



Home Office

Report by the Chief Inspector:

**Imutran Ltd.: Compliance With Authorities Issued
Under the Animals (Scientific Procedures) Act 1986**

2001

Preamble

In response to the Uncaged report 'Diaries of Despair' the Home Secretary instructed the Chief Inspector of the Animals (Scientific Procedures Inspectorate) to review the available evidence and provide a brief report on Imutran Ltd's compliance with authorities issued under the Animals (Scientific Procedures) Act 1986 (ASPAs) for pig and non-human primate xenotransplantation research.

ASPAs Compliance - Summary Findings

This review of Imutran's licensed work 1994-2000 confirms, with the exceptions set out below, compliance with ASPAs authorities.

Confirmation of three instances of non-compliance, previously self-reported or reported by the Inspectorate, not deemed to have caused unnecessary animal suffering, and dealt with as formal infringements:

- Unauthorised re-use of three non-human primates (*self-reported*).
- Induction and maintenance of general anaesthesia without appropriate personal licence authority (*self-reported*).
- Blood sampling without personal licence authority (*reported by the Inspectorate*).

Detection and verification of two previously undetected instances of non-compliance not emerging from the Uncaged allegations and concerns:

- The performance of surgical procedures technically at variance with the project licence authority. It is not believed this resulted in any unnecessary animal suffering.
- Perceived failure to best implement a required humane endpoint.

Significant departures from best practice and errors of judgement:

- In one instance normal operating theatre working practices and safeguards were not followed and a swab was left in the abdominal cavity of a non-human primate that received a renal transplant.
- A renal transplant operation was performed using a kidney damaged during cold storage, and the procedure was not terminated when the transplanted organ malfunctioned.
- On two occasions the drug treatment regimens were compromised due to human error, although it is not believed significant unnecessary animal suffering resulted.

1. Overview of ASPA Compliance Issues

All aspects of compliance with authorities issued under the 1986 Act were reviewed, and the general findings were as follows:

1.1 Project licence authority was secured in all cases before studies were undertaken.

1.2 Project licence authorities were not formally suspended under the provision of Section 13(1) at any time. The suggestion that studies were carried out while authorities were formally suspended is, therefore, unfounded.

1.3 All protected animals used by Imutran were either bred at or obtained from UK designated establishments, or obtained from overseas non-designated sources and used with the knowledge and consent of the Home Office.

1.4 Journey times for imported non-human primates in some instances exceeded the estimated journey times supplied prospectively to the Home Office. The prospective estimates are considered only to represent indicative times. The variation was due to factors beyond Imutran's control, within tolerable limits, and all necessary information relating to the welfare of the animals was provided to the Home Office after their arrival.

1.5 Licence conditions relating to the re-use of Animals were complied with in all cases except one. This case was self-reported and dealt with as a formal infringement in 1997.

1.6 There was no breach of ASPA authorities in respect of the time baboons were held as stock.

1.7 All United Kingdom facilities used for the Imutran pig and non-human primate xenotransplantation studies complied with the relevant provisions of the Home Office Code of Practice.

1.8 Production of genetically modified animals complied with licence authorities.

1.9 Appropriate general anaesthetic regimens were applied and the use of analgesia was also timely and appropriate. The administration of anaesthesia was compliant with one exception. This case was self-reported, did not result in unnecessary animal suffering and was dealt with as a formal infringement in 1997.

1.10 All operative surgery was performed by clinicians (who were also personal licence holders) with experience in the relevant surgical disciplines. One instance was identified of the performance of surgical procedures technically at variance with the project licence authority. It is not believed that this resulted in unnecessary animal suffering. Two instances of significant departures from best practice and errors of judgement with respect to the operative surgery were identified. In one instance normal operating theatre working practices and safeguards were not followed and a swab was left in the abdominal cavity of a non-human primate that received a renal transplant. In the second instance a renal transplant was performed using a kidney damaged during cold storage and the procedure was not terminated when the transplanted organ malfunctioned.

1.11 Post-operative care monitoring schedules matched the perceived clinical needs of the animals and were compliant.

1.12 Where professional judgement was required with respect to the recognition and implementation of welfare-related endpoints it was generally properly exercised. However, in several instances failure to implement the

endpoint earlier did result in unnecessary animal suffering. This finding is a matter of clinical judgement – and I offer it as my opinion rather than an undisputed fact. The decisions that were taken by the surgical team were taken in good faith and based upon their clinical experience and judgement.

