PPL Therapeutics (NZ) Ltd
Whakamaru
Main Road
R.D.1
Mangakino
New Zealand

Tel (07) 882 8543
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6 December 2000

ERMA NZ
20 Customhouse Quay
PO Box 131
WELLINGTON

Attention: [illegible] – Applications Officer

ANNUAL REPORT TO THE ENVIRONMENTAL RISK MANAGEMENT AUTHORITY (ERMA) ON COMPLIANCE WITH THE CONTROLS LAID DOWN IN THE AUTHORITIES DECISION ON GMF98001 DATED 24TH MARCH 1999

Statement:

"PPL Therapeutics (NZ) Ltd has at all times complied with the controls laid down in the ERMA Decision to approve the application "GMF98001 with Controls" on the field test (maintain a manufacturing ewe flock of) transgenic sheep for the purposes of producing a biopharmaceutical (human alpha-1-antitrypsin, hAAT)."

In support of this statement please find the following documents: -

- Appendix 1 – AgriQuality 6-monthly audit report on PPL Therapeutics (NZ) Ltd. This document addresses the specific areas identified in MAFR Standard 154.03.06 section 4.13 which you request comment on. Next audit is due 21 December 2000. 2001
- Appendix 2 – Copy of a corrective action issued during the year.
- Appendix 3 – Breakdown of numbers of transgenic animals on site.

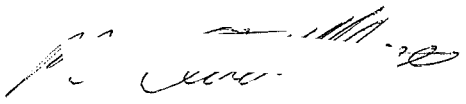
[illegible] and [illegible] ERMA on the 11th October 2000 and spoke with [illegible] and [illegible] We updated them on progress to date, revised breeding programs future, the partnering agreement with Bayer and how this agreement may affect future timetables.

One other event of note was a vehicle accident, which damaged the perimeter fence. A copy of the report to MAF is also included for your information
(Refer Appendix 4).

Also for your information I include a copy of the Bayer Collaboration announcement.

- Appendix 5 – 1 x Bayer announcement, copy of.

Yours sincerely



FARM MANAGER

AgriQuality New Zealand Limited
Huarangi Aotearoa

MA file.

Appendix 1

1046 Rangiuru Street
PO Box 951, Rotorua
Telephone +64 7 349 9720
Facsimile + 64 7 349 9739

26 June 2000

MAF Biosecurity Authority
Box 2526
Wellington

Six Monthly Audit: PPL Therapeutics (NZ) Ltd Registered Sheep Transitional Facility, Whakamaru

As per MAFRA Standard 154.02.02.01, attached is the six monthly audit report for the above facility undertaken on 20 June 2000.

1.0 Primary Facility

1.1 Livestock Tally

Livestock at 14/12/99			
Sheep	104		
Sentinel Goats	8		
Total Stock		**112**	
Livestock Introduced (14/12/99 - 20/06/00)			
Sheep	0		
Sentinel goats	0		
Total additions		**0**	
			112
Less deaths (14/12/99 - 20/06/00)			
Sheep	10		
Sentinel goats	8		
Total deaths			**18**
Livestock on books			**94**
Physical count (20/06/00)			
Sheep		94	
Sentinel Goats		0	
Total livestock			**94**
Discrepancy			**0**

1.2 Comments

- 8 sentinel goats euthanased at 3 years into quarantine period. No evidence of scrapie following histological examination of brain tissue (Ruakura AHL Case Numbers R00085024 to R00085031 inclusive).

- 9 'Original Imports' were euthanased as surplus to requirements. No evidence of scrapie on histological examination.

- 1 non exotic ewe died. Postmortem examination indicated septicaemia as probable cause of death.

- Some transgenic exotic ewes are being milked with the intent of sending frozen milk to UK for trial purposes.

1.3 Genetic Material

1.3.1 Imported Ram Semen

Physical count (05/05/99)

Ram 10122	106	
Ram 10141	146	
Total		**252**

Discrepancy **1**

Physical count 02/02/00

Ram 10122	106 straws
Ram 10141	146 straws
Ram 10141	1 straw (in bottom of tank)
	253

All imported semen straws destroyed by incineration 02/02/2000.

1.3.3 Lymph Node material

- The balance of imported lymph node material is still held frozen within the primary quarantine facility.

2.0 Secondary Facility

PPL's Secondary quarantine facility was approved on 23 March 1998 as a Transitional Facility under section 39 of the Biosecurity Act 1993.

