:...”

1.51 The quote for the 1999 discussion actually refers to the analysis of only a very small proportion of the Imutran research – the final few kidney xenograft procedures conducted under project licence PPL80/1336. This does not equate to a general endorsement of the HO determination of severity limits. Furthermore, the quote itself from the APC report reveals substantive concern about the ‘moderate’ rating despite agreement (based on whatever information the APC was provided with by the HO) with the HO formal interpretation. This issue will be discussed below in connection with the overall assessment of the kidney experiments.

1.52 As we explore the issue of severity, reference will be made to the project licences for the Imutran experiments, particularly sections 17 (‘Background, objectives and potential benefits’), 18 (‘Description of plan of work’) and 19 (Description of the different protocols, including a description of the adverse effects on the animals and the steps taken to minimise those effects). These documents set out the conditions upon which the procedures are licensed. As the Home Office admits,⁴⁵ the statutory assessments of suffering and potential benefit are conducted on the basis of the information in the project licence application. The HO response attempts to focus attention on the need to consider this more detailed information at the expense of the stated severity limits, though – curiously - this information itself is absent from the HO response. In contrast, this paper will refer extensively to the information contained in the project licences.

Analysis of severity of Imutran procedures

1.53 In order to assess the adequacy of the ‘moderate’ classification for the vast majority of the Imutran xenotransplantation experiments, the different protocols undertaken by Imutran are discussed below in chronological order, and will include comparison between:

- the adverse effects listed in the licence,
- the HO version of its determination of severity limits,
- observations made by Imutran about the outcome of their experiments, and
- the actual evidence provided by the leaked study documentation

⁴⁵ At paragraph 17 of their response, for example.

1.54 Before the severity of the Imutran research is discussed in detail, it is worth considering the arguments made by the HO in relation to the clinical signs and other evidence regarding animal suffering adduced by Uncaged.

Informativeness of clinical signs and other leaked documentation

1.55 At various points in the HO response, as well as in the Chief Inspector's ('CI') review of Imutran's compliance, the HO casts doubt on the informativeness of the clinical signs and other documents that describe the xenotransplantation experiments and their effects on the primates.

1.56 Our original memorandum discussed this matter under the heading "Dismissal of animal suffering", and we expressed our deep concern regarding what we perceive to be a glaring lack of integrity on the part of the HO: an indifferent attitude to animal suffering, and an attempt to prevent an informed public debate by downplaying the suffering experienced by the primates involved. Yet the HO persists with this line of argument:

- "Symptomatic and supportive treatments, not detailed in the material obtained by Uncaged, were provided as required." (para 30)
- "However, they give no insight into the clinical management of the animals (for example the degree of clinical oversight, or the treatment provided including the use of analgesics and fluid replacement), and the actual level of suffering experienced." (para 31)
- "A number of the clinical findings in the Uncaged material are indicative of the transplanted organs failing (for example, vomiting was in many cases an indication of renal failure) or of problems with immunosuppression (for example, diarrhoea). However this material does not acknowledge that appropriate supportive and symptomatic treatments (for example the administration of fluids and anti-emetics⁴⁶) were being given, or that some of what seem to [be] the most significant 'problems' recorded (for example lethargy, drowsiness) were in fact consequences of the treatments given (for example analgesics and sedatives rather than being indicative of severely compromised welfare resulting directly from the regulated procedures applied." (para 56)"
- "The material available to Uncaged provides no insights into the clinical management of these animals; the intensity and duration of the symptoms; the supportive, symptomatic and specific treatments given; or the response to treatment. It is not possible to judge the true welfare costs of these procedures without a thorough understanding of all of these factors." (para 94)

⁴⁶ Anti-emetic = a drug used to counter nausea and vomiting.

1.57 These are misleading assertions. As we stated in the June memorandum, logically, the observed conditions of the primates occurred in the context of any attempts to ameliorate the animals' suffering. The leaked Imutran documents repeatedly refer to the use of various "supportive and symptomatic treatments". For example,

- "abdomen extremely distended... fluid aspirated under anaesthetic from distended abdomen."⁴⁷
- "not alert due to pethidine dose"⁴⁸

1.58 The 'clinical signs' to which we refer are found in an appendix to every single study report, and such recordings form a standard part of the experimental protocol. In fact, the observations contained in these appendices are *particularly* informative, as the following quote from study report ITN3 reveals:

"The clinical signs presented in this Appendix are only the first and last observations reported for each day the animal survived. Due to the frequent and numerous procedures performed on the animals throughout the course of each day, the signs displayed by them other than first thing in the morning or last thing in the evening, were considered to be unrepresentative of the underlying clinical condition of each animal."⁴⁹

1.59 As it will be recalled from our June memorandum, Imutran unsuccessfully floated a similar argument on the clinical signs as the HO, but then refused to disclose the additional documentation containing observations of the animals (which, as explained above, appear not be as informative as the clinical signs in the study reports that we have published) and details of their clinical management. It is important to realise that Uncaged actually applied to the High Court for an Order requiring Imutran to disclose these additional documents. On the eve of the scheduled hearing date, Imutran surrendered in their attempt to suppress the documentation and the case was settled.

1.60 Imutran were equally unforthcoming about releasing to the RSPCA additional cited material concerning the animals' clinical condition. Over 500 primates were killed by Imutran in their research programme, yet Imutran only released to the Society two minutes of video footage for one baboon (that has previously been presented to the media in any case) and the surgeon's notes on this single baboon. The RSPCA comments: "We asked Imutran to provide the

⁴⁷ For X530f during study ITN026.

⁴⁸ For A8f in study IAN010

⁴⁹ See beginning of clinical signs appendix for study ITN3. An abbreviated version of the same explanatory note appears for the remaining studies.

surgeon's notes for the other five animals on the particular study for comparison but they were not willing to do so."⁵⁰

1.61 The reticence of both Imutran and the HO to disclose or openly discuss this additional information to which they refer is a clear indicator that is likely to intensify concerns regarding animal suffering and the stance of the HO rather than temper them. Indeed, the RSPCA record that the surgeon's notes supplied by Imutran for the single animal revealed additional welfare problems not recorded in the clinical signs:

"The surgeon's notes for Day 25 indicate that the baboon was taken to the operating room for debridement of the chest wound (mid-ventral operation line) which had been oozing serious matter intermittently since day 2 and had worsened since day 23... Imutran were either not prepared or able to provide the surgeon's notes for the other animals."⁵¹

1.62 In stark contrast to Imutran and the HO, we are extremely keen that these additional documents should be in the public domain in order to give a complete picture of what happened to the animals. They cannot negate the facts revealed in the existing documentation showing that, in supposedly moderate experiments, primates were '**collapsed**', had '**nystagmus**' (rapid involuntary eye movements), '**grinding teeth**', '**rolling eyes**', '**uncoordinated limb spasms**', '**body and limb tremors**', were '**salivating**', had '**very laboured breathing and extreme difficulty trying to walk**', were '**very distressed**', '**in obvious discomfort**', or '**looking miserable, huddled and hunched on cage floor, reluctant to move**,' etc., etc.. The information and documentation referred to but not published by the HO would provide additional, complementary details of the fates of the animals, and it is our hope that any independent inquiry into this matter would have the opportunity to examine them.

1.63 The fact that several monkeys and baboons were 'found dead' in moderate (and substantial) experiments – and that the HO has evaded these incidents - is both an indication of the intrinsic severity of the Imutran xenotransplantation experiments, and confirmation of the overall lack of credibility of the HO's denials of the informativeness of the clinical signs.

1.64 We are entirely happy to accept the plausibility of the Home Office assertion:

"*some* of what seem to [be] the most significant 'problems' recorded (for example lethargy, drowsiness) were in fact consequences of the treatments given (for example

⁵⁰ RSPCA Report: Non-Human Primates in Xenotransplantation Research in the UK, June 2002: 5.

⁵¹ RSPCA Report: Non-Human Primates in Xenotransplantation Research in the UK, June 2002: 35.

analgesics and sedatives) rather than being indicative of severely compromised welfare resulting directly from the regulated procedures applied.” (emphasis added)

1.65 But, by the same token, *some* of the observations of lethargy and drowsiness will be a result of renal failure due to rejection or drug toxicity. Imutran's own confidential project licence application, which they had refused to disclose to the Court but was subsequently leaked from the HO, emphasises how such observations are *indeed* utilised as indicators of acute and lethal illness and its attendant suffering:

"Clinical signs associated with progressive and irreversible renal failure can typically be characterised by a number of common features... Physically the animal becomes progressively quieter (listless) and adopts a huddled/hunched posture, reflecting the rising blood creatinine level."⁵²

1.66 Furthermore, “lethargy” and “drowsiness” are only two of a wide range of ‘significant problems’ recorded by the clinical signs. Other signs (e.g. those related above at paragraph 1.62 and below in the extract from the RSPCA report) are unequivocal in their indication of severe suffering. From a regulatory perspective, the length of time that the animals’ experienced that suffering is not relevant to the determination of the severity limit or the question of whether those limits were breached⁵³ (although duration of suffering would have a bearing on the severity banding of the project as a whole). Therefore, even if it were the case that analgesia were administered in response to perceived animal suffering and had some effect (though bear in mind comments above at 1.30-1.33 explaining the difficulty of ‘caring’ for primates in a laboratory), the initial occurrence of the suffering itself is relevant to the assessment and enforcement of severity limits.

1.67 The RSPCA’s report on the Imutran research refers to the clinical signs and expresses concern at Imutran's unwillingness (which is analogous to the HO attitude) to acknowledge this evidence of suffering:

“Even if these behaviours [i.e. “quiet and huddled”] were not indicative of pain/suffering, other observations made in the clinical signs indicate that severe suffering occurred.

Wolfensohn and Lloyd⁵⁴ state that in primates “acute abdominal pain may be shown by

⁵² See document ND24.23. Rising blood creatinine levels are an indicator of kidney failure. Creatinine is a waste product caused by muscle activity which is usually excreted in the urine.

⁵³ See paragraphs 1.43-1.44 above and paragraph 4.8 of Guidance on the Operation of the 1986 Act (1990 edition).

⁵⁴ Wolfensohn, S. and Lloyd, M. (1998). Handbook of Laboratory Animal Management and Welfare, 2nd Edition. London: Blackwell Science.

facial contortions, clenching of the teeth, restlessness and shaking". The serious and very unpleasant effects listed in the study reports include grinding of the teeth, whole body shaking, infected wounds, wound-weeping, gangrene, haemorrhaging, weakness, vomiting, diarrhoea, abdominal and scrotal swelling and tremors.

It is a matter of extreme concern to the RSPCA that Imutran seem unaware of, or are unprepared to acknowledge, the indicators of suffering described in the clinical observations. This is despite the fact that a fundamental text book on laboratory husbandry and care lists the same signs as indicative of suffering and a cause for concern."⁵⁵

1.68 In a letter to the writer that discusses Imutran's claims regarding how clinical signs indicate animal suffering, Dr Jennings comments:

"[I]f the clinical signs were unimportant there would be no need to record them. Clinical observations are routinely used as indicators of pain, suffering and distress in research and testing establishments designated under the Animals (Scientific Procedures) Act 1986 (ASPA) and for that matter in many situations where animals are likely to be found to be suffering. The observed clinical signs will have relevance to the scientific research being conducted, but are also used as an aid to monitoring the impact of procedures on the animals involved, and also to decide whether a veterinary surgeon should be consulted, pain relief administered, or a procedure terminated as appropriate. This is standard practice and there are many references to this within scientific peer-reviewed literature."⁵⁶

1.69 This letter was disclosed by the writer and Uncaged in the legal proceedings with Imutran/Novartis. We now discuss some of the specific procedures and their effects.

Heterotopic abdominal cardiac xenografting in cynomolgus monkeys

1.70 These procedures were licensed as Protocol 19b4 of Project Licence PPL 80/848: "Heterotopic abdominal cardiac xenografting (discordant)"⁵⁷. The 'moderate' severity limit is quoted at paragraph (ii) on page ND1.32 and the 'moderate' severity banding for the project

⁵⁵ RSPCA Report: Non-Human Primates in Xenotransplantation Research in the UK, June 2002: 34.

⁵⁶ Letter from Dr Maggy Jennings (Head of Research Animals Department, RSPCA) to Mr D Lyons, 11 December 2000.

⁵⁷ Document ND1.32-1.36

licence including these procedures is referred to at section 20 of document ND1.51. These procedures were performed by Imutran under study numbers ITN3 & ITN7, between March 1995 and January 1996.

1.71 It is our submission that this procedure was incorrectly classified as “moderate”, and should instead have been classified as “substantial” or “severe” (which would, in effect, have automatically prohibited the procedures).

1.72 At least three animals – W741m, W264f and W747m - were “found dead” during study ITN3. Paragraph 23 of the HO response explicitly states that death prior to euthanasia is an outcome that corresponds with “substantial” severity (at least) rather than “moderate”. Thus, the severity limit was undoubtedly set incorrectly in respect of these procedures. Furthermore, the failures by the researchers to implement the ‘moderate’ severity limit is a stark regulatory breach, yet no mention of this was made in the CI’s compliance review (see paragraphs 5.47-5.54 below).

1.73 The confidential study report lists “drug toxicity, arising from the immunosuppressive treatment” as an event that would require the “sacrifice”⁵⁸ of the animal.⁵⁹ However, the “Description of the procedure” section of the project licence states: “The blood levels of some [immunosuppressive] agents will be measured to ensure that therapeutic and not toxic levels are being achieved.”⁶⁰ Section 19b(vi) of the licence form requires that applicants set out a “Description of the possible adverse effects, their likely incidence and proposed methods of prevention and control”. In order to do this and therefore fulfil his/her responsibilities under the 1986 Act the project licence applicant must be aware of the effects the research is likely to have on the animals involved. The internal, confidential study report shows that Imutran were aware of the potential for drug toxicity⁶¹ and the Home Office should also have been aware of the potential for drug toxicity (see paragraphs 1.15-1.26 (“Immunosuppression”) above). Yet in this section of the licence under “Possible adverse effects” due to “b) Administration of substances”, the licence refers only to possible infection due to suppression of the animals’ immune response. There is no reference to drug toxicity.⁶²

⁵⁸ “Sacrificed” is the term most often used by the researchers to designate the killing of the primates.

