



Minutes

Date Wednesday, 07/04/2021

Time 09.00am

To Committee Members

At Virtual via Microsoft Teams

Subject AWERB 3Rs Committee

In Attendance:

[REDACTED]

1. Minutes

The previous minutes were approved

2. Matters Arising

[REDACTED] asked for an update of re use of needles. [REDACTED] has no update yet

3. Retrospective Reviews

- **Change of PPLh** - [REDACTED] - The development of rodent cancer models and their pre-clinical use as a platform for drug development and drug evaluation.

The 3Rs committee note that the filling in of this Retrospective Review is part of the PPL name change process. The licence was only granted at the end of January 2021. Thank you for engaging with the process. This Retrospective Review raises no concerns.

- [REDACTED] - Prevention of chronic heart failure
- The 3Rs committee would like to highlight the need for more attention to detail throughout the form. In particular the following sections
 - 2.1 – The numbers do not add up in the table.
 - 2.11 – No source of the animals is given.
 - 3 – The 3Rs answers would benefit from more elaboration, please. Especially 3.8 considering the use of AKITA mice on this PPL.
 - 4.8 – Were there no presentations at meetings? Considering the commendable number of publications?
 - Please make sure that where Yes/No answers occur, that the correct answers are highlighted where necessary.
 - 2.10 – please could clarity be given on whether or not the AKITA mice were indeed bred by the group, and if so under which PPL authority as this one does not contain breeding and maintenance protocols? Should there also be answers in sections 2.7 and 2.8?
 - 2.13 – the 3Rs committee would like to query the answer given here. It would seem that it was quite appropriate to the amend protocol 1 to “severe” as there continued to be animals experiencing severe severity on this protocol in increasing numbers per



subsequent years. The percentage is not relevant, as no animal should experience higher severity than the protocol banding.

- 2.13/ 5.2 – Following on from above, were there not any Standard Condition 18 reports filed for those animals that experienced severe severity on protocol 1 before the licence was amended, and also for those that experienced severe severity on protocol 2?
- 3.1 – the breeding of the “milder genetic model” would be considered a refinement, not a replacement, therefore this information belongs in section 3.7.
- 4.3 – the 3Rs committee were quite concerned to read that MitoSNO failed at the large animal model. The committee strongly urge the group to consider the suitability of their mouse model for its translational and scientific validity. This was a key concern for the 3Rs committee.

4. Amendments

- [REDACTED] - Regeneration in the nervous system – SS Amendment

Substance administration by the Retro-Orbital route

- The 3Rs committee were surprised to receive an amendment asking to re-approach the use of the retro-orbital sinus. Many present had first-hand experience of how adverse it can be and supported the move by UBS away from this practice years ago.
- The 3Rs committee do not support the justification provided in the letter to the Home Office Inspector – figure 1 was not considered a good example of comparable images to demonstrate the point being made, and the interpretation of the Steel et al, 2008 paper was not agreed with.
- The technical aspect of the argument was also disputed by the 3Rs committee:
 - The committee recognise the technical difficulty and increased adverse effect rate of retro-orbital venous access in adult mice and rats, and the justification provided did not reassure as to how the group would overcome this difficulty in neonates.
 - The committee did not agree with the adverse effects and risk levels put forward regarding tail vein injection – UBS can provide skills support for either the procedures themselves or training.
 - The committee would like to know whether or not anyone in the group currently has the competence for retro-orbital venous access i.e. is this amendment written from first-hand experience, if not, how does the group intend to gain this competence?
- The 3Rs committee would like the group to consider whether this procedure would result in a reduction of animal usage, as the committee were not convinced that it constitutes a refinement.
- Did the group intend to have transgene inducing agents also being given by this route (protocol 7) – as tamoxifen could likely result in worse adverse effects than AAV, and would a maximum of 2 injections be appropriate for a transgene inducing agent dosing regimen?

Protocol 21: “Jimpy” mice

- The 3Rs committee would like the proposed amendment to clearer as to whether or not the germline or inducible model is to be used. This should then make the adverse effects and expected life experience of the mice easier for the AWERB to assess.
- The breeding and maintenance of these mice (Steps 1 and 2) would need to be a separate breeding protocol – could this be done under protocol 5 or 6?



- The 3Rs committee appreciate that seizures lasting up to 120s have been granted in the licence. Please re-consider whether or not the science in this protocol is still valid; that an animal is allowed to seizure for this long. The committee also question the appropriateness of twice a day checks to monitor for spontaneous seizures.
- The 3Rs committee note that tail tipping in neonates has been granted in the licence, but please assess the need for it in this protocol and with these mice.
- The 3Rs committee strongly encourage palatability pilot testing of all compounds to be put in drinking water before embarking on full studies.
- The 3Rs committee feel that this part of the amendment would hugely benefit from the addition of details of a “typical experiment” - to highlight the breeding strategy considering the X-linked mutation, the mouse experience of the mutation and of the protocol steps.

Please proof-read the whole amendment for typographical and grammatical errors, especially e.g., “creET2” and “creERT2” – are these two lines, or a typographical error? Please note that the Non-Technical Summaries (of note for now, the amendment summary) are not in lay language. Please write these as you would for a newspaper article i.e., for someone of a reading age 12.

- [REDACTED] – Ageing and therapy in mouse models for neurodegenerative diseases – Change of PPLh to [REDACTED]
- The 3Rs Committee wish [REDACTED] all the best for her new job in The Netherlands.
- The 3Rs committee were hugely impressed and encouraged by [REDACTED] conscientiousness and careful consideration into taking on the responsibility of holding a project licence. The committee offer her their full support and recognise the support from her group and from UBS. Good Luck, [REDACTED]

5. MTA Update

6. Secretariat reviews

7. 3Rs information/reports

8. Feedback from previous Retrospective Reviews*

None

9. Highlights of January & February AOC meeting*

10. Highlights of AWERB January & February Standing & Sub Standing meeting*

11. Any Other Business

- [REDACTED] intro to use of CFA in EAE mice.



The committee recognised key problem areas:

- The volume – they are giving more than [REDACTED] would expect – is that intended/ part of the recurrence of the problem?
- The site – the injection location has been refined by being given on the top of the hips, not on the side of the flank.
- The composition – commercially it is less viscous, so needs wiping away after needle withdrawal as causes ulceration. [REDACTED] taught them how to make it themselves to be more viscous.
- The passing on of skills – SOPs, training and competency records and any other procedural documentation should be assessed, so that these skills are transferred through the team.
- What is the clipped patch in the photo? Check that the mouse was not over grooming to begin with.
- The purpose – it was a previous misconception that the ulceration was needed in order to get the model to work. This way of thinking was successfully changed

The 3Rs committee were surprised that this mouse had been allowed to progress this far.

[REDACTED] kindly offered hers and [REDACTED] support to [REDACTED] from Level 2.

The 3Rs committee asked for guidance documentation from [REDACTED] for future use and access on the 3Rs website.

- The committee discussed in length the UBS website and the changes that will be coming to it in the near future. The committee were asked for their opinions and suggestions. It was suggested that the front page be updated/refreshed regularly. A link to MCMS be put on there and less is hidden behind the Raven log in. All these suggestions will be taken to the UBS website working group.

Date of next meeting: Wednesday 5th May 2021

***Items for information only unless un-starred by committee member**