2.1 Livestock Tally

Livestock at last audit (14/12/99)			
Sheep	1224		
Total		**1224**	
Livestock Introduced (14/12/99 - 20/06/00)			
Sheep (purchased / transferred)	1697		
Sheep (born)	236		
Total Additions		**1933**	
			3157
Less deaths (14/12/99 - 20/06/00)			
Exotic sheep euthanased	56		
Exotic sheep died	12		
Non exotic sheep euthanased	243		
Non exotic sheep died	18		
Total deaths			**329**
Livestock on books			**2828**
Physical Count (20/06/00)			**2828**
Discrepancy			**0**

2.2 Corrective Action Issued

An exotic 18 month ram (PPL 98T 4246) was euthanased in May 2000 because of severe respiratory distress and a post mortem carried out. However, during an AgriQuality NZ 2 weekly inspection, it was found that no tissues were submitted for exotic disease examination. This is contrary to MAFRA Standard 154.02.02 and as a result, a corrective action request was issued (attached). This appears to be an isolated case and was attributed to 'human error'.

2.3 General Comments

- Post mortem reports on exotic and non exotic animals that died or were euthanased on management / welfare grounds indicated a range of conditions which are common in New Zealand. No evidence of exotic disease was found.

3 Supervision in relation to ERMA

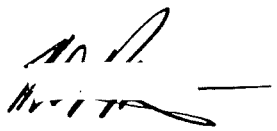
ERMA approved on 17 March 1999 PPL's application to field test (maintain a manufacturing flock) of transgenic sheep for the purposes of producing a biopharmaceutical (hAAT) in the Waikato region, subject to certain controls (Application GMF98001). Examination of the facility and records indicated compliance with ERMA controls.

4 General Comments

- Management of both primary and secondary quarantine facilities including livestock, record keeping and structural maintenance continues to be of a high standard. The non conformance detected appears to be an isolated instance.

5 Acknowledgements

The assistance of and his staff at PPL Therapeutics Whakamaru during this audit is acknowledged.



AgriQuality New Zealand Ltd
Rotorua

cc PPL Therapeutics NZ Ltd

Appendix 2

1046 Rangiuru
PO Box 951, R
Telephone +64 7 34
Facsimile + 64 7 34

19 May 2000

Tokoroa and District Veterinary Services
Box 182
Tokoroa

Dear

Quarantine Postmortems at PPL: Nonconformance Issue

Following an inspection of records at PPL Therapeutics Ltd, Whakamaru on 16 May 2000, a non-conformance was detected to the postmortem standards as detailed in MAFRA Standard 154.02.02 (Standard for Sheep and Goat Quarantine Facilities). The table on page 40 of the Standard summarises actions required

Ram (PPL 98T 4246) which was euthanased on 28 March 2000 because of severe respiratory problems and non response to treatment. Although a postmortem was carried out, no tissues were submitted for laboratory examination. The animal was classified as an 'exotic' and was over 12 months of age. Scrapie examination was thus required by submitting fresh and fixed brain tissue. In addition, if consolidation of the lung is observed, then fresh and fixed samples of lung and lymph node are to be submitted to the laboratory for Visna/maedi and Jaagsiekte testing. The nasal septum is also to be examined and if lesions suspicious of nasal adenocarcinoma are seen, fresh and fixed samples are to be sent for laboratory examination.

Could you please ensure that this standard is complied with in future and advise any staff involved with PPL of the requirements.

Yours faithfully

Veterinarian

cc **Manager, PPL Therapeutics Ltd, RD, Whakamaru**

Appendix 3

NUMBER OF TRANSGENIC ANIMALS AT PPL NZ ON 03 DEC 00

Born 1997	45
Born 1998	71
Born 1999	80
Born 2000	449
Born 2000 Unconfirmed transgenic	489
TOTAL	**1134**

Subject: Re: Fence break
Date: Thu, 26 Oct 2000 08:32:53 +1300
From: "K [illegible] nz>
To: <a.m.aitkenhead@xtra.co.nz>

Many thanks for the notification and prompt repairs. I will add your report to the file.