⁵⁹ Study report ITN3, p.23.

⁶⁰ Document ND1.33.

⁶¹ For example, see point 3 under “Terminal Studies” at p.23 of study report ITN3.

⁶² Document ND1.35-ND1.36.

1.74 In an internal report on these experiments dated 7 August 1995, an Imutran surgeon observes that a major cause of the primate deaths is “general debility and non-specific diarrhoea.” The surgeon deduces that the monkeys lose weight and become weak “due to nausea secondary to the immunosuppressive agents”.⁶³ A published paper admits that “five animals... had to be euthanased due to gastrointestinal toxicity, resulting in severe diarrhoea” as a result of drug toxicity.⁶⁴

1.75 Compare this with the HO claim that these procedures were classified as they were because they “should not seriously impair the welfare of the animals, rather it would cause local problems...”⁶⁵

Pancreatic islet xenografting

1.76 The procedures were licensed as Protocol 19b5 of Project Licence PPL 80/848: “Pancreatic islet xenografting”⁶⁶. The ‘Moderate’ severity limit is quoted at paragraph (ii) on document ND1.37. These procedures were performed by Imutran under study numbers ITN5, between September 1995 (note that this is after the Imutran surgeons’ observations of drug toxicity referenced in the previous section) and March 1996.

1.77 During this study, primates W762f and W774f were both found dead in their cages having been observed diarrhoea and vomiting – the consequences of the side effects of the immunosuppressants. This provides a clear indication of the potentially devastating consequences of the immunosuppressive regimens used by Imutran and, once again, incontrovertibly refutes the ‘moderate’ severity limit allocated by the HO. Yet, no wrongdoing was acknowledged by the CI’s compliance review, neither has any infringement action been initiated.

1.78 As in the previous procedures, assurances were contained in the licence regarding the avoidance of drug toxicity, together with an absence of reference to drug toxicity under “possible adverse effects”.

⁶³ Document hlsapp5b.2

⁶⁴ Van den Bogaerde J and White DJG, “Xenogeneic transplantation”, *British Medical Bulletin*, 1997; 53 (no.4): 915.

⁶⁵ HO response, para 23 first bullet point.

⁶⁶ Documents ND1.37-ND1.39

Heterotopic cervical cardiac xenotransplantation

1.79 This procedure involved the implantation of a transgenic pig heart into the neck of a baboon.⁶⁷ As with all the “heterotopic” transplants, this procedure was given a “moderate” severity limit. These procedures were performed by Imutran under study numbers ITN6 and ITN11, from January to July in 1996. A total of six baboons were used in this procedure. In ITN11, three out of three animals were killed due to technical complications in the surgery, and therefore the model was abandoned.

1.80 During study ITN6, W201m suffered a stroke two days after transplant.⁶⁸ He had been observed prior to “sacrifice”: “Lying on cage floor, uncoordinated limb spasms for approximately 30 seconds, then sits up and appears alert and normal again... Very quiet, with limited use of left side.” The fate of this animal clearly was not limited to merely “local problems” with the organ that are associated by the Home Office with ‘moderate’ severity, but instead signified “significant morbidity” and “significant post-operative suffering” which characterise ‘substantial’ severity at the least.

1.81 These procedures are also discussed by the HO at paragraphs 90 and 91. The HO claims that the adverse effects of these procedures would involve either local problems with the transplant or (with the benefit of hindsight) “systemic problems with drug toxicity”. Both effects are claimed to have been “readily detectable and manageable”. However, the stroke suffered by W201m does not fall into either category of adverse effect, and clearly was not readily manageable.

1.82 The HO notion that complications from this transplant procedure would only have local effects defies the facts of biology as well the evidence of the consequences. The transplant was “fully vascularised” – i.e. connected to the blood supply - and, therefore, had the potential to cause general circulatory problems, such as the stroke suffered by W201m.

1.83 Baboon W205m survived for 21 days.⁶⁹ In this instance, a combination of drug toxicity, graft rejection, and infection complications appear to have resulted in the deterioration of the baboon over a number of days. For the last ten days of his life the transplant and the primate’s neck were observed swollen, with the animal consistently noted to be “quiet and huddled.” The

⁶⁷ Document ND9.2, ND10.1 to ND10.3.

⁶⁸ See table on document ND10.2, animal number 3 (see reference 49).

⁶⁹ See clinical signs for study ITN6.

wound was frequently “seeping yellow fluid” and the primate was also noted to be “unsteady” on several occasions. Eventually, the afternoon *after* it had been observed that the baboon was “showing obvious discomfort” and “reluctant to move”, he was “sacrificed”. The effects of this rare and macabre procedure were therefore not reliably “manageable”, contrary to the HO version of events, and the effects demonstrate that an estimate of ‘substantial’ severity was the minimum appropriate.

1.84 Once again, no wrongdoing has been acknowledged by the Home Office in their report on compliance, nor has any infringement action been initiated.

Heterotopic abdominal heart xenografting in baboons

1.85 The procedures were licensed as Protocol 19b10 of Project Licence PPL 80/848: “heterotopic abdominal heart xenografting”.⁷⁰ The ‘Moderate’ severity limit is quoted at paragraph (ii) on document ND1.55. These procedures were performed by Imutran under study numbers ITN19 and ITN25, between October 1996 and May 1997.

1.86 Once again, primates were found dead or close to death during these procedures. In ITN19, X227m was observed: “Lying on front across perch, no movement, eyes closed” before being “sacrificed”. This indicates that he was enduring “significant morbidity” and was very close to death, and therefore his trauma had exceeded a moderate severity limit. Similarly, in the same study, X214f was observed on her last day: “Collapsed on cage floor. Abdomen swollen and appears fluid filled. Salivating. Very laboured breathing. Extreme difficulty trying to walk”, before she was also “sacrificed”. X222m “Died suddenly”. In study ITN25, X218f was “found collapsed in cage with no detectable respiration or pulse.” Yet again, no wrongdoing has been acknowledged by the Home Office in their report on compliance, neither has any infringement action been initiated.

1.87 Despite extensive previous experience of drug toxicity, there is no reference to drug toxicity under the “Possible adverse effects... (b) Administration of substances” section of the project licence.⁷¹ An Imutran application to the Home Office for further licences states that the procedures involved “oral doses which are about eight times higher than in a human being”⁷², a

⁷⁰ Document ND1.55-ND1.57

⁷¹ Document ND1.56

⁷² Document ND18.7

state of affairs which does not seem consistent with “human clinical practice” and would inevitably have the potential to cause adverse effects in the form of drug toxicity.

Heterotopic renal xenografting

1.88 These procedures were licensed as Protocol 19b6 of Project Licence PPL 80/848: “heterotopic renal xenografting”.⁷³ The ‘Moderate’ severity limit is quoted at paragraph (ii) on document ND1.40. These procedures were performed by Imutran under study numbers ITN4, ITN12, ITN13, ITN16, ITN18, ITN21, ITN26, IAN001, IAN001, IAN002, IAN004, IAN005, IAN008, IAN010, IAN013, IAN017, IAN018 & IAN020 (these studies are those for which reports and clinical signs are available) between July 1995 and when this licence elapsed in April 1999. The final few procedures were performed from April 1999 under project licence number PPL 80/1366.⁷⁴ The only available study conducted under this licence is study IAN022.

1.89 These procedures were different to the other heterotopic transplants in that, although the pig kidney was not transplanted into the normal anatomical position, the ‘native’ kidneys were removed in the vast majority of surgeries, so therefore the xenotransplant was usually life-supporting. However, according to the Home Office version of events, because renal failure (due to rejection, for example) would lead to a “gradual deterioration of the general health of the animal over several days”, there would be “sufficient time for the problem to be identified by the routine blood tests and remedied or for the animal to be killed before the level of suffering merited a ‘substantial’ severity limit.”⁷⁵

1.90 Once again, animals were found dead in these procedures “*before appropriate clinical investigation and management, or euthanasia, could be applied.*”⁷⁶ During study ITN13, monkey W14f was “Found dead” on the morning of day 8. X535f was “Found dead on cage floor” on day 6 during study ITN21.

1.91 Many animals were close to death before being “sacrificed”. In IAN004, monkey Y239m was observed in a pitiful state before his “sacrifice”: “Appears to be in discomfort/ clinging to front of cage, head back, no response to external stimuli, shallow breathing/slow respiration rate, weak, salivating, enlarged abdomen, discoloured gums.” On Y210f’s final day she was

⁷³ See documents ND1.40-ND1.42.

⁷⁴ See document ND24, particularly ND24.16-ND24.20.

⁷⁵ Home Office Response, paragraph 23, second bullet point.

⁷⁶ Ibid, third bullet point.

described: “Collapsed on cage floor, appears weak and unable to get up, breathing shallow and rapid, salivating, heavy lidded eyes, body and limb tremors.”

1.92 During IAN005, Y49m was seen “Lying on cage floor, little reaction to external stimuli, later collapsed on cage floor” before he was killed. A9m, who was experimented upon as part of study IAN010, was killed after being observed “grinding teeth... eyes rolling... sitting on cage floor leaning against side, eyes rolling, heavy lidded, reluctant to move even when stimulated.” Y242f, during study IAN013 was “sacrificed” having been observed: “Lying on cage floor, little response to stimuli, dilated pupils, cold to touch, rapid respiration in lower abdomen, occasional vocalisation, vacant expression, motionless.”

1.93 In study IAN022, under the second project licence, monkey A171f was “Noted prior to sedation: Animal in state of collapse. No response to stimulation. No faeces. Sedated and euthanased.” The final observation for A475m records: “Noted prior to sedation: Sitting on cage floor, resting against perch. Eyelids closed. Little reaction to stimulation. Clear nasal discharge. Sedated and euthanased.” A474f’s last moments were described thus: “Noted prior to sedation: Subdued and huddled, sitting on floor of cage. Eyelids partially closed. Reluctant to move even when stimulated. Sedated and euthanased.”

1.94 For the first licence, which covered the majority of the experiments in this category, assurances of an absence of toxicity caused by immunosuppressive treatments⁷⁷ and lack of acknowledgement of adverse effects caused by drug toxicity⁷⁸ characterise the project licence yet again. The second licence is less inaccurate, admitting: “as a result of immunosuppression, animals may become nauseous, vomit and have diarrhoea.”⁷⁹ However, the project licence goes on to imply that action will be taken to ensure that the animal recovers: “In most cases these symptoms are transitory but should symptoms persist the animals may become dehydrated, this will be treated by antiemetics, administration of fluids and electrolyte therapy and reduction or withdrawal of the immunosuppressive agent until the animal recovers.”⁸⁰

1.95 In fact, withdrawal of immunosuppressives tended to promote rejection of the transplanted kidney and hasten the deterioration of the primates. This helps illustrate the inherent difficulties in treating primates who have been subjected to xenotransplantation procedures.

⁷⁷ Document ND1.41

⁷⁸ Document ND1.42

⁷⁹ Document ND24.19

⁸⁰ *ibid.*

1.96 At paragraphs 27-32, the HO responds to question 1(a) put by the HAC. The HO makes a number of vague, unsupported claims that sidestep the essential point regarding whether procedures that, in fact, caused primates W560f, W548f and V337f to deteriorate to the point of collapse truly fall within a 'moderate' categorisation of severity. Unsubstantiated assertions on the part of the HO regarding the frequency of checks on the animals, 'symptomatic and supportive treatments' etc are irrelevant. A collapsed condition, having been observed 'very weak and unsteady', 'unwilling to move', 'trembling', 'vomiting' etc. is clearly consistent with 'a major departure from the animal's usual state of health or wellbeing... significant morbidity' – the HO's own description of the potential effects on just one animal that would merit a 'substantial' severity limit.⁸¹ Given that some monkeys were indeed found dead some time later in the kidney xenotransplantation programme, it is genuinely difficult to accept that HO statements on this matter are made in good faith.

1.97 The HO statement at paragraph 27 of their response is indicative of the specious approach of the HO argument. It claims that the suffering endured by the animals was at the "upper limit" of 'moderate' severity, but immediately says that it does not "believe" that any of the monkeys "experienced severe, unrelieved pain or distress". However, "severe, unrelieved pain or distress" is supposed to be *two stages* above 'moderate' severity. The intervening stage, and the starting point for an assessment of whether a moderate classification was justified, is 'substantial' severity, but this has been strangely omitted from the HO's argument. Setting aside the actual facts of the case, the structure of the HO argument appears to be designed to confuse readers rather than illuminate the situation.

1.98 The effects of these procedures on the primates were clearly consistent with "substantial" severity or possibly "severe pain and distress", and that therefore a moderate severity limit was a clear underestimation. The discussion above at paragraph 1.49 suggests that the Home Office may have had a collusive relationship with Imutran and or Sandoz and may have sought to deliberately manipulate the severity categorisation for the heterotopic renal xenotransplantation experiments performed under PPL80/848. It is noteworthy that these 'moderate' (as opposed to 'substantial') experiments on captive-bred monkeys would appear to have avoided scrutiny by the Animal Procedures Committee.

1.99 Another Imutran document, 'Progress Review Meeting Minutes' dated 30 March 1999⁸², reports under the heading "Home Office update":

⁸¹ Paragraph 5.42 of Annex B of HO response.

⁸² Document CY24.2

“The new kidney Project License goes before the APC⁸³ next Thursday... The existing kidney Project License expires on the 21st April 1999. [The local Home Office Inspector] has on several occasions expressed his view that the new License will be approved before the existing license is revoked and that Thursday will be merely a ‘rubber stamping’ exercise.”

