Eighty fifth Advisory Committee on Animal Feedingstuffs meeting

26th July 2023 – Hybrid meeting

ACAF	FSA
Nicholas Jonsson (Chair)	Nathan Allen
Martin Briggs	Mark Bond
Emily Burton	Aaron Bradshaw
Katrina Campbell	Alexander Cooper
Olivia Champion	Edward Fuller
Matthew Fisher	Donal Griffin
Hannah Kane	Michelle Hutchison
Oonagh Markey	David Kovacic
Christine McAlinden	Francisco Matilla
Donald Morrison	Hannah Reid
Derek Renshaw	Lucy Smythe
Mike Salter	Shila Sultana
Adam Smith	Johann Trotter
Helen Warren	
Nick Wheelhouse	

1. Apologies

Susan MacDonald sent her apologies.

2. Welcome

The Chair welcomed members of the Committee, Secretariat and observers from the Devolved Administrations.

3. Risk Assessment update

The Regulated Products Team Leader Donal Griffin gave an update on the status of feed additive applications currently being processed by the Regulated Products Risk Assessment Team. Currently one application has been published, and a further 20 are expected to be published in September. Six applications are undergoing suitability checks and fifty-one are ready to commence the assessment process. Twenty-three applications are currently under assessment by the Committee. Lastly, twenty-four applications have been completed or are going through opinion completion.

A new recruitment exercise for members will commence in September.

4. Policy Update

Feed Additives Senior Policy Advisor, Mark Bond, briefed the group on the number of feed additives currently in the system. Members were informed on the launch of the new FSA application portal that is expected to improve the tracking of application

status. A cobalt application was granted an urgent authorisation, allowing it to remain in the market until further assessment is carried out.

5. Minutes from 84th Meeting

The Committee reviewed the minutes from the 84th ACAF meeting and provided feedback to be reviewed by the Secretariat.

6. Dossier for assessment: RP1142 – Ronozyme MultiGrain

Adam Smith declared a direct conflict of interest and was asked to leave the call for the duration of the item.

An application was evaluated for the additive Ronozyme MultiGrain, a formulation of glucanase and xylanase. The application sought renewal of authorisation for its use for poultry for fattening and poultry for laying, and an extension of use for its use for pigs for fattening, under the category 'zootechnical additives', functional group 'digestibility enhancers'.

The Committee noted that the application presented a small change in composition, however the active substances and their proportion in the additive had not changed. No testing for mycotoxins was provided in the application, but members recognised the importance of quantifying mycotoxins in several batches of the final product. **The applicant would be asked to provide test reports for mycotoxins in the final product.** While dusting potential was adequately evaluated, this was not given in mg/m^3, as indicated in the guidance, **therefore the committee requested that the applicant should be asked to provide this information**. When evaluating the production process, members noted no HACCP plan or MSDS for raw materials were provided, so **the applicant would be asked to provide these**.

Stability testing provided was carried out at an inclusion rate of 150 ppm, as opposed to the maximum inclusion rate of 100 ppm proposed in the conditions of use. Despite this higher dosage, recovery rates for the product after the tested period was measured below expected levels in various instances. **The applicant would be asked to provide further clarification on the conditions under which the study was carried out**. Stability in pelleting was deemed to be well characterised, however no certificates for the stability testing method were provided, and **would be requested from the applicant**. A query was raised by members on the homogeneity, as not enough samples were tested, and no homogeneity testing was provided for the liquid formulation of the additive when used in pelleted feed. **The applicant would be asked to provide homogeneity testing for eight to ten samples of the granular formulation in mash, and for the liquid formulation in pellets**.

The applicant presented a proposed inclusion rate of 100 ppm for pigs for fattening, but no conditions of use for the other categories included in the renewal of authorisation were given. **Members requested that the applicant should be asked**

to provide conditions of use for all animal categories proposed under the authorisation.

Evidence from the previous authorisation in piglets was presented by the applicant and proposed to be extrapolated to pigs for fattening. Members noted that the rat sub-chronic toxicological study had a NOAEL of 2000 mg/kg/day. This resulted in a margin of safety of 4.75 to the proposed use level, however, potentially a margin of safety of ten is required for intraspecies extrapolation. **The applicant would be asked to provide further information to support the extrapolation of safety conclusions**. Based on the conclusions from the literature review provided, as well as negative results shown in an Ames test and *in vitro* chromosome aberration test, the Committee concluded that the additive is non-genotoxic and remains safe for consumers as demonstrated in the original application.