>>> A [illegible]@xtra.co.nz> 25/10/00 20:26:40 >>>
K h

This is to notify you of a motor accident on SH 32 which resulted inthe
SQF perimeter fences being broken.
At approx 1200hrs onWed the 25 Oct a light commercial vehicle lost
control and went through both perimeter fences into paddock 119 .The
accident was witnessed by a staff member (MR G Webber) and farm staff
were on hand within minutes. NO stock were in the paddock or any
adjoining paddocks.
After untangling the vehicle it was able to be driven out through the
hole and fence repairs were instigated immediatly
There were no injuries and the scene was investigated by constable Mike
Hudson of the Mangakino police.
Fence repairs were completed by 1830hrs the same day.

Regards

Appendix 44

Appendix 5

Date: Wednesday 16 August 2000

Contacts:

PPL Therapeutics plc
Telephone: + 44 (0) 131 440 4777

[illegible]

[illegible]: + 44 (0) [illegible]

PPL Secures Collaboration Deal for AAT and announces Interim Results

PPL Therapeutics (PPL), one of the world's leading companies in the application of transgenic technology to the production of human proteins for therapeutic and nutritional applications, is pleased to announce a collaboration agreement with Bayer Corporation for the development of its lead product, Alpha-1-Antitrypsin (AAT), together with its interim results for the six months ended 30th June 2000.

The key new points are:

- A collaborative partnership for AAT which provides for:
  - Bayer to make an upfront US$15m (£10m) equity investment and fund clinical trials
  - The payment to PPL of US$25m on the achievement of certain milestones
  - PPL to earn significant future royalties and manufacturing revenues
- Gearing up for AAT Phase III trials
- Toxicology underway to support further BSSL trials
- Potential for improved formulation for Fibrin Sealant
- Discussions with potential corporate partners for xenografts underway

anaging Director of PPL, commented:

"These developments mark an important turning point for the group. PPL's AAT programme has now been validated by this collaboration which provides a clear route to market. The next two products in PPL's pipeline continue to make progress, and there is recognition of the value in PPL's xenograft project."

Agreement with Bayer

PPL and Bayer announce today that they have signed a worldwide licensing agreement to develop recombinant replacement therapies for $alpha_1$-antitrypsin (AAT) deficiency-related emphysema and for cystic fibrosis. PPL and Bayer will collaborate initially to conduct a placebo-controlled Phase III efficacy study for AAT deficiency, and ultimately to manufacture and commercialise an aerosol formulation of transgenically-produced recombinant AAT (rAAT) globally. PPL and Bayer will also collaborate on development of aerosol rAAT in a second clinical indication, cystic fibrosis.

Under the agreement, Bayer Biological Products will be responsible for, and bear the costs of, clinical development and marketing, and PPL will be responsible for exclusive product manufacturing. Bayer will make an up front investment of US$15 million in purchase of PPL equity at £2.15p share. PPL also will receive a string of milestone payments totaling US$25 million as progress is made in registering these indications and in driving sales growth. Of this, a total of $15

million will be paid up to, and at the time of, approval of the product for AAT deficiency-related emphysema. In consideration of its clinical development of rAAT to date and its ongoing production responsibilities, PPL Therapeutics will receive production revenues and royalties on product sales.

Martyn Breeze, Commercial Director of PPL, said: "This agreement is a strong affirmation of the value of PPL's technology and is expected to provide a significant revenue stream in the coming years. Bayer is the best possible partner for this product. It is already in the congenital deficiency market with its plasma-derived AAT, Prolastin®. The combination of this presence together with Bayer's technical knowledge of the field will allow us to meet future patient needs in this growing market."

Jan Turek, Senior Vice President and General Manager of Bayer's Biological Products Global Business Unit, said: "For Bayer, this agreement is the first step in greatly increasing AAT supply and convenience to patients. Bayer's commitment to this therapeutic category, combined with PPL's recombinant AAT technology, is a natural collaboration for future advances. The Bayer/PPL co-operation puts us squarely in the forefront of the development of a recombinant replacement therapy in an aerosol formulation, and represents a significant development for the company. We are eager to begin the Phase III trial in Q4 2000."

AAT deficiency is a potentially lethal hereditary disease affecting more than 200,000 people worldwide. The clinical development of emphysema due to AAT deficiency is characterized by shortness of breath, wheezing, coughing, and recurrent lung infections. Bayer's Prolastin® is given i.v., and is currently the only available product for chronic replacement of AAT in congenitally AAT-deficient patients with clinically demonstrable panacinar emphysema.