1.100 Once again, this evidence suggests a collusive relationship between the Home Office and the licensees, combined with a lack of respect for the advisory Animal Procedures Committee.⁸⁴ According to the APC report for 1999 (paragraphs 31-35), the recommendation to approve the new license was actually touch-and-go:

“In the main Committee, we were concerned about why some of the individual procedures themselves did not merit a substantial rating (though we accepted that the Home Office Inspectorate had interpreted the rules properly). After much discussion we agreed, on balance, to advise the Home Secretary that the license be granted.”⁸⁵

1.101 Given the actual severity of the procedures as revealed in the clinical signs, and the evidence of a close and apparently collusive relationship between Imutran and the Home Office Inspectors, we are deeply concerned that the ‘moderate’ rating was ascribed by the Inspectorate and reluctantly granted formal confirmation by the Committee through a biased and manipulated process, and without the Committee being in full possession of all relevant information. Consequently, if the Committee had been fully aware of the true level of severity of the experiments they may not have recommended that the research be licensed. The RSPCA report on the Imutran research hints at this, though the lead author, Dr Maggy Jennings, who was a member of the Committee at the time, was subject to confidentiality limits when she wrote this:

“Thus, the application to renew the licence should have been informed by the results of the previous studies, and therefore would have been expected to accurately reflect the adverse effects previously seen in practice.”⁸⁶ (emphasis in original)

⁸³ APC = the Animal Procedures Committee. The new license referred to is the second licence granted for renal xenotransplantation, PPL 80/1366.

⁸⁴ See below at paragraphs 4.19-4.28 for further discussion of Inspectorate-Imutran relationship.

⁸⁵ Paragraph 32 of the APC report for 1999 refers to a ‘substantial’ rating for all the procedures – this refers to the severity *banding* rather than the severity *limit* for the actual procedures. Intriguingly, the substantial severity banding is not referred to in the minutes for the relevant meeting (April 1999), and contradicts the banding indicated in the draft licence at ND24.28.

⁸⁶ RSPCA Report: Non-Human Primates in Xenotransplantation Research in the UK, June 2002: 36.

1.102 Finally, the HO explanation for the specific examples of suffering presented in the original Uncaged memorandum merits comment. At paragraph 29 of the HO response, it is claimed that the surgical complication that caused an alarming deterioration in the condition of two primates was 'not foreseen'. If a source of suffering is not foreseen then breaches of the 'moderate' severity limit may be permitted. However, it seems implausible that "damage to the transplanted ureter" should be unexpected given that the description of the surgical procedure in the study report describes a series of incisions and sutures applied to the ureter in order to attach it to the monkey's bladder, and speaks of the consequent risk of narrowing ('stenosis') at this point, which could lead to an obstruction of the ureter – the cause of death for the two monkeys in this instance.⁸⁷ Furthermore, this complication with the ureter has been widely reported in humans following kidney transplantation, especially in a paediatric context which, it is claimed by both Imutran and the HO, raises a similar difficulty in this particular aspect of the procedure because of the small size of the recipients.⁸⁸ Ureteric obstruction was, therefore, another foreseeable source of animal suffering, contrary to the HO assertion.

2. Benefits of the research

2.1 The Department of Health's xenotransplantation advisory committee, the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA), having considered the Diaries of Despair documents together with the obvious lack of progress, stated that the likelihood of clinically-viable pig organ transplants was 'receding'⁸⁹ – which was, as the New Scientist put it, a polite way of saying that the technology was 'dead in the water'.⁹⁰ A transplant surgeon and member of the UKXIRA described Imutran's research as a 'blind alley'.⁹¹

⁸⁷ ITN4, p20.

⁸⁸ Jones et al, Transplantation Proceedings (1993); 25: 1038.

⁸⁹ UKXIRA Third Annual Report, September 1999 - November 2000. Department of Health, published February 2001, paras 6.8-6.15.

⁹⁰ New Scientist, "Waiting for a miracle - time is running out for organ transplants from animals", 12.1.02, p.3.

⁹¹ Transcript of UKXIRA Open Meeting, Wed 7 Feb 01.

2.2 The RSPCA's own report on the Imutran documentation, published while the injunction was still in force, concluded: " ... we do not consider that a significant and justifiable benefit was being achieved."⁹²

2.3 At paragraphs 38-9, the HO response lists seven "predicted benefits" for the Imutran research, claiming that the first six were achieved, with only the final scientific objective set out on the Imutran applications remaining elusive:

"Specifically, the studies performed did not identify an immunosuppressive strategy to control delayed xenograft rejection that was sufficiently safe and effective to be adapted and considered for use in human clinical practice."

2.4 In fact, the first three achieved objectives listed by the HO in its recent response:

- "Proof of concept was demonstrated"
- "Genetic modification of 'donor' animals"
- "Prevention of hyperacute rejection"

are all aspects of **one** potential 'benefit' achieved by Imutran – preventing hyperacute rejection. The HO list of benefits derived from Imutran's work is a distorted representation of the aims and achievements of the research programme. It tries to expand the single preliminary objective attained by Imutran and present the subsequent failures to overcome delayed xenograft rejection – listed as the fourth and fifth bullet points at paragraph 38 - as 'benefits'.

2.5 In addition to the fundamental failure of Imutran's research to achieve its scientific objectives, further evidence exists which suggests that whatever data was gained may be of limited validity in any case. This would further decrease the potential benefits of Imutran's studies. An Imutran internal email between leading executives, dated 17 September 1999 (towards the end of the research programme) contains this passage:

"I have read your meeting minutes from the "Task Force" meeting of 27th August and over the past couple of weeks put a lot of thought into how Imutran management (and you and I in particular!) addresses the severe problems posed by the current state of the primate research data."⁹³ (emphasis added)

2.6 The sixth objective listed in the HO response, regarding the assessment of the risk of transferring viruses from pigs to humans, is merely an incidental aim of the research and its practical relevance was entirely dependent upon the achievement of the ultimate objective – viable pig-to-human organ transplants. Furthermore, because of immunological differences

⁹² RSPCA Report: Non-Human Primates in Xenotransplantation Research in the UK, June 2002: 39.

⁹³ Document hlsapp8b

between baboons, cynomolgus monkeys and humans, affecting their relative susceptibilities to particular pig viruses, the relevance of any findings in the primate experiments to the human situation was questionable.

2.7 In contrast to the HO response, the actual project licence is *the* reliable record of the considered aims and potential benefits that set out the terms on which the Imutran research was permitted. At the very beginning of the experimental programme in 1994, the project licence lists three scientific objectives to be achieved in order to attain the primary potential benefit of the research: “The ultimate object of our work is to be able to transplant animal organs into humans successfully.” Those three objectives are listed at paragraph B at document ND1.7, and consisted of:

1. Prevent hyperacute rejection and elucidate subsequent rejection mechanisms
2. Achieve long-term xenograft survival through an effective immunosuppressive protocol
3. Assess the ability of the organ to function sufficiently to maintain life of recipient

2.8 These three also happen to correspond to the objectives listed by the CI in his review of Imutran’s compliance.⁹⁴ However, in this latest response, the HO has stretched out objective one to encompass five out of the seven different objectives on their own list, while the third licensed objective is not even listed in the HO response. We therefore believe that the HO’s presentation to the HAC of its assessment of the benefits of Imutran’s research is seriously misleading.

2.9 In fact, the only objective that it could be argued was achieved by Imutran was the first half of objective one on the project licence – preventing hyperacute rejection. Furthermore, Imutran already had strong evidence for this following experiments where transgenic pig tissues had been perfused with human blood. This was ‘confirmed’ very early on in the primate research programme.⁹⁵ Thus, in an update to the project licence dated February 1995, the licence states:

“Experiments undertaken as outlined in the plan of work as submitted on 16th February 1994 and as modified on 5th October 1994 have demonstrated that the possession of a transgene for human decay accelerating factor does protect a discordant pig heart xenograft from hyperacute rejection by a primate. These data therefore, provide the answer to the question addressed in B(i) section 17.”⁹⁶

⁹⁴ Paragraph 3.1.

⁹⁵ Once again, because of evidence of significant immunological differences between the various species of primates under study – baboon, cynomolgus monkey and human - there are question marks over the relevance of the primate experiments to the human situation.

⁹⁶ Document ND1.11.

2.10 B(i) refers to bullet point one above and, as we have just noted, Imutran only answered the first half of this question. The vast majority of the primate suffering caused was in a failed attempt to achieve the remaining two and a half objectives. According to paragraphs 41-42 of the HO response, Imutran were permitted to continue primate experiments for over four years before any apparent attempt was made by the HO to intervene meaningfully in the research programme.⁹⁷

2.11 The HO's responsibilities in its assessment of benefits is encapsulated by this statement from a former HO minister:

"In deciding whether to grant a licence for any regulated procedure, the 1986 Act requires that the likely benefits of the programme be weighed against the likely adverse effects on the animals concerned (the cost/benefit assessment)... We must also be satisfied that the procedures are likely to achieve the stated objectives."⁹⁸

2.12 In his Note on the Cost/benefit Assessment (Published in the APC Report for 1997, pp50-59)⁹⁹, the CI states that the assessment of benefits should be an ongoing process rather than a one-off event at the initial licence application stage:

"The cost/benefit assessment is a process rather than an event. Licensed work is scrutinised to determine that the benefits are being realised in practice and that the costs cannot be further reduced." (para 6.2)

2.13 The project licence authorities and HO statements indicate that the main and ultimate objective of the Imutran research was to develop pig organs for human transplantation. This is further demonstrated by section 14 of the project licence, where "control of disease, ill-health, abnormality" is listed as the primary purpose for which the project was authorised. By the HO's own admission, this was not achieved. They were startlingly incorrect in their satisfaction – over at least five years - that the procedures were likely to achieve the stated objectives.

2.14 The tactic of the HO since concerns have been raised about its licensing conduct has been to claim that the mere generation of data related to some of the possible biological problems with xenotransplantation was the basis upon which this intensely damaging and lethal research was licensed. If this were the case then, for a start, "advancement of biological or behavioural science" would have been listed as the primary purpose for the project licence. The HO claim is (a) untrue, (b) if it were true it would not represent a defensible operation of the cost-

⁹⁷ But see paragraphs 2.32-2.42 for evidence casting doubt on this HO claim.

⁹⁸ Hansard, Written Answers for 28 June 2000, Mike O'Brien, 125262 "Xenotransplantation".

⁹⁹ Also produced by the HO in their response at Annex D

benefit assessment – it is not how the HO publicly justified the licensing of the experiments while they were taking place.¹⁰⁰

2.15 Further discussion of matters relating to the assessment of benefits can be found below at paragraphs 5.8-5.46, which reply to paragraphs 74-89 (“Distorted cost benefit assessment”) of the HO response.

Assessing the likelihood of success

2.16 The specific question (2) put to the HO by the HAC asked:

“At what point did it become clear that the experiments were unlikely to produce successful results?”

2.17 The HO appears to claim that, with regard to the primary licensed objective of achieving the criteria for clinical trials, this occurred in mid 1999. We will analyse this claim below at paragraphs 2.32-2.42.

2.18 We submit that thorough and objective scrutiny at the very outset of the programme would have more accurately predicted the immense difficulties posed by pig-to-primate organ transplantation. For example, concerns about the scale of the immunological obstacles alone had been raised prior to Imutran’s research (see paragraphs 1.15-1.16), but they were not reflected in the licensing of the research (1.18-1.19), which appears to have mirrored Imutran’s over-optimistic view of the viability of xenotransplantation.

2.19 Similarly, there does not appear to have been any serious thought given to the question of the physiological compatibility of pig organs, despite the fact that, as one leading researcher put it: “clearly this question is of greatest clinical importance.”¹⁰¹ While some scientists will doubtless claim that in order to find out whether a pig organ will function in a primate one has to perform the experiment, it is possible to look at theoretical considerations and other data in order to try to carry out an optimum cost-benefit assessment before the event, as required by the law. It is simply not acceptable or legitimate for the Home Office to allow *animal* researchers to

¹⁰⁰ This responds to the implicit answer given by the HO to question 2(a) posed by the HAC: “What results did the Home Office expect, and within what timeframe to justify the suffering to animals involved?”

¹⁰¹ Platt, J (1998). New Directions for organ transplantation. *Nature* 392 (supp): 11-17.

explore any hypotheses no matter how flawed and no matter how much suffering is caused.¹⁰² Any fair and honest cost-benefit assessment, including the one demanded by the regulatory framework for animal experimentation, contains a requirement to assess the likelihood of success (see above at paragraph 2.11). The bald fact that the Imutran research did not realise its core objectives vindicates the relevance of the considerations related below, and reinforces the need for some kind of independent review.

2.20 One fundamental theoretical consideration regarding the compatibility of pig organs in the human body is the enormous evolutionary distance – 180 million years - between pigs and humans (see paragraph 1.29 above). Also, pre-existing empirical data revealed systemic species disparities concerned with blood circulation and coagulation.¹⁰³

2.21 Kidneys perform crucial complex metabolic and hormonal activities, and there are numerous species differences in the specialist functions of this organ.¹⁰⁴ While the heart is commonly viewed as a pump for the circulation, in fact it is constantly responsive to small changes in the demands of the body via several feedback control systems. It also responds to hormonal control and to pressure, flow and resistance factors. Direct anatomical comparison of pig and human cardiac structure has highlighted several potential significant differences.¹⁰⁵ Additionally, there appear to be a number of incompatibilities related to the nerve supply necessary for a pig heart to function in the human body.¹⁰⁶

2.22 Furthermore, the danger of transferring novel viruses into the human population via animal transplants has dogged the question of whether the procedure would be beneficial. Viruses from animals pose one of the greatest risks to public health, with HIV/AIDS providing a salutary precedent. Some research has confirmed this theoretical possibility.

¹⁰² It is, of course, perfectly legitimate for scientists to conduct whatever research they like so long as that research does not cause harm to others. The ethical and legal requirement for the cost-benefit assessment arises because of the harmful effects on others of such action.

¹⁰³ Hammer, C (1991). In: Xenotransplantation – The Transplantation of Organs and Tissues Between Species. Eds. Cooper, Kemp, Reetsma & White, publ. Springer-Verlag, pp429-438.

¹⁰⁴ See, for example, Poulsen. K et al (1976). 'On the specificity of human renin. Studies with peptide inhibitors'. Biochim. Biophys. Acta 452: 533-537. (Cited by Langley, G and D'Silva J, Animal Organs in Humans (1998): 36.)