1.13 All blood sampling schedules undertaken for research purposes were as authorised by the project licences. An infringement relating to the taking of blood samples from pigs was identified and reported by the Inspectorate in 1997. This did not result in unnecessary animal suffering and was dealt with as a formal infringement at the time.

1.14 With the exception of the unauthorised re-use of three non-human primates all other regimens for the administration of pharmaceutical agents for experimental or other scientific purposes were in compliance with the licence authorities. However, on two occasions the drug treatment regimens were compromised due to human error, although it is not believed significant unnecessary animal suffering resulted.

1.15 Discharge of protected animals from the controls of the 1986 Act was compliant.

1.16 Where required, submission of periodic summary progress reports was generally timely, but further enquiries were at times necessary to elicit supplementary information or to verify the accuracy of the information supplied. In some cases the information supplied is now considered to have been incomplete or inaccurate.

2. Introduction

2.1 In September 2000, Uncaged submitted to the Home Office a report entitled 'Diaries of Despair'. The Uncaged report makes a number of allegations against all of the parties involved in the conduct and regulation of xenotransplantation studies performed by Imutran Ltd - including allegations that Imutran did not comply with the terms and conditions of licences issued by the Home Office under the Animals (Scientific Procedures) Act 1986 (ASPA).

2.2 The Uncaged report is compiled largely from draft reports of, and other documents relating to, Imutran's pig to non-human primate xenotransplantation research conducted in the UK. Imutran did not authorise the disclosure of these documents, and has obtained an injunction preventing further unauthorised use or misuse of much of the material.

2.3 On 27 November 2000 the Home Secretary instructed the Chief Inspector of the Animals (Scientific Procedures) Inspectorate to *"...examine, as part of the Inspectorate's normal statutory inspection and reporting function, the available evidence relating to compliance with authorities granted to Imutran for its xenotransplantation work between 1995 and 2000."*

2.4 The scope of the Chief Inspector's review and report, in line with the Home Secretary's instruction, is limited to Imutran's compliance with the authorities issued to Imutran staff under the Animals (Scientific Procedures) Act 1986 for pig and non-human primate xenotransplantation research.

2.5 This report sets out the Chief Inspector's findings.

3. Background

3.1 As part of Imutran Ltd's research programme, project licences were obtained under the Animals (Scientific Procedures) Act 1986 to produce genetically modified pigs designed to control or eradicate xenograft hyperacute rejection, and for the studies using pigs and non-human primates with the intention of:

- Demonstrating proof of concept.
- Evaluating immunosuppressive regimens to tackle other forms of xenograft rejection.
- Studying the biocompatibility and performance of solid-organ and tissue xenografts.

3.2 In considering whether and on what terms to grant the project licence applications the Home Office judgement of 'potential benefit' was based upon the 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 potential benefit. The 'cost' was assessed on the basis that there would be significant animal welfare problems as a direct consequence of the regulated procedures applied (mainly the surgery and immunosuppressive regimens), and additional contingent suffering experienced by wild-caught non-human primates required for some of the studies. Such project licence authorities were in place from 1994-2000.

3.3 During the second quarter of 2000, prior to the publication of Uncaged's concerns and allegations, Imutran's parent company decided to close Imutran and transfer the technology to a new company in North America. All extant project licences, other than that authorising the conventional breeding and keeping of established lines of genetically modified pigs, were voluntarily

surrendered for revocation at that time. All Imutran employees were made redundant or transferred elsewhere in the parent company.

4. Methodology

4.1 The review was undertaken by the Chief Inspector of the Animals (Scientific Procedures) Inspectorate. It has involved in excess of 250 man-hours of work and included seven visits to Imutran to view original study documents and interview management and staff, and four visits to other sites.

4.2 During the course of the review the Chief Inspector: -

- Considered all of the material contained in and appended to the Uncaged report.
- Reviewed all of the original study documentation, including available video footage of study animals.
- Reviewed all of the recorded information maintained by the Home Office on the Imutran research programme.
- Interviewed Imutran management and staff, and other third parties, thought to have essential information relevant to the review.
- Sought supplementary information, clarification and comment from the Imutran management, and others, as required.

4.3 This review thus includes information not previously available to the Home Office, and not available to Uncaged.

4.4 All of those contacted for information and comment co-operated promptly and fully.

4.5 Where there are discrepancies between the draft study reports, the final reports, and the original study documents the last are assumed to be the definitive records.

