

Annex A

RELEVANT EXTRACTS FROM PROJECT LICENCE MINUTE SHEET

06.02.03

Application is well justified but 19b procedures require clarification, particularly with respect to end points. Meeting arranged for ■.

20.02.03

Revised application received – all of the comments discussed ■ have been addressed. PPL Abstract and assessment completed and placed on file. (Docket 4&5).

Rec:

1. Grant licence for five years.
2. Add standard condition [PPL 8] allowing continued use from PPL ■.

05.04.06

■  
My experience of the work of this group using pigs has shown high standards of care  
■

Annex C

RELEVANT INFORMATION FROM THE ASPI VISIT (INSPECTION)  
REPORTS

23 June 2005

“█ Testicular biopsy of a pig carried out by █ This pig had been treated with busulphan per os for 2 wks, and would continue and have a second biopsy in 2-4 weeks. 1 of a group of 3, one already done was recovering well. Surgery was competently performed. Licence authorities checked █”

5 July 2005

“Pig operated on 2 weeks ago (see VR.23/6/05) appeared to be doing very well, no adverse effects of surgery observed.”

30 June 2006

“█ Inspected pigs on Busulfan treatment █”

6 July 2006

“█ Met with... and the team working on █ production of Tg pigs with a view to modifying organs for transplant research.

Advised that I am concerned that they appear to be planning to continue the current (licensed) pilot study to investigate the new method of producing Tg pigs into a breeding programme (not licensed). Advised that this would not be considered as an amendment to the current PPL but would have to be a new PPL application, but, I would consider an amendment to the current PPL to extend the survival times of the currently used pigs if a new application to use them for breeding was intended within the foreseeable future. This would avoid having to repeat the current procedure.

Also advised that any new application should give specific scientific benefits of doing this work in pigs: future use in xenotransplantation alone might not be an acceptable benefit █”

28 July 2006

“█ Pigs undergoing gene transfection and having been biopsied 1 week ago were doing well █”

PPL ABSTRACT PROFORMA

1. PPL Number [REDACTED]

2. Title (1) **T H E C O N S E Q U E N C E S O F A R E N**  
**A L T R A N S P L A N T I N T H E P I G** N

3. PODE (Y or N) (13) N

4. Permissible purposes (enter: 1 - primary purpose; 2 - secondary purpose) (14)

A	Prevention, diagnosis or treatment of disease, ill-health or abnormality or their effects in man, animals or plants	1
B	Assessment, detection, regulation or modification of physiological conditions in man, animals or plants	-
C	Protection of the natural environment in the interests of the health or welfare of man, or animals	-
D	Advancement of knowledge in biological or behavioural sciences	-
E	Education or training otherwise than in primary or secondary schools	-
F	Forensic enquiries	-
G	Breeding of animals for experimental or other scientific use	-

5. Referral (tick box)

APC	Cosmetics	-
	Tobacco	-
	Microsurgery	-
	Wild-caught primates	-
	Hominoidea	-
	Substantial procedures in primates	-
	Other	N
Internal/second opinion		N
External assessor		

6. Brief overview of project (2 sentences maximum, giving context and stating why the work is worth doing)

In view of the tremendous shortfall in the supply of organs for transplantation it is appropriate to examine the potential use of pigs as donors; this project will address the hurdles that must be overcome before this can be achieved - notably hyperacute rejection. The crisis in organ supply for transplantation is so acute that xenotransplantation offers the best chance of an early radical solution to the problem.

7. Species justification (tick box) (18)

	Cat	Dog	Equidae	Primate		Endangered species	Animal taken from wild
				OW	NW		
Availability of background data							
Required by regulatory authority							
Best model for human responses							
Condition studied is species specific							
Other (specify)							

8. Use of neuromuscular blocking agents (Y or N) (18, 19) N

9. Overall severity (tick box) (20)

Substantial	-
Moderate	✓
Mild	-
Unclassified	-

10. Signature of inspector [REDACTED] Date 20 FEB 2003

PPL ASSESSMENT PROFORMA

(4)