¹⁰⁵ Crick S.Y. et al., (1998). 'Anatomy of the pig heart: Comparisons with normal human cardiac structure'. Journal of Anatomy; 193 (1): 105-119. Although this study was carried out after the commencement of Imutran's research, it was a relatively simple task that could have been undertaken beforehand.

¹⁰⁶ Bharati, S. et al., (1991). 'The conduction system of the swine heart', Chest; 100(1): 207-12.

2.23 To ascertain the potential benefits of xenotransplantation in the context of a cost-benefit assessment, the focus has to be on 'marginal' benefits – in other words benefits from pig organs that could not be obtained from anywhere else. In that respect, the prospects for other therapies for patients with heart failure, for example, are a relevant factor. As early as 1982, a patient was kept alive for 112 days with a total artificial heart,¹⁰⁷ far longer than any life-supporting pig heart transplant has achieved. The UKXIRA's review of the physiological aspects of xenotransplantation comments on the prospects for such devices:

“In summary, it may be concluded that the recent and rapid advances in the technology of mechanical cardiac assist devices provide suitable bridge to transplant support for many patients, particularly those who deteriorate waiting for a human donor. This therapy may also provide a viable and safe alternative to cardiac xenotransplantation and even allotransplantation for many patients suffering from end-stage cardiac disease and must be carefully considered when weighing up the pros and cons of initiating clinical trials in cardiac xenotransplantation.”¹⁰⁸

2.24 Thus, the question arises as to what extent the Inspectorate were content to rely on Imutran's inaccurate interpretations and reports before and then during the research programme, some of which were, in fact, explicitly criticised for their lack of informativeness. In one letter, the Home Office complain to Imutran:¹⁰⁹

“The Committee shared our concerns about the direction of this work and unanimously felt that your report did not address the specific questions raised in my letter in particular, it did not: describe the experimental design for the comparative immunology study for which the use of these animals is authorised...”

2.25 The CI concedes in his compliance review:

“There were times when the material disclosed to the Home Office by Imutran was incomplete”¹¹⁰

2.26 In the absence of thorough scrutiny, Imutran's misplaced optimism and confidence was allowed to determine what is supposed to be an independent assessment of their research.

¹⁰⁷ Nuffield Council on Bioethics, 'Animal-to-Human Transplants: the ethics of xenotransplantation' (1996), paragraph 2.17.

¹⁰⁸ Dept of Health (2002), "The Physiology of Xenotransplantation": 43.

¹⁰⁹ See Document ND15.1.

¹¹⁰ Paragraph 5.19.1

2.27 If, for the sake of argument, the pre-existing factors undermining the plausibility of pig organ transplants are set aside, we can consider what happened as the research went ahead. As the research continued, there were a number of indications of difficulties in understanding and overcoming the rejection of pig organs.

2.28 During enquiries into Imutran's "unauthorised" change in their pattern of baboon experiments in late 1996-early 1997, the Animal Procedures Committee stated:

"Members expressed concern about the continuing high loss rates in the immunosuppressive programme."

2.29 In the predominant research programme, involving pig-to-monkey kidney transplantation, the average survival times (in days) for the reported studies (not including the control studies involving non-transgenic kidneys where lengthy survival was not expected) that took place between mid-1995 through to early 1999, even excluding those primates killed by surgical complications, were: 15.4 (ITN4), 6.75 (ITN12), 6.75 (ITN13), 12.4 (ITN16), 7.7 (ITN21), 27.6 (ITN26), 23.8 (IAN001), 5.25 (IAN004), 16.6 (IAN009), 33.4 (IAN013), 34.6 (IAN010), 7 (IAN008), 13.5 (IAN017), 16.8 (IAN018), 7 (IAN020), 20.4 (IAN022). The minimum criteria for commencement of clinical trials was approximately 90 days median survival, with some animals surviving over a year. Imutran achieved a maximum of 78 days. Furthermore, concerns have been expressed that such fluctuating survival figures that were achieved were done so using techniques and drug protocols that would not, in any case, be acceptable in clinical practice. In other words, quality of survival is as significant as quantity (1.23-1.25).

2.30 At the 4th International Xenotransplantation Conference, held in Nantes in Autumn 1997, there was a clear realisation of the lack of knowledge regarding subsequent rejection mechanisms. The same report in *Nature* quoted one analyst:

"The immune system is unbelievably complicated and poorly understood, making xenotransplantation one of the most speculative of all areas of biotechnology."¹¹¹

2.31 Whatever one's view on the question of when it became clear that the research would be unsuccessful, the key concern we have regarding the Home Office is that they did not scrutinise Imutran's application with sufficient rigour or conviction to address the question adequately and fulfil their duties under the 1986 Act.

¹¹¹ *Nature*, 22 January 1998, Volume 391, No 6665.

Cessation of Imutran UK primate xenotransplantation research

2.32 The claims regarding a belated HO intervention in the middle of 1999¹¹² are highly dubious, especially given the efforts made by the HO to facilitate the approval of a new five year project licence to permit a continuation of kidney xenograft experiments in April 1999. The HO cites a high technical failure rate as a cause for concern, and there is evidence that a kidney xenotransplantation study in mid 1999 had a technical failure rate of 50%. The high technical failure rate is indeed disturbing, but this does not appear to have troubled the HO earlier during the research programme. One of the very first major studies¹¹³ conducted by Imutran in 1995-6 resulted in an even higher rate of technical failure. The technical failure rate went up and down throughout the Imutran research, hitting 100% in one early study,¹¹⁴ despite prior claims from Imutran that the surgical procedure would not be problematic.¹¹⁵

2.33 Most extraordinary is the stark inconsistency between the HO description of the latter stages of Imutran's research in the recent response, and the version published by the HO in the CI's compliance review. (The HO version also contradicts Imutran's statement to the High Court on this matter.) In that compliance review, published in July 2001 while Imutran and Novartis were attempting to gain a permanent injunction preventing Mr Lyons and Uncaged disseminating the leaked documents, the CI claimed:

“Nevertheless in 1999, as the result of one study with an unexpectedly high technical failure rate, Imutran's operative surgery programme was halted whilst protocols and practice were reviewed and revised to ensure that the likelihood of problems had been minimised. *This moratorium was voluntarily proposed and implemented by Imutran management* to address its own, and the Home Office's concerns. Work did not restart until Imutran and the Home Office were of the view that all reasonable steps had been taken to ensure that the likelihood of technical failures had been minimised.”¹¹⁶
(emphasis added)

¹¹² Paragraph 41-42 & 65 of HO response.

¹¹³ ITN3 – technical failure rate 33/61.

¹¹⁴ ITN11 – three out of three wild-caught baboons were killed during or immediately after failed neck-heart transplant surgery.

¹¹⁵ See document ND6.8-6.9. Yet another example of a failure of the HO to scrutinise adequately the claims made by Imutran regarding the likely outcome of the procedures.

¹¹⁶ Paragraph 5.12.3.

2.34 This gives the impression that Imutran were acting in accordance with their responsibilities as licence holders and voluntarily implemented a moratorium to deal with technical difficulties in their research. There is no mention of a fundamental lack of progress in the research in terms of developing an effective immunosuppressive regime. From Imutran's perspective, these two factors were relevant to the question of whether there was a public interest in disclosure of the Imutran documents and provided a helpful impression for them to put before the High Court.

2.35 However, with the proceedings over and the HO now apparently determined to exonerate itself, a completely different version of events has been provided by the HO in their recent response:

“By the middle of 1999 inspection findings, and supplementary enquiries made with respect to progress reports supplied by Imutran, indicated that Imutran was not making substantive progress... and the incidence of surgical failure was rising...

The Inspectorate advised Home Office licensing staff that the technical failure rate was a cause for concern, and that, from the findings to date, there appeared to be insufficient weight of evidence that Imutran's preferred strategy would ultimately yield success. *This was not resolved by negotiation with the project licence holder, and the Home Office implemented a moratorium on Imutran's main programme of work. Some work was allowed to continue in pursuit of other secondary objectives.*¹¹⁷ (emphasis added)

2.36 This description of the same sequence of events paints the HO as the brave defender of the regulatory system, standing up to Imutran and imposing a moratorium on Imutran's experiments, not simply due to technical failures but also due to a fundamental lack of progress.

2.37 The HO claims that experiments “were allowed to continue in pursuit of other secondary objectives” is noticeably vague and raises concerns about what those “secondary” objectives were and whether they were properly accounted for in the cost-benefit assessment. Imutran documents reveal that primate research continued into February 2000 at least, and there is no indication of any significant change in the direction of the research. Indeed, the problem of technical failures does not appear to have been adequately addressed, despite the problems in mid-1999. An email circulated by a Novartis executive on 3 February 2000 states:

¹¹⁷ Paragraphs 41-42.

“In view of the recent experimental failures and as discussed with [name redacted], I would like you to interrupt any further experiments until better understanding of the reason for these failures has been determined.”¹¹⁸

2.38 Later the same day, an Imutran manager sent a response in which she confirms the decision to halt the research, adding further reasons for the suspension:

“I have interrupted the programme at HLS until there is:

- a process for retrospective reporting of past studies in place based on checked secure data
- the management control measures in place for *future primate studies* to allow the programme to be performed in an appropriately controlled fashion.”¹¹⁹ (emphasis added)

2.39 To say the least, there appears to be a great deal more to the circumstances surrounding the eventual cessation of Imutran’s research than indicated by the HO response. The only other information in the public domain regarding Imutran’s closure appears in the minutes for the October 1999 meeting of the APC:

“7.4 Dr Jennings [Maggy, of the RSPCA] told the Committee about a claim to UKXIRA by a company engaged in primate work that it had taken this from the UK to Canada because the Inspectorate would not allow animals used in an invasive procedure to undergo a subsequent biopsy. The CI said that the company concerned had not been refused authority for biopsy work on those grounds.”

2.40 In fact, three animals had had to be killed following biopsies of the transplanted kidney due to complications rising from what is a technically difficult procedure in primates. With the APC having required that Imutran produce regular progress reports on their experiments under the new project licence, the HO would have come under greater pressure to make interventions. Imutran, on the other hand, were very keen to perform biopsies in order to gain ‘live’ information about the rejection and performance of xenotransplanted organs.

2.41 It is possible that a dispute with the HO over biopsies was a factor behind the decision of Imutran/Novartis to move their experiments to North America. On the other hand, to the best of the writer’s knowledge and contrary to the HO story, there is no reference to any dispute

¹¹⁸ Quoted at p.128 of Diaries of Despair report. The quote is from document hlsapp8e, the original of which has not been published. The Home Office has a copy of this document, as do Uncaged’s solicitors Bindman and Partners.

¹¹⁹ Ibid. These suggest further problems with the quality of the data as discussed above at paragraph 2.15.

between the HO and Imutran over technical failure rates or “insufficient weight of evidence that Imutran’s preferred strategy would ultimately yield success”¹²⁰ in any leaked document, Ministerial statement (including Written Answers to questions directly pertaining to the contemporary state of xenotransplantation research)¹²¹, Home Office publication or, even, any of Imutran’s pleadings to the High Court. Perhaps most significantly, the CI’s compliance review states that the two project licences for xenotransplantation procedures continued up until the 2nd quarter of 2000 at which point Imutran “*voluntarily surrendered*” them for revocation¹²² (although even this is inconsistent with Imutran’s pleadings which state that one of the licences was still in force as late as 21 September 2000, the date that Uncaged first attempted to publish the Diaries of Despair report and Imutran documentation).

2.42 In short, what little information there is available regarding the cessation of Imutran’s primate xenotransplantation research is incomplete and conflicting, with the HO giving a different version at different points. In the circumstances, the latest impression painted by the Home Office - a belated realisation on their part that Imutran were not going to achieve the main objective of their work - seems at best a half-truth. It would certainly be helpful for understanding the enforcement of the 1986 Act if the true circumstances were to be uncovered.

3. Severe suffering

3.1 Paragraph 44 of the HO response states that experiments causing “severe pain, distress or suffering that cannot or will not be alleviated” may not be licensed. (The subsequent examples supplied by the HO refer to *wilful* withholding of treatment or proper analgesia to control the ‘severe pain’, rather than protocols involving severe pain that would substantially frustrate attempts at control and alleviation.)

3.2 It is our contention that it is at least plausible to conclude that the intrinsic difficulties involved with pig-to-primate organ transplant procedures and the severity of the various adverse effects, which could and did combine to intensify animal suffering and make treatment more difficult, resulted in ‘severe’ suffering, whether one employs a common-sense view or a legal definition. In fact, legal definitions of ‘severe suffering’ have been virtually non-existent, though in its response the HO states:

¹²⁰ Paragraph 42 of HO response

¹²¹ E.g. Mike O’Brien, 28 June 2000.

¹²² Paragraph 3.3

“An example in the present case would be if Imutran had intended to produce severe renal failure and to withhold treatment with the intention of determining when animals would die as a result.”

3.3 The evidence indicates that the Imutran procedures produced similar levels of suffering. The determination of ‘severe’ suffering is based on the impact on the animals, irrespective of any ‘intentions’ of the researchers to withhold treatment etc.. It was virtually inevitable that, for example, the kidney transplant experiments would lead to renal failure and/or serious drug toxicity and/or serious complications with infections. The treatments administered clearly had, on numerous occasions, a very limited effect in terms of controlling the suffering and distress of the primates.¹²³ Some animals were ‘found dead’ rather than being euthanased, however belatedly. Intentionally or not, Imutran’s procedures produced severe and deadly adverse effects in primates.

3.4 Paragraphs 53 and 57 of the HO response suggest that the prevention of severe suffering relies on ensuring that the procedures are analogous to human clinical practice. The discussion above at paragraphs 1.15-1.37 describes four fundamental disanalogies between the primate xenotransplantation experiments and human clinical practice, rendering unsound the HO’s rebuttal of the charge that animals experienced severe suffering:

1. Immunosuppressive regimens and therapies used by Imutran would not be acceptable in human management.
2. Xenotransplantation of solid organs is a highly speculative and novel procedure with no clinical precedent.
3. Huge differences in the ability to manage primates in a research laboratory compared to a human in a hospital.
4. Heterotopic transplantation is extremely rare in humans, and the procedure in animals is very different to the human situation.