4.6 Section 5 of this report reviews all aspects of formal ASPA compliance. It also comments on several events, not strictly or necessarily representing ASPA non-compliance, where I believe that proper judgement was not exercised or where there were significant departures from best practice.

5. ASPA Compliance Issues

5.1 For convenience these are listed in the order they normally occur when licensed studies are undertaken.

5.2 Project Licence Authority Secured Before Studies Undertaken: *compliance confirmed.*

5.3 Allegation That Regulated Procedures Were Performed Whilst Project Licence Authority Was Suspended: *compliance confirmed.*

5.3.1 The Uncaged report makes reference to regulated procedures being performed whilst a project licence was 'frozen' pending an infringement being dealt with by the Home Office.

5.3.2 The project licence had not been suspended under the provisions of ASPA Section 13(1): the extant project licence authorities remained in force whilst the Home Office dealt with the infringement.

5.3.3 'Frozen' was the shorthand term used in the Imutran documentation to indicate that the Home Office would not process pending or proposed project licence amendments until the Secretary of State had considered, and taken action with respect to, the infringement.

5.4 Source of Animals - Provenance: *compliance confirmed.*

5.4.1 All protected animals used by Imutran were either bred at or obtained from UK designated establishments, or obtained from overseas non-designated sources and used with the knowledge and consent of the Home Office.

5.5 Authority To Use Animals From Overseas Non-Designated Sources – Journey Times: *compliance confirmed.*

5.5.1 The Uncaged report notes that the actual journey times for imported non-human primates in some instances exceeded the estimated journey times supplied prospectively to the Home Office.

5.5.2 The expected journey times supplied prospectively in support of these requests are based upon reasonable estimates of likely transit times and are used to judge the likely contingent welfare costs. They are regarded as indicative times. Imutran supplied details of actual journey times, and other information relating to the welfare of the animals, to the Home Office after the arrival of each shipment of animals.

5.6 Re-use of Animals: *Compliant with one exception: a previously self-reported instance of re-use of protected animals without the permission of the Secretary of State, and dealt with at that time as a formal infringement, was confirmed.*

5.6.1 On one occasion three non-human primates that had previously been used on, and had recovered from, an unrelated procedure were re-used without the express consent of the Secretary of State. This was due to human error, was self-reported, and was dealt with as a formal infringement. It is not believed that any significant unnecessary animal suffering resulted.

5.6.2 The unauthorised 're-use' consisted of the administration of prophylactic drugs to reduce the risk of anaemia following surgery: the error was discovered and reported before any surgical procedures had been performed.

5.6.3 Re-use under similar circumstances had previously been allowed with the consent of the Secretary of State.

5.7 Allegation That Baboons Were Held As Stock Beyond The Time Scale Prescribed By The Home Office: *no compliance issue.*

5.7.1 Although the Home Office expected that the animals would not remain as stock for longer than necessary, the Home Office did not prescribe the length of time they might be held before use, and thus no breach of ASPA authorities occurred.

5.8 Animal Accommodation: *compliance confirmed.*

5.8.1 All UK facilities used for the Imutran pig and non-human primate xenotransplantation studies complied with the provisions of the relevant Home Office Code of Practice.

5.8.2 Concerns in the Uncaged report that the facilities were understaffed are unfounded. The documents obtained by Uncaged relate primarily to an inability to increase the amount of xenotransplantation research being conducted without a concomitant increase in support staff.

5.9 Production of Genetically Modified Animals: *compliance with licence authorities confirmed.*

5.10 Anaesthesia And Analgesia (Regimens): *compliance confirmed.*

5.10.1 Appropriate general anaesthetic regimens were applied. There was active veterinary input.

5.10.2 The Uncaged report (and the Imutran documents upon which it is based) makes reference to the anaesthetic complications caused by the administration of 'very high doses' of diazepam. In fact the doses administered were within the normal clinical range, and post mortem findings established that the main clinical findings and outcomes were due to other processes and pathologies.

5.10.3 The use of analgesia was timely and appropriate. There was active veterinary involvement and oversight.

5.11 Anaesthesia (Administration): *Compliant with one exception: a previously self-reported instance of non-compliance, not resulting in unnecessary animal suffering, dealt with as a formal infringement at the time, and not mentioned in the Uncaged document.*

5.11.1 Two personal licensees induced and maintained general anaesthesia in pigs – a species not listed on their personal licences. The omission of this species was an administrative error when the licence applications were prepared. The issue was legal competence rather than technical competence (both licensees were trained and technically proficient). The procedures were competently performed and no unnecessary animal suffering resulted.