Applying the principle of precaution, members agreed it should be considered a potential respiratory sensitiser, and that worker exposure should be minimised. Based on updated literature data and previous studies, members concluded the additive is not irritant to skin or eyes and is not a skin sensitiser.

The study design of the efficacy trials presented was deemed to be adequate, however, the levels of enzyme recovery did not align with the dosage proposed in the conditions of use. Members agreed that positive effects were shown at the higher dosage level, but **the applicant would be asked to provide further evidence of efficacy at the proposed condition of use of the additive**, before concluding further on its efficacy.

7. Dossier for assessment: RP1055/1582 – Huvezym Nexo

Adam Smith declared an indirect conflict and remained in the meeting for discussion.

Two applications were evaluated requesting new authorisations of Huvezym neXo as a feed additive for its use in all poultry species, ornamental birds and piglets (weaned and suckling) (RP1055) and in pigs for fattening, sows, minor species for fattening and reproduction (RP1582). The additive falls under the category “zootechnical additives”, functional group “digestibility enhancer and other (performance enhancer)”. As both applications share most of the data for Sections II and III, the two applications were evaluated together.

Members noted that the applicant had not tested their additive for *Bacillus cereus* as outlined in the guidance and so **the applicant would be asked to provide results for *Bacillus cereus* or justify their exclusion**. The Committee evaluated the manufacturing process and found it to be well-detailed, but commented on the lack of a HACCP plan and documentation of certification. **The applicant would be asked to provide a HACCP plan and the relevant certificates.** It was noted that the homogeneity of the granular additive was calculated based on three samples from a single bag and not the whole batch. **The applicant would be asked to calculate a co-efficient of variation across each of the whole of the batches sampled.** The effect of pelleting at 85°C for 25 seconds was determined, however this was not

considered long enough for poultry breeder mash which could be held at 85°C for up to 6 minutes. **The applicant would be asked to provide data showing that the granular product can sustain these temperatures for a longer retention time or justify the shorter retention times used.**

Members found the literature review performed by the applicant to be comprehensive. The Committee discussed the tolerance studies provided, noting that according to the guidance, the tolerance data for laying hens can be extrapolated to other birds kept for egg production, however the extrapolation can only be applicable to breeders if an additional limited study in breeding hens is submitted, considering only performance endpoints. **The applicant would therefore be asked if they accept this conclusion or would like to submit the additional limited study**. Regarding the tolerance studies for sows and minor pig species for reproduction, members noticed particular details had not been provided and so **the applicant would be asked to provide further information on how the animals were weighed and how back fat mobilisation was measured in these studies.** Additionally, the applicant **would also be asked to provide a frequency distribution of the return to oestrus intervals to support their statements about the possible reasons for low reproductive performance.**

The Committee observed that in the 90-day rat toxicity study, no analysis had been included on dosing solutions, therefore **the applicant would be asked to provide this analysis, including how the dosing solutions were prepared and how they were stored**. An *in vitro* mammalian cell micronucleus test was provided by the applicant, however a positive control for clastogenicity without metabolic activation was not included, therefore **the Committee requested that the applicant should be asked to provide a justification of the absence of this positive control.** For user safety, skin corrosion had been tested in-vitro and found to be negative, but no data was included for skin irritation, and this endpoint requires a separate in-vitro study. **The applicant would be asked to either provide the required data or in the absence of data accept a conclusion that the additive has the potential to be a skin irritant.**