3.5 The CI himself has stated that, as a rule of thumb, a reasonable way to judge the level of suffering experienced by animals is to put oneself in their shoes.¹²⁴ To that end, a consideration of the clinical observations for the Imutran primates would enable the reader to assess whether, if they were experiencing those symptoms, whether they would personally regard that as ‘severe’ suffering?

¹²³ See paragraphs 1.62, 1.80, 1.83, 1.86, 1.90-1.93, 4.12 of this paper.

¹²⁴ J Richmond, “Cost-benefit assessment: the United Kingdom experience” (2000). Developments in Animal & Veterinary Sciences, vol. 31A p821-827.

4. Format of Government Response

Cost-benefit assessment

4.1 Paragraph 62 of the HO response states that the reason that an inquiry into the adequacy of the cost benefit assessment was not held was that “HO records indicate that the cost-benefit assessments of these applications were properly and thoroughly carried out.” It should be noted that the form and scope of the examination of the issues raised by Diaries of Despair was determined by the HO within two months of the submission of the Diaries of Despair report and documents in late September 2000. Therefore, for the HO assertion to have a hope of being true, the HO must have satisfactorily reviewed all of the necessary records relevant to the operation of the cost-benefit prior to 29 November 2000 at the latest.

4.2 The HO is claiming that it would be necessary to examine all of the original study documentation including all the surgeon’s records, all of the clinical observations and all the records of supportive and symptomatic treatment administered to the animals in order to ascertain precisely the levels of suffering experienced by the animals, and therefore make a judgment on the adequacy of the cost-benefit assessment. However, the HO did not examine these before deciding the format of the Imutran review. The HO could not have made an informed decision on the adequacy of the cost-benefit assessment prior to any review or investigation specifically designed to address that question. No such review or investigation has ever been undertaken by the HO, never mind in October and November 2000. The decision to order an internal review of Imutran’s compliance was an entirely defensive and tactical one, rather than being an open and balanced response to the concerns raised in Diaries of Despair.

4.3 In fact, a letter from Home Office Minister Mike O’Brien to Mr Lyons, dated 29 September 2000 – just a week after the HO receipt of the documentation – strongly indicates that a narrow scope for the HO inquiry was already the preferred option:

“Your recommendation (e)¹²⁵ encompasses a number of allegations relevant to the Home Office and calls for a judicial inquiry. On the face of it however, none of them would appear to merit investigation by means of such an inquiry. They all relate to

¹²⁵ “Most importantly, an independent judicial inquiry should be instituted to investigate possible breaches of UK and European law that may have taken place during the course of this research; and the conduct of the Home Office itself.”

administrative or regulatory issues and my immediate thoughts are that it would be entirely proper for the Home Office to investigate them subject to certain conditions.”

4.4 At a meeting on 2 November between My Lyons and Mr O’Brien (plus HO officials) to discuss the Government’s response to ‘Diaries of Despair’, Mr O’Brien stated that he had not even read the ‘Diaries of Despair’ report and he was not in a position to discuss the facts of the case.

4.5 The HO goes on to state that the Animal Procedures Committee (APC) considered the applications. In fact, the APC only considered a small fraction of the Imutran procedures, and the information upon which those deliberations were based came from Imutran and the Inspectorate. On 20 March 2001, the Chairman of the APC wrote to HO minister Mike O’Brien for the second time to try to extract a justification for the decision to initiate a ‘routine review’ in the Imutran case.¹²⁶ The Chairman said:

“Some members asked why the CI’s review is not to include a retrospective assessment of the cost/benefit assessment. A degree of concern was expressed about this, not least because the Committee itself played a part in that assessment. It would therefore be helpful if you could comment on this as well please.”

4.6 Mr O’Brien responded on 10 April 2001:

“There is very little that I can add to my letter of 12 February... As to the issue of the cost benefit assessment, a review based on fresh information not available when the original assessments were carried out would have no relevance to the decisions reached at the time.”

4.7 This is, as the RSPCA commented, an astonishing statement.¹²⁷ The Society noted that the Government itself has recently introduced Ethical Review Panels at establishments that conduct animal research, and one of the requirements of the panels is that they should conduct exactly such retrospective reviews in order to constantly assess and improve their own cost-benefit analyses. Every organisation in the modern world that strives for competence has systems for reviewing their work.

4.8 The Minister’s statement is unsound for other reasons. It gives the impression that cost-benefit assessments were one-off decisions made at the stage of the initial project licence application, when in fact HO statements explicitly describe cost-benefit assessments as

¹²⁶ See minutes for APC February 2001 meeting, section 6.

¹²⁷ RSPCA Report: Non-Human Primates in Xenotransplantation Research in the UK, June 2002: 55.

processes throughout the life of the project licence. The Imutran documents were not ‘fresh information not available’ during the research, they were contemporaneous documents produced as the research programme progressed. If the HO were not aware, for example, that primates were being found dead under ‘moderate’ protocols then they certainly should have been.

4.9 Finally on this statement, it should be noted that the Minister did not take the opportunity to answer the APC, as they have answered the HAC on an identical question, that HO records indicated a satisfactory cost-benefit assessment. If the HO had really determined this prior to 29 November 2000, then one would imagine that the APC would have been informed at this point, five months after the format of the HO response had been determined. In any case, the Minister’s statement indicates that no such cost-benefit assessment had taken place and that the HO felt it was inappropriate, directly contradicting the recent claim by the HO to the HAC at paragraph 62.

Substantial severity¹²⁸

4.10 Only 16 out of some 460 xenotransplantation procedures were allocated a substantial severity limit. The discussion above demonstrates that the ‘moderate’ classification for the vast majority of the xenograft procedures was an underestimation of the severity of those procedures.

4.11 The small proportion of procedures allocated a substantial severity limit specifically involved *orthotopic* heart xenotransplantation, which necessarily involves profoundly invasive surgery: splitting the breastbone, or ‘sternum’, and opening up the chest cavity. The intrinsic severity of the surgical procedure, regarded as even more traumatic than the major abdominal surgery involved in most of the heterotopic procedures, was the reason that the HO had no option but to set the substantial severity limit.

4.12 The HO has stated that the key to the assessment of severity is in the detailed information in the project licence. In a similar manner to the heterotopic procedures, the licence for the orthotopic procedures fails to acknowledge the potential for drug toxicity.¹²⁹ For W213m, the doses of the immunosuppressant cyclophosphamide led to “serious side effects”¹³⁰: bone marrow damage leading to pancytopenia, a catastrophic depletion of blood platelets and red and

¹²⁸ Paragraph 63 of HO response.

¹²⁹ See document ND1.62-1.63

¹³⁰ M Schmoekel et al, “Orthotopic heart transplantation in a transgenic pig-to-primate model”, *Transplantation*, 65, 1570-1577, No.12, June 27, 1998.

white blood cells. As well as causing increased susceptibility to infection, it also leads to anaemia and bleeding. On day 7, W213m was huddled, shivering and passing blood-stained diarrhoea. He collapsed the following day, with persistent diarrhoea. He had vomited and was bruised around the injection sites. By the morning of day 9 he was still diarrhoeic, and was unsteady with body tremors. The bruising had spread around his body. He was finally sacrificed later that afternoon.

4.13 The HO states at paragraph 59 that orthotopic transplants were classified as ‘substantial’ because of the potential for sudden deterioration and death of the animal before effective clinical management could be provided. Once again, this appears to be a retrospective justification at odds with the available contemporary evidence. In the description of possible adverse effects, there is no suggestion that primates might die prior to euthanasia in the project licence.¹³¹ Furthermore, in a report submitted to the Home Office, it states for the fifth animal that: “The animal became breathless and within a very short time was humanely sacrificed.”¹³² However, the confidential study report contradicts this, revealing that baboon W211m was in fact “found dead”. It is uncertain whether this misleading report was considered by the APC in its assessment of Imutran’s applications.

4.14 If it is acknowledged that procedures have the potential to cause severe suffering then they cannot legally be licensed. However, the HO attempt to justify its severity assessments does not make it clear (to this writer, at any rate) how ‘substantial’ severity and ‘severe’ suffering differ. This ongoing ambiguity between ‘substantial’ and ‘severe’ has been observed by other commentators. The RSPCA state in their report with regard to the ban on severe pain: “It is not clear, however, how this relates to the fact that procedures classified as ‘substantial’... are allowed.”¹³³

4.15 The HO response itself states:

”[A] substantial severity limit would have been appropriate if Imutran had intended to study the effects of uncontrolled advanced renal failure ... where... treatment [was] to be withheld...”¹³⁴

4.16 Whereas its perception of severe suffering would be:

¹³¹ Document ND1.62-1.63

¹³² Document ND7.3-7.4 .

¹³³ p.20.

¹³⁴ Paragraph 49.

“...if Imutran had intended to produce severe renal failure and to withhold treatment with the intention of determining when animals would die as a result.”¹³⁵

4.17 Paragraph 3.4 above discusses how similarity to human clinical practice is said by the HO to be a condition for avoiding ‘severe’ suffering, yet the HO also states that substantial severity would be appropriate if “any animal experienced pain or distress of a nature not encountered, or denied treatment, in clinical practice.”

4.18 In summary, the HO reference to the grading of some procedures as ‘substantial’ does not indicate an accurate assessment of severity and therefore ‘costs’ for the following reasons:

- Only a tiny proportion of the procedures were classed as substantial rather than moderate.
- Most of the moderate procedures were in fact of substantial severity, at least.
- Examination of the project licences reveals a failure to account for all sources of suffering, even where the potential for ‘substantial’ severity (at the least) is admitted.
- The emphasis on the potential for animals to die prior to euthanasia appears to be retrospective rather than properly acknowledged during the licensing process.
- It is not clear that there is a meaningful difference between ‘substantial severity’ and ‘severe suffering’.

“Rubber-stamping” of animal research application

4.19 At paragraph 64, the HO comments on the repeated ‘rubber-stamping’ assurances given by Imutran’s local HO inspector, discussed above at paragraphs 1.98-1.100. The HO claims “the APC is an independent, advisory body...and neither the Inspectorate nor other Home Office officials are in a position to speculate as to the advice the APC might or might not decide to present to Ministers on such an issue. It follows that they could not, and would not, seek to guarantee the outcome of its discussions.”

4.20 It is a matter of some concern that it has taken over three years for the HO to even begin to address the issue of the Inspectorate’s seemingly indulgent relationship with Imutran as revealed by this documentation. One would have anticipated, if the HO were concerned to ensure a fair and unbiased implementation of the 1986 Act, that the conduct of the Inspector in question would have been investigated as a matter of some urgency when the evidence was first submitted. Instead, the HO offers unsubstantiated and implausible comments that strongly

¹³⁵ Paragraph 44.

indicate an automatically defensive response to strong prima facie evidence of bias and misconduct.

4.21 In actuality, the APC, which is composed of volunteers most of whom have connections with the animal experimentation industry, is heavily dependent on information and advice from HO officials in its consideration of licence applications. As already stated, Inspectors, who have experience of liaising with the APC, work with licence applicants in the drawing up of project licenses. Inspectors are, therefore, clearly in a position to work with applicants to maximise their chances of successfully negotiating APC scrutiny. In an earlier communication between Imutran and HLS, in relation to the APC meeting described on several occasions by the HO Inspector as a 'rubber-stamping' affair, an Imutran official relates:

"For your information he [the Inspector] also told me that our application for a kidney transplant licence has been reviewed by the inspectorate and that we should expect to have some 'I's to dot and some T's to cross' before it goes to the APC."¹³⁶

4.22 Other documents provide further glimpses of the close relationship between inspector and inspected. The same Inspector worked with Imutran to investigate the deaths of 3 monkeys while being transported from the Philippines to England in August 1998. The crates that the monkeys had travelled in had broken regulations on minimum size and ventilation requirements, an important feature omitted from a reference to the deaths in the APC's report for 1998¹³⁷ and in a subsequent Written Answer.¹³⁸ An internal Imutran memo dated 8 December 1998 states:

"close review of the IATA [International Air Transport Authority] requirements did lead to [the Home Office Inspector] and I agreeing that in minor details the crates did NOT comply with the regulations... As far as we are concerned I believe this to be the last we should hear on this matter, please note that throughout this investigation I have orchestrated it such that Imutran are entirely anonymous."

4.23 It does appear extraordinary that Home Office Inspectors and researchers can collaborate on matters involving lethal breaches of regulations behind a mutually-understood veil of secrecy.

4.24 A few months later the same Inspector reassured Imutran regarding the lifting of a suspension of the supplier of the primates who had died. Imutran were eager to import further primates from the supplier and were informed by the Inspector that: "he felt this issue would be

¹³⁶ Document CY7.2

¹³⁷ Report of the Animal Procedures Committee for 1998, paragraph 34.

¹³⁸ Hansard, Written Answers for 28 June 2000, Mr O'Brien, [125262], "Xenotransplantation".

resolved soon... In short I am to contact him again late next week when he feels (confidently!) that he will be able to give me definitive answers.”¹³⁹

4.25 Based on the available evidence, and in the context of the strong evidence of a biased cost-benefit assessment, the Inspectorate’s “exacting and time consuming”¹⁴⁰ consideration of Imutran’s applications appears to have been motivated by a desire to steer the controversial applications successfully through a complex process rather than subject them to objective scrutiny. The HO response makes an imprecise reference to “a number of Imutran applications took up to 12 months to consider”. It is hard to judge the significance of this without details about the applications, how long they actually took, the context of the decision-making process and who was responsible for scrutinising the application. We believe that the HO may be referring to an application made by Imutran to import wild-caught baboons from Kenya. In a letter to the HO dated 12 January 1998, the Imutran project license holder complains:

“It is now more than 11 months since I applied for permission to import baboons into the UK. I have paid to have caging built to HO specifications in Kenya to comply with concerns raised by the APC yet still there is no decision.”¹⁴¹

4.26 The time period for this decision appears to have resulted from concerns raised by the APC during 1997 regarding experiments on wild-caught baboons that contradicted the terms upon which the APC had recommended their approval. The APC did not have the opportunity to scrutinise the majority of the experiments involving captive-bred cynomolgus monkeys. Having first demanded an explanation in March 1997,¹⁴² the APC was dissatisfied and “incensed” with Imutran’s response, felt that Imutran had “violated the trust extended to them”, and expressed its concern about the direction of Imutran’s baboon research.¹⁴³

4.27 A month later, after the APC had considered Imutran’s response, the Committee remained deeply dissatisfied with Imutran’s conduct. Imutran appeared to have experimented on two baboons in direct contradiction of an order to pause their experiments:

“Members strongly expressed the view that your response was still not satisfactory and that the failings listed above indicate a cavalier attitude to the controls of the Act. They

¹³⁹ Document CY7

¹⁴⁰ Paragraph 65 of HO response.