5.11.2 The lapse was detected by the in-house controls, was self-reported to the Home Office, and was dealt with as a formal infringement.

5.12 Operative Surgery: *One instance of technical non-compliance, not referenced in the Uncaged report and not resulting in unnecessary animal suffering, was established.*

5.12.1 All operative surgery was performed by clinicians (who were also personal licence holders) with experience in the relevant surgical disciplines.

5.12.2 The number of operative 'technical failures' (early graft failures not related to rejection) for the programme of a whole was of the order of 20% - consistent (and directly comparable) with reported rates in human paediatric practice. The incidence of technical failures varied from study to study, but the available evidence does not indicate that the technical competence of any individual surgeon was substandard.

5.12.3 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.

5.12.4 The one instance of technical non-compliance with operative procedures detailed on a project licence related to a study involving the transplantation of pig meniscal cartilage into the knees of non-human primates. The project licence specified that the xenograft would be placed in the right knee of the recipient animal: in some cases it was placed in the left knee instead. It is not considered that additional

animal suffering was caused. It is not clear why the technical authority was drafted in this way, or why the variation on the prescribed procedure was performed.

5.12.5 There are two other events where I believe the judgement of those performing surgical procedures is called into question.

5.12.6 In one instance a swab was unintentionally left inside the abdomen of an animal that had received a renal transplant: this was not disclosed to the Home Office in a progress report submitted shortly thereafter. The operation was performed without the normal complement of theatre staff. This background information emerged during the course of this review. The decision to operate in the absence of a trained theatre nurse was, in my opinion, both a significant error of judgement and the causal factor. It is my opinion that in clinical practice this decision would not have been defensible.

5.12.7 The Uncaged report (and some Imutran documentation) makes reference to a kidney destined for transplantation being 'frozen solid' during a period of cold storage. The kidney was not 'frozen solid' – but did show evidence of surface frosting. This was caused by human error and was the result of contact between the kidney and other material held in cold storage at the same time. Contrary to the Uncaged report the damaged kidney was transplanted into a recipient animal: the decision to proceed was taken by the surgical team aware of the problem during storage. The kidney, when re-perfused, did not show immediate normal function or appearance. The surgeon did not terminate the procedure at that point, and the animal died before recovering from the general anaesthesia. The fact that the kidney had been damaged in storage was notified to the Home Office in a progress report supplied shortly after thereafter. However the summary report did not supply details of the intra-operative problems. The damage in

cold storage was due to human error. It is my opinion that, in retrospect, it is not possible from the information available to offer an informed opinion about the judgement exercised by the surgical team to transplant the damaged organ. However, I believe the decision not to immediately terminate the procedure when abnormalities were apparent after the organ was re-perfused was an error of judgement.

5.13 Post-operative Care: *compliance confirmed.*

5.13.1 The records of the clinical condition of animals reproduced, interpreted and commented on in the Uncaged document are not informed by, and therefore do not take into account, the active clinical management of, and the specific, supportive and symptomatic treatments provided to, the animals.

5.13.2 Monitoring schedules matched the perceived clinical needs of the animals. The records available to Uncaged record only the first and last observation of each day. Normally of the order of six observations a day were made and recorded, in some cases the frequency was three times this, and when appropriate animals were continuously monitored.

5.13.3 Records confirm that both veterinary and medical staff provided 24-hour-a-day clinical cover.

5.14 Implementation of Endpoints: *perceived non-compliance with respect to the implementation of a humane endpoint.*

5.14.1 Detailed endpoints were specified on the project licences for each of the authorised protocols. Some required the exercise of professional judgement in determining whether the endpoint had been reached and on what action should be taken, others did not.

5.14.2 A thorough review of all of the available documentation for all of the animals subjected to surgical procedures and/or drug treatment suggests that where professional judgement was required with respect to the recognition and implementation of welfare-related endpoints it was generally properly exercised. When there were differences of opinion amongst those exercising these professional judgements, due weight was given to the opinion of the attending, independent veterinary surgeon.