An aerosol formulation of rAAT would be delivered directly to the lungs via a nebulizer. The formulation is expected to provide improved patient convenience and compliance. A recent survey conducted by Bayer indicated that more than 80% of patients would prefer daily aerosol delivery. In addition, the transgenic source will increase supply of the product, making replacement therapy available for more AAT-deficient patients. As much as 1.5 million grams per year may be required for treatment of this condition, a volume that PPL will to be able to produce using transgenic animals.

Ron James, Managing Director of PPL Therapeutics said: "The terms of this agreement validate PPL's strategy to use its expertise to become involved with manufacture as well as drug development. Taken together the royalties and production revenues equate to a substantial share of end product sales."

In February, PPL announced that it had agreed in principle to a funding package to build a production facility in Edinburgh to purify large-scale quantities of its rAAT. One of the conditions for this funding was that PPL secure an arrangement with a major pharmaceutical company for marketing of rAAT. Today's announcement represents the fulfillment of that condition.

PPL will shortly seek formal approval from shareholders for the disapplication of pre-emption rights to allow the allotment of new shares to Bayer, and will at the same time seek formal approval from shareholders to commission the building of the production plant.

Notes

Bayer Corporation is a research-based company with major businesses in health-care, life sciences and chemicals. The company had 1999 sales of $8.9 billion and employs approximately 22,200 people. Bayer Corporation is investing $9 billion in capital expenditures and research and development from 2000 through the year 2004. 2000 capital investment and R&D expenditures are projected to total $1.6 billion. Bayer Corporation, with headquarters in Pittsburgh,

Pennsylvania, is a member of the worldwide Bayer Group, a $29 billion international life sciences, polymers and specialty chemicals group based in Leverkusen, Germany.

AAT deficiency is characterized by low or no levels of AAT in blood cells. AAT protects the body from an enzyme found in white blood cells that may cause damage to the air sacs in the lungs. Lack of this protection substantially increases the risk of emphysema in adults. Many symptomatic patients die from pulmonary causes in their 5th and 6th decades of life.

The World Health Organization stated in a 1997 report that AAT deficiency is one of the most prevalent, potentially lethal hereditary diseases. It is currently often overlooked by health care professionals, resulting in a high number of undiagnosed cases. Many individuals who have AAT deficiency often do not have symptoms of the disease. AAT deficiency is easily identifiable by a blood test done by a physician and the disease can be managed through therapy.

Cystic Fibrosis is a disease caused by a single gene defect in the CFTR gene. One result of this genetic defect is that patients accumulate viscous mucus in their lungs which tends to harbour bacteria which, from time to time, multiply to the point where the patient is clinically infected. Some of these infections (known as exacerbations) are life threatening and require hospitalised intravenous antibiotic treatment. The body's own response to infection is to flood the infected area with neutrophils (white blood cells) which combat infection. One of the actions of neutrophils is to release large quantities of a protease called elastase. Excess elastase causes a progressive degradation of the lung tissue which reduces lung function to the point where patients cannot get the oxygen essential to support life and death results. AAT complexes with the elastase and this is believed to reduce the damage to the lung tissue.

Interim Statement

The PPL Group (Group) is continuing to apply its resources predominately to progress its four lead products, while supporting a limited number of feasibility studies and enabling research which have the potential to add near term value and extend the Group's product pipeline.

Inevitably, a significant proportion of the Group's effort in the review period has been directed towards negotiating deals with prospective collaborative partners for Alpha-1-Antitrypsin (AAT) which has culminated in today's announcement. Significant progress has also been made in other areas.

AAT

The announcement in February 2000 of the positive results of the Phase II trials of intravenous and inhaled administration of AAT in AAT deficient patients (fully reported in the 1999 Annual Report), coupled with the announcement two weeks later that PPL had secured an 'in principle' funding package to build in Scotland its large scale production facility to purify AAT, brought about the anticipated revival of interest from prospective collaborative partners for AAT. The process since then has been one of refining a short list, undergoing a detailed and exhaustive examination of past development and future capabilities by the preferred collaborative partner and agreeing a deal structure that we believe will deliver shareholder value.

Two AAT clinical trials are still ongoing: the long term (1 year) safety study of 250mg daily of AAT delivered by nebuliser to Cystic Fibrosis patients, an interim analysis of the results of which was given in the Annual Report; and the deposition study which seeks to compare the efficiencies of different nebulisers. The final results of both studies are expected in Q3 2000. Preliminary results of the deposition study have already been compared with similar studies recently carried out on Prolastin™ by Bayer AG, and will aid the decision on which device to use in Phase III trials later this year.