¹⁴¹ See document ND23.4

¹⁴² See document ND13.1. At this point in time, the HO communicated on behalf of the APC.

¹⁴³ See document ND15.1-15.2

are also extremely concerned that this attitude may extend to the care and welfare of animals.”¹⁴⁴

4.28 During the second half of 1997, the APC remained dissatisfied with the lack of detail in Imutran’s application for a new project licence for pig-to-baboon heart transplantation research, leading to the delay in the consideration of the application to import baboons for the research project. Thus, rather than being a result of vigorous scrutiny by the HO, the lengthy consideration of the baboon import application appears to have been driven largely by the APC’s dissatisfaction with Imutran’s conduct and Imutran’s failure to complete the licence form adequately.

APC by-pass

4.29 We feel that the most likely explanation for the HO decision to exclude the APC from an investigation into the Imutran research was to maximise the HO’s control over the process and conceal discrepancies between the conduct of the research and the advice provided to the APC by the HO Inspectorate.

4.30 In April 2000, the APC expressed serious concerns about the adequacy and balance of a report by the HO Inspectorate into allegations against a breeding establishment:

“... it was felt by a majority of members that the Inspectorate’s report left a number of outstanding questions. Many members felt that the report sought to exonerate Harlan-Hillcrest, with the risk of creating the impression that the conditions which prevailed there were deemed acceptable by the Inspectorate

Looking to the future, a majority of the Committee were in favour of encouraging the Home Office to consider incorporating an independent element into any enquiries that might be initiated into allegations which suggested not merely particular breaches of the Act, but the possibility of a more generally significant failure of the system of compliance, monitoring and enforcement.”¹⁴⁵

4.31 An unequivocal policy announcement was made via a Written Answer the day before a meeting between the HO and Uncaged to discuss the need for an independent judicial inquiry into the Imutran case. In answer to an enquiry from Eileen Gordon MP regarding “incorporating

¹⁴⁴ See document ND17.1-17.2

¹⁴⁵ Paragraphs 5.6-5.7 of minutes for April 2000 meeting: <http://www.apc.gov.uk/reference/apr00.htm>

an independent element in future investigations by the Animals (Scientific Procedures) Inspectorate of allegations against establishments and individuals licensed under the Animals (Scientific Procedures) Act 1986”, Mike O’Brien told Parliament:

“I have considered the introduction of an independent element into future investigations under the Animals (Scientific Procedures) Act 1986.

I have concluded that the appointment of a small independent scrutiny team, drawn from the Animal Procedures Committee, and reporting directly to the Secretary of State would be the best means of providing assurance that any future Inspectorate investigations have been carried out with the necessary objectivity and thoroughness. I am grateful to the Committee for agreeing to undertake this role following an approach to them in June 2000.”¹⁴⁶

4.32 It should be noted that the allegations contained in the Imutran documentation and the Diaries of Despair report go beyond the “establishment and individuals licensed under the Act” as referred to in the PQ, raising wider questions about the operation of the most fundamental aspects of the regulatory system, such as the cost-benefit assessment. The HO now claims that the reason why the APC was excluded stemmed from the fact that the CI was asked to review Imutran’s compliance “as part of the Inspectorate’s normal statutory inspection and reporting function.” This is a transparently arbitrary manoeuvre, based on semantic games rather than the facts of the case. Furthermore, the review and production of the report into Imutran’s compliance is *not* an example of the Inspectorate’s routine work. On the contrary, it appears unprecedented: the writer has no knowledge of *any* previous similar ‘routine’ exercise.

4.33 On 20/3/01, the Chairman of the APC, Rev Prof Banner, wrote for a second time to the relevant minister:

“The Animals Procedures Committee discussed this matter at its meeting on 14 February and on behalf of the Committee I have been asked to write to you again. It would be helpful if you could explain why a routine review by the CI was chosen in this case. Members of the Committee remembered the earlier allegations about Harlan-Hillcrest, where the Home Office response was an Inspectorate investigation carried out by Inspectors who had not been involved in dealing with Harlan-Hillcrest before. As the allegations about Imutran are arguably more serious than those about Harlan-Hillcrest, members were surprised that the Home Office chosen investigation was not given a more wide ranging remit.”¹⁴⁷

¹⁴⁶ Written Answer, Mike O’Brien MP, 1 November 2000 (PQ by Eileen Gordon MP (136225)).

¹⁴⁷ See Annex to <http://www.apc.gov.uk/reference/feb01.htm> .

4.44 The APC noted following the Minister's reply:

"4.6 In the first place Members noted that shortly before the allegations by "Uncaged" were publicised, the Committee had been concerned with allegations made by the BUAV about conditions at Harlan-Hillcrest. Following the APC's discussions of the Home Office response to those allegations, the Home Office had itself suggested that in future investigations the APC might be asked to supply a panel in order to quality assure the Inspectorate's report. The Chairman had twice asked for an explanation for the reasons in the case of the "Uncaged" allegations for deciding against commissioning an investigation by the Inspectorate, with a quality assurance panel provided by the Committee. There was general agreement that no satisfactory explanation had been given, and the Committee agreed that the Chairman should write to the Minister again."

4.45 The HO's circular argument at paragraphs 66 & 67 corresponds with the text of a letter from the then Home Office Minister Angela Eagle to the Chairman of the APC following his *third* letter. Most importantly, the HO had still failed to provide a substantive explanation as to why, in the Diaries of Despair case, the HO should treat a review of the case as 'routine'. Not surprisingly, a majority of APC members thought that the HO decision to exclude the APC was unreasonable.¹⁴⁸

Huntingdon Life Sciences (HLS)

4.46 The HO response claims that the performance of HLS staff involved with the Imutran research was considered and addressed in the CI's review. This is misleading in the extreme. Extraordinarily, the name "Huntingdon Life Sciences" does not even appear in the CI's review.

4.47 The Diaries of Despair report presented specific evidence that Huntingdon Life Sciences failed to fulfil the conditions of its Certificate of Designation, which issued by the Home Office in order to permit animal experiments at a "Designated Establishment". In HLS's case, further conditions had been applied by the Home Office following the "brutal" abuse of dogs and the falsification of test data at the company revealed by the "*Countryside Undercover: It's a dog's life*" documentary broadcast in 1997.¹⁴⁹

¹⁴⁸ See para 3.12 of minute for Feb 03 meeting: <http://www.apc.gov.uk/reference/feb03.htm>

¹⁴⁹ The conditions are listed at Appendix D to the 1997 report of the APC, p.24-25. Two members of staff were convicted as a result under the Protection of Animals Act 1911.

4.48 The Imutran documentation describes the illegal re-use of monkeys and, subsequently, two errors involving incorrect blood sampling and a quadruple overdose. These mistakes were the direct responsibility of HLS staff and managers. For example, following, the quadruple drug overdose, a senior Imutran manager wrote to HLS:

“Frankly, I do not understand how this could occur as every step in the procedures is double checked by a second person. I can only believe that the double check procedure is not in place or that it is not taken seriously by the people looking after Imutran’s animals.”¹⁵⁰

4.49 HLS admit culpability:

“We would like to take this opportunity to apologise for the recent errors that have taken place at Huntingdon during the ongoing Xenotransplantation work. There are no excuses that can be made for the failure of individuals to follow the operating procedures that have been set down to ensure the smooth conduct of studies...”¹⁵¹

4.50 The CI’s review deals briefly with the three failures and admits that they were due to human error¹⁵², but fails to reveal where the responsibility lay for the errors and, most significantly, does not discuss them in the context of Huntingdon’s fulfilment of its licence conditions. Any member of the public reading the review would be entirely unaware of Huntingdon’s non-compliance with regulations and would presume that responsibility for errors lay with Imutran.

4.51 The illegal re-use was dealt with by the HO as merely a ‘formal infringement’ (thereby incurring no sanctions or punishment)¹⁵³, while no breach of compliance was deemed to have occurred with regard to the blood sampling and overdose errors, despite their direct relevance to the fulfilment of the conditions of Huntingdon’s licence.

4.52 The CI’s review includes a heavily qualified acknowledgment of failures to euthanase monkeys at the prescribed time during kidney xenotransplantation experiments.¹⁵⁴ Such failures would implicate the ‘Named Animal Care and Welfare Officer’ and the ‘Named Veterinary

¹⁵⁰ Document hlsapp7c

¹⁵¹ Document hlsapp7d

¹⁵² Sections 5.6, 5.17.2 and 5.17.4 .

¹⁵³ To the writer’s mind, this seems analogous to the courts ignoring speeding offences if no actual injury is caused, and thus symptomatic of the HO’s lax attitude to enforcement of the 1986 Act.

¹⁵⁴ Paras 5.14.3 – 5.14.6. See also below at paras 5.47-5.54.

Surgeon', both nominated by the relevant "Designated Establishment" under section 6(5) of the 1986 Act: in this case Huntingdon Life Sciences.

4.53 A "Certificate of Designation" is issued to the person who represents the governing authority of the establishment and who is ultimately responsible to the HO for ensuring that the conditions of the certificate are observed.¹⁵⁵ Those responsibilities include ensuring that the named day-to-day care person and named veterinary surgeon discharge their duties effectively, and that "the establishment is appropriately staffed at all times to ensure the well-being of all protected animals".

4.54 Under section 6(6) of the 1986 Act, the named day-to-day care person and the named veterinary surgeon must notify the personal licensee, or make arrangements for the care or destruction of the animal, if the health or welfare of any 'protected' animal in the establishment gives rise to concern¹⁵⁶, having familiarised themselves "with the project licences in use, including severity limits and severity conditions, adverse effects and humane endpoints."¹⁵⁷ The effective fulfilment of these responsibilities is a condition of the Certificate of Designation.¹⁵⁸

4.55 However, despite their central role in ensuring compliance with severity limits and minimising suffering, there is no indication whatsoever regarding any culpability on the part of Huntingdon staff or problems with the operating systems at the establishment. Nor is there any perceptible indication of infringement action being taken against Huntingdon staff regarding these failures which would have resulted in additional, severe suffering for the primates involved.

4.56 The discussion above at section 2 explains how severity limits were broken in a much wider range of procedures than those admitted and acted upon thus far. The failure by the HO to acknowledge and punish such fundamental breaches relates to both the Imutran project licence holder and the relevant aforementioned staff at the Huntingdon establishment.

4.57 The CI does make a vague and unsubstantiated claim that the "facilities used by Imutran" (which would, by implication, include Huntingdon) complied with HO Codes of Practice.¹⁵⁹ Such codes are related to welfare issues extraneous to the performance of the procedures, i.e. housing and environmental issues. The Diaries of Despair report did not raise specific issues

¹⁵⁵ Guidance on the Operation of the Animals (Scientific Procedures) Act 1986, published 1990, para 2.2.

¹⁵⁶ *ibid.*, paras 2.10 & 2.11.

¹⁵⁷ *ibid.*, paras 2.10(vi) and 2.11(vii).

¹⁵⁸ *ibid.*, Appendix II, no.11.

¹⁵⁹ Section 5.8.1

related to the 'Codes of Practice' but rather to the aspects of the regulatory structure related to the severity of the procedures.

4.58 The Diaries of Despair report also revealed concerns expressed privately by Imutran staff about the suitability of HLS's facilities for Imutran's procedures and the failure to achieve standards of Good Laboratory Practice in certain studies.¹⁶⁰ Such concerns are relevant to the HO's cost benefit assessment rather than the specific responsibilities of the Designated Establishment. There has been no examination of these concerns as no independent (or otherwise) review of the cost-benefit process has been conducted.

5. Content of the Chief Inspector's compliance review

5.1 In the June 2003 memorandum, we had complained that the CI's review "contains several significant inaccuracies and omissions, downplays the suffering of the animals and attempts to shield the Home Office, Imutran and Huntingdon Life Sciences from legitimate criticism". The Home Office denies this.

"Unauthorised experiments hidden"

5.2 Replying to our charge that, contrary, to the CI's review, experiments were performed on primates without the prior knowledge or consent of the HO, the HO response claims that the unexpected use of an additional sixteen baboons on one protocol by Imutran was not considered an infringement of their licences on the grounds of a technicality:

"... Imutran explained that the precise distribution of animals between experiments was not specified on the licence and that no further Home Office consents had been required."¹⁶¹

5.3 The HO states that this explanation was not presented in the Uncaged memorandum. This is because, having reviewed the available correspondence on this matter, the writer can find no reference to this explanation. Instead, Imutran repeatedly claimed in its defence that they had formed the impression that the use of the extra baboons had been explicitly consented to by

¹⁶⁰ Diaries of Despair, sections 7.2-7.4.

¹⁶¹ Paragraph 71.

the APC. This claim is said to have “particularly incensed”¹⁶² the Committee, none of whom had any recollection of such authority being given.

5.4 The background to this episode is that the APC based a recommendation for approval of an Imutran application to use 39 baboons to investigate **four** different immunosuppressive therapies on the basis of Imutran’s proposal to use 9 baboons for each investigation. Imutran ignored this, using an additional 16 baboons in one investigation. Imutran appear to have escaped punishment because the licence documentation itself, which forms the legal basis for the conduct of the experiments, did not reflect the detailed requirements set out in the APC recommendation. The APC complained:

“The Home Office and the Committee have recognised the importance of your work and we have given you some latitude within the authorities granted in your project licence to make small modification to your studies to take account of the results of your research and the rapid developments in the science.¹⁶³ In doing so, we extended to you a degree of trust that you would continue to work within both the spirit and the letter of the controls of the 1986 Act. Subject to further explanation, both the Home Office and the Animal Procedures Committee feel that you have violated this trust.”¹⁶⁴

5.5 The real issue here appears to be the failure of the regulatory system to exercise effective control over Imutran’s research, to the frustration of the Animal Procedures Committee.

