AUT-F0476	FORM
VERSION 2	EFFECTIVE DATE 7 MARCH 2019

EVALUATION RECORD FOR REVIEW OF RETROSPECTIVE ASSESSMENT

PROJECT AUTHORISATION NUMBER	[redacted]
CASE NUMBER	[redacted]
PROJECT TITLE	**DETERMINATION OF THE POTENCY VALUE FOR [redacted] BOTULINUM TOXIN PRODUCTS USING THE MOUSE POTENCY ASSAY**
PROJECT MANAGER	[redacted]

A. ANIMAL NUMBERS AND SEVERITY

1. Comment on whether the animal numbers differed from the original project authorisation and the reasons for this.

31,200 mice were originally approved for use under this authorisation, and to date only 3,001 have been used. Testing is still ongoing under this authorisation, and the applicants have submitted a renewal to extend testing beyond the current date of expiration of the authorisation, which is [redacted] Therefore, additional animals will be used in future under this authorisation.

2. What was the actual overall severity of the project and was this as predicted in the original project evaluation? If there was a difference, can you identify any reasons for this?

Overall severity was severe as predicted. However, the percentage of animals that experienced an actual severity of severe was higher than anticipated – 40% were predicted to experience an actual severity of severe since this testing was being performed without humane endpoints being implemented (these have not yet been validated for this product). However 68% of the 3,001 mice used to date have been reported as experiencing an actual severity of severe. The reason for this increase above what was predicted is that this testing had been moved from a CRO in [redacted], and during the first two studies performed at [redacted], the potency of the test item was found to be much higher than expected based on previous results from the [redacted]

B. IMPLEMENTATION OF THE 3RS

3. Detail any elements identified that may contribute to the further implementation of the 3Rs, should similar work be conducted in future.

Replacement

The sponsor is currently working on the development of a CBPA, however it is estimated that regulatory acceptance for this assay and its use in GMP release could take some years. [redacted] It is hoped that this assay will be ready to be handed over to the sponsor by [redacted] and then the process for obtaining regulatory acceptance will commence (which could take several years).

Reduction

The minimum number of mice required were used, and this number could not be further reduced without affecting the integrity of the potency assay.

Refinement

[redacted]

[redacted]

[redacted] humane endpoints for Dose Groups A and B will be validated immediately and a variation to the Marketing Authorisation will be submitted to include the implementation of humane endpoints for Dose groups A and B. The investigation into humane endpoints for Dose Group C will continue in parallel to this submission. The immediate forecasted testing includes the validation of the test method and humane endpoints for Dose Groups A and B, once the renewal of this Project Authorisation is granted, i.e. testing will commence at the beginning of [redacted] and a variation will be submitted as soon as possible. Once the variation has been submitted, the sponsor will inform the Project Manager and Compliance Officer, who will communicate this update with the HPRA. This is a very positive development, as the implementation of HEs for Dose groups A and B should reduce the percentage of animals experiencing severe suffering by roughly 40%.

[redacted]

C. WELFARE CONCERNS, UNEXPECTED ADVERSE EVENTS AND DEVIATIONS

4. Comment on any welfare concerns, unexpected adverse events and deviations which may have arisen during the course of the project, and describe how these were dealt with.

N/A

D. ACCURACY OF ORIGINAL HARM-BENEFIT ANALYSIS AND ACHIEVEMENT OF OBJECTIVES

5. Were the proposed objectives of the project actually achieved? If not, outline the reasons for this.

The proposed objectives are currently being achieved, and this will continue as work progresses under the renewed authorisation.

6. In retrospect, was the original harm-benefit analysis accurate and in line with the actual harms that occurred and the benefits that were achieved? If not, outline the key areas in which this differed, and any possible reasons for this.

Significantly less animals have been used to date than were originally anticipated to be used in the first year of testing (3,001 used versus 31,200 approved), so from that perspective the harms

incurred have been much less than predicted. However, of the animals used, a higher % than expected have experienced severe severity (68% versus 40% predicted). This is because this testing has been moved from [redacted] and [redacted] are finding the potency of the product to be higher than reported by the [redacted] However, the HBA still remains favourable, and now that [redacted] and the sponsor have agreed to my suggestion of pursuing regulatory acceptance for HEs for Dose groups A and B, whilst simultaneously continuing to investigate HEs for Dose group C, the harms incurred as a result of future testing should be reduced.

E. FEEDBACK PROVIDED TO PROJECT MANAGER

Enter the feedback to be given to the project manager below.

Dear [redacted]

Thank you for providing the completed retrospective assessment report for the above project authorisation. We have reviewed your assessment and are satisfied with the outcome of this project to date.

Please do not hesitate to contact us if you need any clarification on the content of this e-mail or the retrospective assessment process.

F. FEEDBACK FOR SCIENTIFIC ANIMAL PROTECTION ASSESSORS

Outline the key points of the feedback for the scientific animal protection team below.

- The implementation of HEs for testing for this sponsor [redacted] is ongoing and is vitally important in order to bring about a reduction in the severity experienced by animals used under this authorisation.
- [redacted]
- Development work on the CBPA for this product is ongoing, but the CBPA is not expected to gain regulatory acceptance until [redacted] at the earliest.

G. KEY FINDINGS FOR THE NATIONAL COMMITTEE

Outline the key findings from this retrospective assessment which can be provided to the National Committee in the future, if required.

N/A

EVALUATOR CODE: [redacted]

DATE: **24/05/2021**