[REDACTED]			
UK resident		Y	
Knowledge of this area of work		Y	[REDACTED] is an experienced personal and project licence holder.
Experience of this area of work		Y	
Training modules (or equiv)	1, 2, 5	Y	The work will be funded by a grant [REDACTED]
	3, 4	N	
Experience as PIL-H		Y	
Senior member of workgroup		Y	
Experience as PPL-H		Y	
Access to resources/funding		Y	
Commitment to 3Rs		Y	
Commitment to manage project		Y	
Deputy (11a) (11b)		Y/N	Reason: [REDACTED]
Knowledge of delegated area of work		Y	[REDACTED] is an experienced personal licence holder. [REDACTED] has been the surgeon for all of the procedures under the current licence.
Experience of delegated area of work		Y	
Training modules (or equiv)	1, 2, 3	N	
	4	N	
	5	Y	
Experience as PIL-H		Y	
Senior member of workgroup		Y	
Deputy (12a) (12b)		Y/N	Reason: [REDACTED]
Knowledge of delegated area of work		-	[REDACTED] is an experienced personal licensee and has a veterinary qualification.
Experience of delegated area of work		-	
Training modules (or equiv)	1, 2, 3	-	
	4	-	
	5	-	
Experience as PIL-H		-	
Senior member of workgroup		-	
Primary availability (13a)		Y/N	Reason: [REDACTED]
Suitability of facilities		Y	Both the staff and facilities are satisfactory for this type of work.
Suitability of staffing		Y	
Secondary availability (13a-o)		Y/N	Reason: [REDACTED]
Suitability of facilities		-	
Suitability of staffing		-	
PODE availability (13)		Y/N	Reason: [REDACTED]
Adequate description of location		-	
Identified 19b protocols at PODE		-	
Duration (16)		Y/N	Reason: [REDACTED]
Less than 5 years		5	
Appropriate		Y	
Background (17)		Y/N	Reason: [REDACTED]
Account of current state of knowledge, products or services	Full	Y	In view of the tremendous shortfall in the supply of organs for transplantation it is appropriate to examine the potential use of pigs as donors. This project will address the hurdles that must be overcome before this can be achieved - notably hyperacute rejection.
	Balanced	Y	
	Up-to-date	Y	
General aims	Clear	Y	
	Valid	Y	
Basis for objective(s) eg working hypothesis	Clear	Y	
	Valid	Y	

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		Y/N	Reason
Specific		Y	To test a strategy for the prevention of hyperacute rejection by the inhibition of coagulation mechanisms using novel genetic constructs introduced into allograft endothelial cells; To develop and appraise a non-invasive method for visualising endothelial cell activation and renal blood flow; To assess the contribution <i>in vivo</i> of phagocyte recognition of xenogeneic tissue to graft rejection; To determine, in principle, the possibility of rendering porcine spermatozoa transgenic by introducing DNA into the testis.
Well-defined		Y	
For permissible purpose	a	1	
	b	-	
	c	-	
	d	-	
	e	-	
	f	-	
	g	-	
Potential benefit (17)		Y/N	Reason
Outputs of programme well-defined		Y	The crisis in organ supply for transplantation is so acute that xenotransplantation offers the best chance of an early radical solution to the problem.
Use of outputs of programme explained		Y	
Significance of outputs of programme credible		Y	
Plan of work (18)		Y/N	Reason
Overview of strategy	Clear	Y	The <i>in vivo</i> pig allograft model will be used. Control and genetically modified tissues (arteries and whole kidneys) will be transplanted to assess the development of hyperacute rejection. In addition, non-invasive methods of assessing renal blood flow will be investigated using contrast agent ultrasound techniques. The possibility of rendering porcine spermatozoa transgenic by the injection of DNA into the testis will also be investigated.
	Valid	Y	
Special justifications	Clear	Y	
	Valid	Y	
Design of plan	Clear	Y	
	Valid	Y	
Design of protocols	Clear	Y	
	Valid	Y	
Special justifications (18)		Y/N	Reason
Additional availability	Designated establishment	-	
	PODE	-	
By species	Cat	-	
	Dog	-	
	Equidae	-	
	Primate	-	
	Endangered species	-	
By origin	Schedule 2	-	
	Cat	-	
	Dog	-	
	Primate	-	
	Wild	-	
By history	Continued use	-	
	Re-use	-	
By procedure	Use of NMBA	-	
	Release to the wild	-	
	OW primate in toxicology	-	
Design of plan (18)		Y/N	Reason
System mechanics or operation	Replication	Y	Group sizes and repetitions have been determined by statistical evaluation. Between five and fifteen pigs will be necessary for each experimental group in order to achieve statistically significant results, depending on the experimental end-point.
	Randomisation	Y	
	Local control	Y	
Group number	Factors	Y	
	Levels	Y	
Group size	Power analysis	Y	
	Other	Y	
Description of biologicals production	Process	-	
	Efficiency	-	
	Final product	-	
Group size set by efficiency		-	