The Committee assessed a number of efficacy studies. Concerns were raised regarding the mortality rate in the second efficacy trial provided for weaned piglets and it was decided that members would not accept this study. **The Committee requested that the applicant should be asked whether they accept the decision that efficacy could not be concluded upon, or to provide the data for a replacement study.** For chickens for fattening, members noted that further information was needed for the second trial before they can conclude positively. **The applicant would be asked to provide further details on the apparent metabolizable energy (AME) collection method, describing how samples were collected and analysed. The applicant would also be asked to provide an explanation for why only 16 of the 17 reps were analysed for each treatment.** In the efficacy studies for laying hens, it was noted that the first trial was conducted in 50-week-old laying hens and the feed had a background corrected xylanase recovery that was 44% higher than the target. **The applicant would be asked to provide a replacement short term study for this trial for the Committee to**

conclude positively on the efficacy of the additive in laying hens. Members discussed the calcium levels used in the third trial for laying hens, noting that the level of calcium in the feeding diet is not in line with EU/GB standards. A disparity was also noted as the trial protocol sheet gives a value of 30.5 g/kg of calcium as opposed to 27.8 g/kg in the main document. **The applicant would be asked to clarify the level of calcium in the feeding diet, as well as justify why this level of calcium is not in line with EU/GB standards**. Members highlighted that for the sow trials provided metabolizable energy was only evaluated in the second trial. As this is a requirement in the guidance, **the applicant would be asked to evaluate this parameter for the first and third trial. The applicant would also be asked to provide clarity on the experimental unit for the first and second trial, as the sow cannot be considered an experimental unit when they are group housed.**

8. Dossier for assessment: RP1111 – *Bifidobacterium longum* PP102I

Hannah Kane declared an indirect conflict of interest and remained in the meeting for the discussion.

An application was evaluated for the additive PP102I (*Bifidobacterium longum*). The application sought new authorisation under the category “zootechnical additive”, functional group “physiological condition stabiliser” for its use in dogs and cats.

The Committee noted discrepancies between the methods reported within the identity and characterisation section of the dossier and those presented in the associated annex documentation. **The applicant would be asked to amend the reporting of the methodologies accordingly.** The results for dusting potential and the associated clarification in response to RFI were assessed, the Committee considered that the response did not adequately address the queries raised owing to the particle size distribution of the additive. The Committee concluded that the additive was potentially dusty because, although the results of the Steuber-Heubach test found no dust produced from the additive, the particle size distribution showed a large proportion of small particles that would be expected to form a dust upon handling and could be inhaled deep into the lungs of workers. Members noted the manufacturing process was lacking in detail of the critical control points. **The applicant would be asked to provide further detail of the manufacturing process including detail of all critical control points. HACCP documentation for the process would also be requested.**

Members noted inconsistencies in the conditions of use of the additive throughout the dossier, resulting in uncertainty regarding the final form of the additive and the proposed method of administration. Owing to the inconsistencies in the conditions of use, the stability data for the additive could not be assessed. **The applicant would be asked to clarify the final form of the additive and the proposed conditions of use, following which the applicant would be asked to clarify the stability data and how this relates to the proposed conditions of use.** It was not clear how users might determine the correct doses for animals of varying weights and feed intakes. **The applicant would be asked to clarify how the defined dosage would be achieved by the end user.** The Committee noted that the applicant states that no

interactions or contraindications are expected from the additive, **the applicant would be asked to explain the justification for this statement.** A conclusion could not be drawn on the suitability of the in-house analytical methods to determine concentrations described in the application, and it was decided these would be reviewed offline before a request for information was issued to the applicant.

Safety was assessed by the Committee, highlighting that the additive's name on the MSDS did not match that on the application. **The applicant would be asked to provide an amended version of this document.** Owing to the absence of primary eye and skin testing, the Committee concluded that the additive should be considered an eye and skin irritant and skin sensitiser. **The applicant would be made aware of this conclusion and given the option to provide primary studies for assessment, in the absence of these studies an updated SDS and label will be required to reflect this precautionary labelling.**

Members reviewed the efficacy data provided and concluded that no further information was required from the applicant at this time, however, the information provided will be reviewed when the conditions of use have been clarified by the applicant.

Addendum: Following the meeting, the queries relating to the suitability of the in-house analytical methods were addressed and it was determined that no further information on the analytical methods was required from the applicant.

9. Dossier for assessment: RP1154 – BioPlus 2B

An indirect conflict of interest was declared by Martin Briggs who was allowed to remain in the discussion.

An application was evaluated for BioPlus® 2B (*Bacillus licheniformis* + *Bacillus subtilis*). The applicant requested a new authorisation for calves for fattening, other growing ruminants at the same development stage and piglets (suckling and weaned), under the category "zootechnical additives" and functional groups "gut flora stabiliser".

