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 discusses 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,

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[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.

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[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