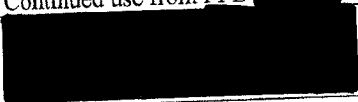
PPL ASSESSMENT PROFORMA

OECD, ICH guideline or similar	-										
Group size set from guideline	-										
Other (state)	-										
Satisfactory method for group size (describe)	-										
<b>Design of Protocols (18, 21)</b>	1	2	3	4	5	6	7	8	9	0	
No reasonably practicable alternative to use of living animal	Y	Y	Y	Y	Y	Y	Y	Y	Y		
Most likely to produce satisfactory results	Y	Y	Y	Y	Y	Y	Y	Y	Y		
Minimum number of animals	Y	Y	Y	Y	Y	Y	Y	Y	Y		
Lowest degree of neurophysiological sensitivity	Y	Y	Y	Y	Y	Y	Y	Y	Y		
Least pain, suffering distress or lasting harm	Y	Y	Y	Y	Y	Y	Y	Y	Y		
Schedule 2A compliant	1	2	3	4	5	6	7	8	9	0	
<b>Specification of Protocols (19)</b>	Y	Y	Y	Y	Y	Y	Y	Y	Y		
Short title suitable	Y	Y	Y	Y	Y	Y	Y	Y	Y		
Severity limit suitable	Y	Y	Y	Y	Y	Y	Y	Y	Y		
Species, stage of development and number/year adequately specified	Y	Y	Y	Y	Y	Y	Y	Y	Y		
PPL details for animals bred or used under licence adequately specified	Y	Y	Y	Y	Y	Y	Y	Y	Y		
Regulated procedures adequately specified	Y	Y	Y	Y	Y	Y	Y	Y	Y		
Adverse effects and likely incidence adequately specified	Y	Y	Y	Y	Y	Y	Y	Y	Y		
Methods of prevention or control of adverse effects adequately specified	Y	Y	Y	Y	Y	Y	Y	Y	Y		
Fate adequately specified	Schedule 1 kill	Y	Y	Y	Y	Y	Y	Y	Y		
	Non-schedule 1 kill	Y	Y	Y	Y	Y	Y	Y	Y	N	
	For continued use, re-use	N	N	N	N	N	N	N	N	N	
	For release from control of the Act	N	N	N	N	N	N	N	N	N	
<b>Estimated numbers by severity limit (19)</b>	U/C	Mild	Moderate	Substantial							
Birds, fish, reptiles, rabbits, rodents		6	211								
Farm animals											
Cats, dogs, equidae											
Primates											
CITES species											
Other											
<b>Comments on assessment of likely benefits</b>											
The crisis in organ supply for transplantation is so acute that xenotransplantation offers the best chance of an early radical solution to the problem.											
<b>Factors taken into account</b>										Y/N	
Potential benefits										Y	
Likelihood of production of satisfactory results										Y	
Suitability of applicant										Y	
<b>Comments on likely severity</b>											
It is essential to use the pig as a model as this is the species being considered for clinical use. To minimise the number of animals required and the invasiveness of the procedure, before attempting renal transplantation experiments, the question of rejection will be studied in the carotid artery. By attempting to develop a technique for the production of transgenic animals by testicular injection, the number of animals and invasiveness of the procedure will also be reduced.											
<b>Factors taken into account</b>										Y/N	
Severity of protocols										Neurophysiological sensitivity	Y
										Proportion of animals by severity	Y
										Duration of exposure to severity	Y
Weighting of protocol by number of animals										Y	
<b>Overall severity (20)</b>											
Unclassified										-	
Mild										-	
Moderate										Y	
Substantial										-	

## PPL ASSESSMENT PROFORMA

In my opinion, the potential benefits outweigh the cost to the animals and this project should be granted.

Balance of likely benefit and likely severity (tick)	Positive	√
	Uncertain	-
	Negative	-

Recommendation		Y/N	Details
Internal referral		N	
2 <sup>nd</sup> availability		N	
Changes made to application		Y	
Grant licence		Y	
Duration			
Overall severity	Unclassified	-	
	Mild	-	
	Moderate	Y	
	Substantial	-	
Additional conditions		Y	Continued use from PPL
Signature of Inspector			
Date			20 FEB 2003.