5.14.3 One endpoint prescribed the action to be taken when renal transplant recipients developed irreversible renal failure. This endpoint was to be implemented if the findings were thought to be caused by *irreversible* renal failure; if a specific biochemical abnormality was confirmed (in a number of instances the biochemical finding was transitory, not due to irreversible renal failure, and normal renal function was rapidly restored); and the general health of the animal was failing as a result (in a number of instances the biochemical endpoint was reached whilst the animals appeared in good general health). Experience and clinical judgement were required to determine, based upon knowledge of the clinical condition of the animal and access to the laboratory findings, if the endpoint had been reached.

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 a 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. I conclude that, in these cases, failure to implement the endpoint earlier did result in some unnecessary animal suffering.

5.14.6 This finding is a matter of clinical judgement – and I offer it as my opinion rather than an undisputed fact. The decisions that were taken by the surgical team were taken in good faith and based upon their clinical experience and judgement. In addition to access to the recorded information available to me for the purposes of this review, they were present and examined the animals at the time. Nevertheless, with the benefit of hindsight, I believe that in some instances the available evidence was, on balance, indicative of irreversible renal failure up to 24-hours before the endpoint was applied.

5.15 Blood Sampling (Regimens): *compliance confirmed.*

5.15.1 All sampling schedules undertaken for research purposes were as authorised by the project licences.

5.16 Blood Sampling (Performance): *one instance of previously detected non-compliance confirmed. This did not result in unnecessary animal suffering and was dealt with as a formal infringement at the time. It is not referenced in the Uncaged report.*

5.16.1 An infringement relating to the taking of blood samples from pigs was identified and reported by the Inspectorate in 1997. On one occasion blood samples were taken by a person without appropriate personal licence authority: the technique was competently applied and no unnecessary animal suffering resulted. It was dealt with as a formal infringement.

5.17 Drug Administration (Regimens and Performance): *other than the unauthorised re-use reported above, compliance confirmed.*

5.17.1 The issue of the unauthorised re-use of three non-human primates is dealt with separately above. All other regimens for the administration of pharmaceutical agents for experimental or other scientific purposes were in compliance with the licence authorities. Expert judgement was generally properly exercised in matching the day-to-day dosing schedules to the clinical condition and laboratory findings of individual animals.

5.17.2 The Uncaged document does however identify, and this review confirms, two unrelated events where, due to human error, the drug administration regimens were compromised.

5.17.3 In the first instance an error in calculating the dose to be administered resulted in an animal receiving four-times the prescribed dose of an immuno-suppressant. This was detected shortly after the drug had been administered, the subsequent dosing regimen was adjusted, and normal therapeutic blood levels were re-established within 24 hours. Although the animal was killed on welfare grounds the day after the mis-dosing, the clinical records and post-mortem findings strongly suggest that the animal's failing health was not due to drug toxicity.

5.17.4 In the second instance a blood sample to establish the 'trough' level of a drug was taken after rather than before the animal was dosed: the purpose of the procedure was to inform the dosing regimen for the following day. This mistake was recognised the same day. As a result the dosing regimen for the following day was determined on the basis of the animal's clinical condition and standard laboratory test results rather than also being informed by knowledge of the circulating trough level of the drug. It is not believed that any unnecessary animal suffering resulted.

5.18 Discharge Of Protected Animals From The Controls Of The 1986 Act: *compliance confirmed.*

5.19 Submission Of Special Reports: *general compliance confirmed.*

5.19.1 A number of the Imutran project licences were subject to a condition of issue requiring the periodic submission of summary progress reports. These were generally timely and informative. Further enquiries were at times necessary to elicit supplementary information or to verify the accuracy of the information supplied. As indicated above, there were times when the material disclosed to the Home Office by Imutran was incomplete.

6. Conclusions

6.1 This report reviews a seven-year programme of work involving many thousands of animals and regulated procedures.

6.2 Imutran supplied the Home Office with large amounts of summary information relating to the studies, and the Home Office inspection programme specifically targeted the operative procedures and post-operative care of the animals. Nevertheless the complete picture of events only became clear when substantial additional resource was found for all of the original study documentation, not previously available to the Home Office or Uncaged, to be scrutinised in detail.

6.3 Although compliance on most fronts was confirmed, several instances of non-compliance (most previously detected/reported and dealt with as formal infringements) are described. In one instance, the apparent delays in diagnosing irreversible renal failure, I believe some unnecessary animal suffering did result.

**Chief Inspector
ASPI
2001**