5.6 In any case, Imutran once again ignored a further direction from the Home Office and experimented on primates in contravention of a requirement to cease research while the initial additional use was being investigated. A letter from the Home Office to Imutran dated 10 June 1997 states:

“Two animals X220 and X198 are listed as having been used on 6 May, after we notified you that we had accepted the Committee’s advice that no further work should be authorised at this time... [T]his work clearly post-dates the letter sent at the end of March which said ‘Before any further work takes place, we expect an explanation for the change in use and a justification for any further work including a description of the current experimental design for the comparative immunology study’.”¹⁶⁵

¹⁶² Documents ND15.1-15.2.

¹⁶³ This sentence indicates that the HO and the APC were under the impression that Imutran’s research had, and was likely to make, rapid progress.

¹⁶⁴ ND15.2

¹⁶⁵ Document ND17.1

5.7 Once again, no reference to this conduct appears in the CI's review. Even if, formally, this did not represent an actual breach of the law, the complete failure of the CI to discuss this "cavalier attitude to the controls of the Act" that the APC considered this behaviour represented is indicative of the lack of openness on the part of the HO and their indulgent and biased attitude towards Imutran.

"Distorted cost benefit assessment"

5.8 This section actually focusses on the 'benefit' side of the cost-benefit assessment. Paragraphs 74-77 of the HO response give a confusing description of how benefits are assessed in the cost-benefit assessment. At paragraph 76 the HO refers in passing to "the potential value or use to be made of the knowledge or product of the proposed animal research" which is indeed cited in a background policy paper. However, the overarching impression that the HO appears to be trying to give is that, in the final analysis, 'benefits' are determined by the HO in very narrow 'scientific' terms: in other words, whether the proposed research programme is likely to answer a scientific question or puzzle (i.e. "new scientific insights that might be gained"¹⁶⁶). This impression is reinforced by the HO assertion at paragraph 82: "It was the *intrinsic* value of these hypotheses that was considered in the relevant cost/benefit assessment." (emphasis added)

5.9 The practical implication of the way the HO has presented its policy in this instance is that instead of conducting a meaningful cost-benefit assessment along the lines stated in background policy documents, in fact it places overriding value on the mere potential for the 'advancement of scientific knowledge', irrespective of the actual utility of that knowledge. **In fact, this does appear to be the reality (as opposed to the impression normally given by the HO) of how the policy is implemented.** But there are extremely serious problems with the legitimacy (both legally- and democratically-speaking) of this form of implementation and the HO's presentation of it here:

- (a) it contradicts stated policy
- (b) it contradicts the Imutran applications and project licence authorities
- (c) it contradicts earlier Government statements regarding its assessment of the benefits of Imutran's research

¹⁶⁶ Para 3.2 of the CI report, reproduced at para 74 of the HO response.

(a) Contradiction of stated policy

5.10 Policy statements regarding the operation of the cost-benefit assessment do not assert that 'benefits' are calculated on the basis of the intrinsic scientific value of hypotheses. The CI's note on the cost/benefit assessment, published in 1998, is reproduced by the HO at Annex D to their response, and it formed the organizing framework for the analysis contained in our Diaries of Despair report. Paragraph 5.23 of that Note states clearly:

"When applications for the development of new materials are assessed, the utility of the new material is one of the main determinants of benefit. In the case of new medicines, this may be deemed to be high; in the case of cosmetics, low."

5.11 Naturally, in any genuine attempt to calculate potential benefit, it would not *simply* be enough for an applicant to simply state 'cancer research'¹⁶⁷ in order to obtain a research licence. The "likelihood of success" (para 2.4) is claimed to be an essential determinant of benefit by the CI, and that in turn requires an assessment of the plausibility of the scientific goals, including an assessment of the scientific value of the hypotheses. So, publicly at least, the policy on cost-benefit assessment states that it is a combination of factors.

5.12 At paragraph 77, the HO claims that "any single project licence can only cover a small fraction of the work that is required to take potential new therapies from the concept stage through to clinical practice." In fact, Imutran's project licence authorities were not based on cautious references to the research's potential contribution to the eventual development of xenotransplantation. Instead, progress to the point of clinical trials is stated as the unequivocal goal of the specific licensed research. Furthermore, in his note on the cost/benefit assessment, the CI himself states that in the assessment, "the 'benefits' relate only to those which might reasonably be expected to arise *directly* from the programme of work for which the licence authorities are sought."¹⁶⁸ (emphasis added)

5.13 Single project licences may cover differing proportions of the research conducted prior to clinical trials of a drug or device, depending on the length of the project licence (Imutran's covered the maximum period, five years), how far down the development path the research project occurs, and the soundness of the science underpinning the research. As described below, Imutran explicitly advanced in their applications the claim that their research was at the final pre-clinical stage, and they repeatedly gave the impression that the remaining obstacle to

¹⁶⁷ See paragraph 76 of HO response.

¹⁶⁸ See annex d to HO response, paragraph 2.4.

be overcome before clinical trials could take place was the tweaking of the immunosuppressive regimes. This is consistent with Imutran's public claims of imminent clinical trials.

5.14 However, the HO seems to be claiming that it permitted the Imutran research *purely* on the basis of the value of the hypotheses, with *no reference* to the "likelihood of success" or the "utility of the new material", which are supposed to be "main" or "essential determinants of benefit" as related just above. Given the failure of Imutran over five years to achieve the first significant stated aim of their research – to overcome acute vascular rejection (the next stage after hyperacute rejection, see section 2 above) – then there seems to have been on the part of the HO either a huge overestimate of the "likelihood of success", or otherwise a complete disregard for this regulatory requirement.

5.15 This indicates, in the case of the Imutran research, a breach of stated policy in the form of a distorted cost-benefit assessment. Instead, it appears that the HO judges applications on very narrow criteria specific to some PhD theses, rather than a thorough and balanced cost-benefit assessment which, according to stated policy, involves a vastly broader set of factors. Scientific validity is a necessary, not a sufficient condition according to public policy statements. The fact that this inadequate cost-benefit assessment has taken place in the context of possibly the most severe and controversial animal experiments in the last decade raises particular concerns about the overall operation of the 1986 Act.

(b) Contradiction of Imutran applications and project licence authorities

5.16 The CI's report juxtaposed two extreme versions of the possible judgments of benefit by the HO:

"In considering whether and on what terms to grant the project licence applications the Home Office judgment of 'potential benefit' was based upon *new scientific insights* that might be gained. Imutran did not advance, and the Home Office did not consider, claims of *imminent clinical trials* as a realistic short-term benefit."¹⁶⁹ (emphasis added)

5.17 There is, of course, a huge gap between the mere testing of hypotheses and the "realistic" prospect of an "imminent" (however those terms are defined) commencement of clinical trials. (In the context of the development of new drugs or other medical technologies, five years is a relatively short time scale.) Though the time scale indicated in the Imutran applications seemed to vary and was usually not precise, what is clear is that, at the very least, tangible progress towards clinical trials was key to the licence authorities. Imutran's licence authorities

¹⁶⁹ Paragraph 3.2, reproduced at paragraph 74 of HO response.

were not limited to the abstract goal of merely *ascertaining whether it was possible* to elucidate and overcome rejection processes subsequent to hyperacute rejection. There was clearly an expectation that it *would be possible* for Imutran to achieve the preconditions for clinical trials, and this expectation was fundamentally incorrect.

5.18 The licences and other submissions demonstrate that the Imutran experiments were repeatedly approved by the Home Office on the basis of:

1. exaggerated claims made regarding the 'success' of the earlier research in terms of understanding and overcoming the immune response to pig organs subsequent to the initial hyperacute rejection process, and
2. the likelihood of further 'benefits' involving extending survival times of xenotransplanted organs sufficiently to warrant clinical trials of the organs.

5.19 The document referred to by the HO response at paragraph 81 is part of a project licence cited by Uncaged to show that the achievement of the objective of clinical trials was – officially at least - part of the licensing process. Unhelpfully, the HO quotes a different statement to the one to which it claims to be responding. In any case, whether the benefits forming the basis of the licence included clinical trials as the 'objective' or the 'ultimate objective' (both terms were used by Imutran and approved by the HO in this application), this still negates the CI's claim that "new scientific insights" or, as stated by the HO response at this paragraph, "the intrinsic value of the hypotheses", formed the basis of the HO's judgment of benefits in licensing the research.

5.20 At paragraph 82, the HO refers to a second document cited by Uncaged, particularly the statement:

"These data suggest that organs taken from our transgenic pigs would provide a useful source of organs for transplantation into man. It is our intention to demonstrate the long-term viability of these xenografts by transplanting them into cynomolgus recipients which would then be immunosuppressed with clinically acceptable drug protocols."

5.21 This was part of a progress report on pig-to-primate heart transplants submitted by Imutran in 1995. The HO response suggests that we have construed this as a declaration that clinical trials are imminent. In 1995, Imutran publicly predicted that they would be in a position to commence clinical trials of pig hearts the following year. If Imutran had succeeded in their above-stated 'intention' to the HO, then they would indeed have been in a position to apply, either in the UK or the US, to commence clinical trials of pig hearts. It is, therefore, not unreasonable for us to interpret this Imutran statement as a confident prediction to the HO that they would achieve the necessary scientific objectives to be in a position to apply to perform clinical trials.

5.22 It should also be noted that another leaked document¹⁷⁰ from early 1995, where an Imutran executive recaps on action points following a meeting with a senior researcher, reveals that Imutran did advance the prospect of imminent clinical trials in a meeting with their HO inspector:

“[The researcher] agreed to talk to [an Inspector] at the Home Office re technical failures¹⁷¹, life supporting heart in baboon and to generally *chew the cud and ensure smooth and rapid passage of forthcoming 19b application*¹⁷². Important that [the Inspector] understands the issues (technical difficulty, imminence¹⁷³, etc.) and *will give us upward support of the application* for orthotopic work. We have to work to *make him look like a jolly good bureaucrat and yet achieve our goals as well!*” (emphasis added)

5.23 While this particular contact between Imutran and the HO does not have the same formal status as the project licence, it is implausible to contend that such discussions had no effect on the HO considerations and did not create a general climate of expectation. Later, the Imutran memo discusses plans regarding clinical trials:

“9. 1st Human Clinicals. With early Q4 1995 as a goal for 1st human clinicals (over one year ahead of original schedule there are a host of other issues with varying lead times that need immediate further discussion and resolution...”

5.24 Paragraph 83 of the HO response refers to two statements from a document cited by Uncaged to demonstrate the falsity of the CI’s assertion that “Imutran did not advance... clinical trials in the near future as a realistic benefit.” The document, leaked from the HO, is entitled “Application for Licence for Heterotopic and Orthotopic Transplantation of Transgenic Pig Hearts into Non-Human Primates.” In one of the statements Imutran assert:

“Preclinical trials: Studies extending over the last ten year period have now led us to this application for the final trial before human utilisation of the techniques.”¹⁷⁴

¹⁷⁰ Document I3

¹⁷¹ “Technical failures” refers to failures in the xenotransplantation surgery causing the death of the primate and the failure of the procedure. This means that the primate died without any information being gained – a waste of a life. The overall technical failure rate was very high at approximately 25%.

¹⁷² This refers to a new application for permission to conduct xenotransplantation experiments.

¹⁷³ This refers to Imutran’s claims that they would be in a position to commence clinical trials of pig organs in the near future.

¹⁷⁴ Document ND5.7

5.25 In the other statement, Imutran explain their plans for the procedures based on the assumption of primate survival times of over one year, which would signify achievement of the criteria to apply for permission to conduct clinical trials:

"Biopsies [of pig hearts in baboons] would be taken at day 10 after the operation and then at three weekly intervals for three months. Until the first anniversary biopsies will be done two monthly and thereafter annually!!!"¹⁷⁵

5.26 The statement by the CI in his report is clearly untrue, and gave the false impression during the court case that Imutran had not exaggerated the prospects of their research being successful. However, the HO response inserts the qualification "formally": "Imutran never formally advanced..." This qualification was not in the CI's report and the HO's insertion here is specious in the context of a discussion about the veracity of the CI's report.

5.27 The HO claim that the document in question "*appears* to be part of an outline for a licence application rather than a formal application." (emphasis added) Firstly, as explained above, such a claim is irrelevant to the question of the veracity of the CI's report.

5.28 Secondly, given that the document is a HO document, it seems odd that the HO gives the impression of being unsure about the precise status of the document – outline or formal. It is also unclear as to what practical difference such a distinction would make.

5.29 Thirdly, if such a document was seen by the APC, it would have formed part of the deliberations of that Committee regarding its recommendations to the Home Secretary concerning the licensing of this research. Was this document seen by the APC and, if so, how was it presented to the Committee by the Inspectorate? Were adequate caveats provided in respect of the impression of likely imminent trials given by Imutran?

5.30 At paragraph 84, the HO refers to an application made by Imutran addressed, it claims, to the APC rather than the HO. The validity of the distinction between the APC and the HO seems dubious, given that the APC is physically situated within the HO, its Secretariat is supplied by the HO,¹⁷⁶ the Committee relies on HO Inspectors for interpretation and advice on

¹⁷⁵ Document ND5.22

¹⁷⁶ An odd incident arose following the initial submission of the papers to the APC. While the APC's Secretariat were assuring members of the public that members had received all of the documentation including the crucial primary evidence generated by Imutran, in fact, it later emerged by accident, following an enquiry from the writer, that members had only been supplied with the short summary of the report.

how it should consider applications, and the Committee then advises the Home Secretary. In the application, Imutran state:

"This information is an important step forward in progressing the xenograft procedure to the clinical setting. However there is still a requirement to work out the optimal immunosuppressive drug protocol before pig xenografts can be used clinically in man... [I]t is hoped that the APC will agree to consider requests at a later date in such a way as to facilitate a continuous research programme to define the best immunosuppressive regime to allow xenografts to be tested clinically in man."