Additional staff have been recruited into the pilot production plant and quality control in anticipation of producing additional supplies of product for the Phase III trials, and in Assay Development to validate the numerous assays to be used in monitoring production and in evaluating clinical samples collected from patients. The first milk from PPL's AAT production flock in New Zealand has been sent to Scotland for check processing. Ongoing dialogues with US and European Regulatory Agencies by PPL and separately by Bayer will now be combined as the final trial design is agreed.

A preliminary review of other indications which could benefit from AAT therapy will be followed up as resources allow.

Bile Salt Stimulated Lipase (BSSL)

The successful outcome to a Phase II proof of concept study of the ability of BSSL to release fats from lipids in adults with pancreatic insufficiency was announced in April 2000 and again fully reported in the 1999 Annual Report.

Purification process development and sheep breeding is continuing and has already produced sufficient BSSL for the necessary pre-clinical (toxicology) studies which will allow longer term clinical trials in adults and ultimately in pre-term infants.

Further single dose studies in adults to refine the required dose level are planned for later this year with a longer adult trial targeted for 2001.

Fibrinogen

Smith and Nephew's work on an orthopaedic product is progressing well.

PPL has held discussions with the FDA concerning potential clinical trials with its wholly recombinant fibrin sealant produced by the catalytic action of cell culture produced Factor XIII and Thrombin on its sheep produced Fibrinogen. These discussions have resulted in the need to either reformulate the product or to re-derive one of the cell culture components. Re-deriving a component would introduce unacceptable delays into this programme, so, PPL is now in negotiation to acquire alternative technology which, if successful, will still allow a fibrin sealant/haemostat to be produced within the timescales previously envisaged.

Xenografts

The announcement that PPL's US subsidiary had produced the world's first cloned pigs (14 March 2000) heralded a resurgence of interest by potential corporate partners in PPL's xenograft programme. A corporate partner would be preferred to the alternative of a venture capital backed spin-out company, because it would leave ownership of the technology in the hands of PPL's shareholders, but the Board also recognises the need to provide independent funding for this project sooner rather than later.

On the technical front, the individual steps which make up the new method used to clone the pigs are being optimised, and several approaches are being made to knock out the enzyme (α1-3 galactosyl transferase (α1-3 GT)) primarily responsible for hyperacute rejection of unmodified pig organs by humans, alongside negotiations to acquire rights to corresponding intellectual property. Genetically modified mice have been produced to further test some of the strategies developed to overcome rejection.

PPL continues to monitor the safety issues surrounding xenotransplantation but is unaware of any new data which raises new safety concerns.

Other Projects

Some of the enabling research mentioned above is directed at improving PPL's peptide production technology, and the Group is in discussion with a number of companies concerning feasibility studies on a variety of peptides. We have been requested to keep the details confidential unless and until they progress to full scale contracts.

Financial Review

Revenues for the half-year were £0.3m, operating expenses were £6.4m and the net loss for the period was £5.9m after net interest received of £0.2m. The decrease in the loss over the comparable period in 1999 was £1.2m and was primarily due to reduced costs following the restructuring of activities in November 1999, reflecting the Group's focus on its near market products.

Capital expenditure in the period was £0.2m.

Net cash outflow for the six months to 30 June 2000 totalled £3.7m leaving cash and cash equivalent balances of £8.0m at the end of the period. Net assets were £21.0m.

The injection of new funds from Bayer will reduce the pressure for near term funding but the Board will continue to assess its options in the light of possible further developments, including any future collaborations, anticipated expenditure and stock market conditions. This may lead the Board to conclude that a further equity funding in the next twelve months would be appropriate.

Year 2000

To date, the Group has experienced no major 'Millennium Bug' problems either with its own or third party systems. Whilst it is believed that any future such failures are becoming increasingly unlikely, the Directors continue to believe that the Group remains at an acceptable state of readiness for any issues that might arise and that any associated costs would not be significant.

Future Prospects

The past four months have been demanding for PPL's management and staff alike, but the Group now stands on the brink of potentially the most fruitful phase yet of its development into a profitable biotechnology company. We are excited about our future.

Ron James
Managing Director
16 August 2000