5.31 The information referred to by Imutran at the beginning of the statement refers to an earlier set of experiments on baboons. Imutran clearly give the impression that those studies have permitted significant progress towards clinical trials. That was untrue. The subsequent reference - to the need to "optimise" the drug protocols before commencing clinical trials - gives the impression, we submit, that the fundamental problem of preventing delayed xenograft rejection has been essentially overcome and all that is needed now is some tweaking of the immunosuppressive regime before clinical trials can commence. This impression is also inaccurate.

5.32 It seems entirely justifiable to interpret these Imutran comments as advancing the false claim that significant progress towards clinical trials had been made and that, with the remaining task consisting of merely "optimising" the immunosuppressive drug protocols, it was realistic to expect clinical trials to commence in the relatively near future. Contrary to the impression given by the HO, it is therefore certainly not the case that Imutran's applications concentrated on the mere intrinsic value of performing the experiments. The prospect of clinical trials is explicitly there, notwithstanding arguments over specific timeframes.

5.33 Paragraph 85 of the HO response also contains a specious argument, and includes a partial quote from the document we cited in support of our claim that the CI was inaccurate in asserting that Imutran did not advance clinical trials as a realistic consequence of their experiments. Contrary to the HO claim, the "objective" that Imutran were citing as their reason for their application involved "the move to the clinic", and was not simply an abstract desire to test scientific hypotheses.

5.34 Paragraph 86 of the HO response refers to a project licence application to conduct liver xenotransplantation experiments. The document states:

“Potential Benefits: It is our objective that the transplantation of organs [in this case livers, see below] from transgenic animals to humans will provide a solution to the current shortage of donor organs.”¹⁷⁷

5.35 Although the HO response says the application came from a collaborator with Imutran rather than Imutran themselves, the application is completed and signed by an Imutran employee. The reason why we cited that document was that it was yet another case of Imutran making unrealistic claims regarding the potential benefits of their research proposals: the achievement of clinical trials of porcine livers. It is important to note that pig-to-human liver xenotransplantation is acknowledged to be an extremely speculative proposal, greater even than cardiac and renal xenotransplantation, “due to the complexity of the biochemical interactions of the liver with the rest of the body... [and] incompatibilities between a pig’s liver functions and what a human needs.”¹⁷⁸ This was particularly important in the context of the legal proceedings where the accuracy of Imutran’s project licence applications was relevant to the public interest in disclosing their confidential documentation. However, the CI’s characterisation of Imutran’s applications gives the false impression that no such unrealistic claims were advanced by Imutran.

5.36 The HO response also states that this liver xenotransplantation research was not licensed. This does not explain why though. The 1998 Report for the APC indicates that the applicants chose not to pursue the application in the light of advice received from the UKXIRA regarding the potential utility of liver xenotransplantation.¹⁷⁹ To reach the APC, Imutran (and their collaborators) are likely to have liaised with the HO Inspectors in the drafting of the application – that is the standard practice. Given the acknowledged difficulties inherent to porcine liver xenotransplantation, any role that the HO may have had in promoting the application is a source of concern for us.

5.37 Paragraph 87 of the HO response refers to a statement cited by Uncaged contained in Imutran’s correspondence with the APC’s Secretariat at the HO, where Imutran state that their objective in proposed baboon experiments was to achieve the pre-conditions for an application to conduct clinical trials. The HO claims that this is consistent with its approach, but, as we have seen, it has in fact tried to exclude the essential determinants of benefit - “likelihood of success” or the “utility of the new material” – from its version of its assessment of Imutran’s applications.

¹⁷⁷ Document ND12.2.

¹⁷⁸ Kennedy Report, paras 2.44-2.45.

¹⁷⁹ Paragraph 47. Although the UKXIRA agreed with a small-scale pilot study, despite the overwhelming evidence of incompatibilities.

5.38 At paragraph 88 of their response, the HO attempts to explain away Imutran's unambiguous reference *in a project licence* to their intention to achieve progress to allow a commencement of clinical trials.¹⁸⁰ However, Imutran are claiming that the results of the experiments for which permission is applied for (i.e. the experiments conducted under that particular project licence) are required to be presented to UKXIRA in an application to conduct clinical trials. Therefore, they *are* advancing the realistic possibility that those experiments will successfully answer the remaining scientific questions and puzzles in order to achieve the preconditions for clinical trials – consistent long-term survival due to reliable control of the delayed xenograft rejection processes. This claim – in a project licence - is in direct contradiction to the CI's claim that the HO only considered benefits in terms of "new scientific insights".

5.39 Paragraph 89 of the HO response appears to be discussing a different document to the one cited by Uncaged. In any case, the HO claim that lengthy negotiations with Imutran on one issue indicates rigorous scrutiny are discussed above at paragraphs 4.25-4.28.

(c) Contradiction of earlier Government statements and actions

5.40 Correspondence from the HO reveals unequivocally that the department licensed the Imutran research on the basis that "the main and ultimate benefits of this research can only accrue if xenotransplantation can be used in clinical practice."¹⁸¹ In responding to the submission by Uncaged of a cost-benefit analysis of the Imutran research which concluded that the experiments should not be licensed, the Home Office defended its decision to permit Imutran's research by explaining that "Xenotransplantation is a potential solution to this shortage [of donor organs for transplant]" in its discussion of the "potential benefits to humans" that were weighed against the "welfare of the animals involved in the development of xenotransplantation". This weighing process being "a fundamental aspect of the Animals (Scientific Procedures) Act 1986."¹⁸²

5.41 At paragraph 78 of their response, the HO tries to give the impression that the 'fact' that the regulatory framework has yet to be fully defined suggests that there has never been any realistic prospect of "imminent" solid organ xenotransplants in the United Kingdom. In fact, the

¹⁸⁰ Document ND21.8

¹⁸¹ Letter from Steve Wilkes, Home Office, to Dan Lyons, 3 March 1998.

¹⁸² Letter from Steve Wilkes, Home Office, to Alistair Currie, 28 April 1998.

regulatory framework is, to say the least, well-developed, and this development took place with some urgency in the erroneous expectation of possible clinical trials up until at least 2000. The previous year, the HO Office had issued a draft code of practice to make “provision for the welfare, care and accommodation of animals used as source animals for clinical xenotransplantation”¹⁸³ (emphasis added) for consultation purposes. The APC report for 1999 discusses the Committee’s comments on the draft code, and the development of the draft appears to have been proceeding into 2000. It seems that a final draft has not been completed since it became clear that previous expectations, that had informed the calculation of benefits in the assessment of Imutran’s primate research proposals, has been misplaced.

5.42 Furthermore, the Department of Health did in fact publish its guidelines for companies wishing to prepare applications for clinical trials on 30th July 1998. A package of measures was unveiled, including a Health Service Circular to ensure that all hospitals complied with procedures to make xenotransplantation applications by the UKXIRA, together with details from UKXIRA on application requirements for clinical trials in humans.¹⁸⁴

5.43 Finally, in response to this HO claim regarding the likelihood of clinical trials, it should be noted that in spring 2000 Imutran and Novartis Pharma embarked on an 18 month programme to try to achieve the effective management of rejection and substantial increases in survival times towards criteria laid down by the United States regulatory body, the Food and Drug Administration (FDA), as a prerequisite for clinical trials.¹⁸⁵ Clearly, then Imutran and Novartis *still* laboured under the misapprehension that they might be able to achieve tangible progress, although meeting the FDA’s targets would have required a quantum leap in their research compared to that achieved by Imutran in the previous six years. At least they believed it was a gamble worth taking given the potential financial rewards of success¹⁸⁶ – and it would be the primates and pigs paying the main price anyway. In any case, the strategy was abruptly halted in September 2000 following Uncaged’s first attempt at disclosure of the Imutran documents.

¹⁸³ Draft Home Office Code of Practice for the Housing and Care of Pigs Intended for use as Xenotransplant Source Animals (1999): paragraph 1.3.

¹⁸⁴ Dept of Health Press Release, Thursday 30th July 1998 (R1012-01), “Frank Dobson announces further steps to regulate animal to human transplants”.

¹⁸⁵ Diaries of Despair report, p.17. Document reference hlsapp9a-3. The document itself remains injunctioned as the relevant information is contained in the now-published Diaries of Despair report. The Home Office has a copy of this document, as do the solicitors who acted for Mr Lyons and Uncaged, Bindman & Partners.

¹⁸⁶ Estimated at \$11 billion per annum according to some analysts (Stephen D Moore. “Novartis Picks up Pace in Xenotransplant Race”. Wall Street Journal (Europe), 10 October 1997: 4.)

5.44 The HO's present claim that there was never any realistic prospect of "imminent" clinical trials is accurate in retrospect, but it does not reflect their statements issued during the research programme which were designed to justify their ongoing licensing of the primate experiments. Nor does it represent the legal basis – exaggerated predictions of achievement of scientific objectives towards clinical trials put forward by Imutran - upon which the research was licensed. The assertion that the research was licensed purely on the basis of the intrinsic value of the performance of the experiments, irrespective of any likely practical benefit, not only contradicts the evidence of the licensing process and policy statements on the operation of the cost-benefit assessment, but represents an extremely dubious cost-benefit assessment on the part of the HO. The APC's considerations of the licence proposals explicitly included an assessment of the likely clinical outcome of the experiments:

“Clearly, we would have to consider whether the transplantation of animal organs or tissue into humans might become viable when considering what advice to give on the use of animals either in research or as sources of organs to be transplanted into humans.”¹⁸⁷

5.45 One final point that we would like to make regarding how scientists often view their field of work repeats an observation made by the RSPCA:

“... the international xenotransplantation research community is now far less optimistic about the likely success of whole organ transplantation, although the field of research seems to have developed its own self-perpetuating momentum...”¹⁸⁸

5.46 This underlines the vital necessity for the HO to start undertaking objective and thorough scrutiny of research applications in order to implement the law and stated policy, and reflect the wishes of Parliament and the public.

“Horrific procedures ignored”

5.47 Under the heading “Horrific procedures ignored”, the Uncaged memorandum stated that the neck transplant procedures “and others... caused severe suffering, were classified as ‘moderate’, but, incredibly, no breaches were found by the Inspector.” The failure by the CI to acknowledge the fact that several primates were found dead under ‘moderate’ procedures provides stark evidence of the inadequacy of the CI review.

¹⁸⁷ 1997 Report, p.13, para 95.

¹⁸⁸ RSPCA Report, p.38.

5.48 At paragraphs 90-91 the HO makes claims regarding the neck (cervical) transplant procedures, and these claims are discussed above at paras 1.81-1.84. However, the HO response does not even attempt to deal with the concern raised in our original memorandum under this heading, regarding the failure of the CI to acknowledge the ‘substantial’ or ‘severe’ suffering caused in other types of xenotransplantation procedures.

5.49 If, for example, animals “*die before appropriate clinical investigation and management, or euthanasia, could be applied*”¹⁸⁹ then the responsible personnel have by definition failed to implement an endpoint in the procedures consistent with a moderate severity limit. The CI’s compliance review was claimed to have been based on an examination of all the information handed to the Home Office by Uncaged, plus a thorough review of other documentation that remains confidential. This would include the records for the animals “found dead” in the moderate heterotopic xenograft experiments, and the Home Office will have been aware of this evidence.

5.50 Section 5.14 of the CI’s review discusses “Implementation of Endpoints”. Although his discussion does acknowledge “perceived non-compliance” in respect of the implementation of endpoints in some unspecified renal xenotransplantation experiments where monkeys were suffering renal failure, this appears to be a symbolic or token concession that does not even correlate to many examples of the most severe suffering endured by primates under this particular protocol (and, of course, there is no reference whatsoever to any breaches under the other protocols). In his review of Imutran’s compliance,¹⁹⁰ the CI states:

“5.14.4 In every instance where irreversible renal failure was diagnosed by the surgical team animals were humanely killed when, or before these criteria were fulfilled.

5.14.5 However, I am of the opinion that in several instances there is, in retrospect, sufficient evidence (as recorded in the original study documents) for irreversible renal failure to have been diagnosed up to 24 hours before the endpoint was applied.”

5.51 These admitted instances of non-compliance are described vaguely, but there are strong reasons to conclude that not all severity limit infringements under this protocol have been acknowledged or dealt with openly and adequately.

¹⁸⁹ This is the description of ‘substantial’ severity in the HO Response paragraph 23, third bullet point.

¹⁹⁰ “Report by the Chief Inspector: Imutran Ltd.: Compliance With Authorities Issued Under the Animals (Scientific Procedures) Act 1986”, Home Office, 2001.

5.52 In their recent response, the HO states that the reason for categorising the renal xenotransplantation experiments as ‘moderate’ was that:

“Untreated non-transient [i.e. irreversible] renal failure would result in gradual deterioration of the general health of the animal over several days – sufficient time for the problem to be identified by the routine blood tests and remedied or for the animal to be killed before the level of suffering merited a ‘substantial’ severity limit.”¹⁹¹ (emphasis added)

5.53 The CI’s compliance review states that the infringements he acknowledges involved a delay of merely “up to 24 hours” in “humanely killing” the animals. Given that the deterioration of these animals due to renal failure was supposed to be a “gradual” process lasting “over several days”, it seems unlikely that a delay of only “up to 24 hours” in euthanasing the monkeys caused animals to be found dead or collapsed and on the verge of death, which is what happened in some cases.

5.54 Alternatively, if the monkeys were found dead or collapsed for reasons other than irreversible renal failure,¹⁹² then there has certainly been no acknowledgment of this, nor has there been any infringement action taken. In either case, the HO has knowingly failed to acknowledge and respond to infringements on the severity limits during these experiments.

“Dismissal of animal suffering”

5.55 See “Informativeness of clinical signs and other leaked documentation” at paragraphs 1.55-1.69 above.

¹⁹¹ Paragraph 23, second bullet point.

¹⁹² Due to drug toxicity or surgical complications, for example.