It was noted by members that the batch-to-batch analysis of the additive were all over five years old. **The applicant would be asked to provide certificates of analysis for batch-to-batch variation within the last 5 years.**

It was discussed whether testing for *Enterobacteriaceae* would be required, as the guidance specifies the need to test these for microorganisms as additives. It was also noted that the testing was over five years old, and no actual results were provided in the annex. The Committee discussed that the analytical data on the impurities of the additive for at least 3 production batches should be produced within the last 5 years. **The applicant would be asked to provide data for *Enterobacteriaceae*, provide the missing data, provide analysis from batches within the last 5 years and provide clarification on the testing subject.**

Members noted that the data for the Whole Genome Sequence (WGS) of the additive was not provided in the application, so **it was stated that the applicant should be asked to provide this data**. There was a discussion on the time limit for phenotypic testing and Minimum Inhibitory Concentration (MIC) values, as the guidance does not specify a date limit for testing, but members stated that the results were acceptable.

It was noted by members that the FAMI-QS certificate was expired so **the applicant would be asked to provide an up-to-date certificate**. They also discussed the HACCP plan; although the applicant stated this was provided, it could not be found in the application. **The applicant would be asked to provide the complete HACCP plan.**

The stability and homogeneity data were discussed and some discrepancies in the concentration level of the additive between the data provided and the application were identified. **The applicant would be asked to clarify the source of these discrepancies.**

Members noted that the ingredient MSDSs were not up to date, that they were not provided for all ingredients, and that clarification would be needed for which the ingredients were used at which stage of the manufacturing process. **The applicant would be asked to provide this information.**

It was discussed that an exposure assessment would not be required for the safety of the user/worker. The additive was regarded as a respiratory sensitiser. Members referred to the SDS which requires adequate ventilation and the use of P3 respiratory filtration which does not reflect on the proposed conditions of use and label. **The applicant would be asked to provide up-to-date conditions of use and label sections referring to the use of ventilation.** In the absence of any data to the contrary, the additive should be regarded as an irritant to skin and eyes and as a skin sensitiser. No further concerns were raised on the safety section of the additive.

The Committee discussed the extrapolation of results for efficacy and the extrapolation of calves for rearing to calves for fattening. They considered that there is limited distinction between calves for rearing to calves for fattening but that the applicant did not perform the studies for the length required in the guidance of 84 days for calves for fattening. Members noted that the applicant attempted to extrapolate between categories of the same species at different production stages, however the technical guidance states that this should not be done. Members discussed that the product could be effective in older animals, but agreed that the plethora of criteria not met for extrapolation made this proposal not viable. Therefore, a conclusion could not be made on the efficacy for the extrapolation of results to calves for fattening.

For the extrapolation of efficacy for piglets (suckling and weaned), a conclusion could not be drawn. Members noted that EFSA had previously stated that there was insufficient evidence to conclude on efficacy in piglets during the sucking and weaned period. As there was no new evidence provided for efficacy in suckling

piglets, an extrapolation could not be made to the same species at a different production stage, as stated by the guidance. Members noted that, as efficacy was confirmed in weaned piglets, this allowed for its use in the suckling period in which solid feed is given.

10. Response to RFI: RP634 - Chromium propionate

No conflicts of interest were declared for this item.

The Committee requested the input of a poultry efficacy specialist to determine the validity of the efficacy trials presented in the application. The external expert concluded that the trials should be considered valid despite the unexpected results. Members evaluated the external expert's report and agreed in accepting the validity of the trials, however, it was pointed out that efficacy had only been demonstrated in three trials at the higher proposed inclusion rate of 400 ppm, but not at the lower proposed inclusion rate of 200 ppm. **The applicant would be given the choice to provide further evidence of efficacy at 200 ppm or accept the Committee's conclusion.**

11. Response to RFI: RP593 – Hostazym C

An indirect conflict of interest was declared by Adam Smith, and he was allowed to remain during the discussion.

Prior to the meeting, the Secretariat had asked the applicant to provide the retention time data for the stability trials provided in the application. Members reviewed the information and concluded the information was accurate, requiring no further clarification. The application will move into the Safety Assessment drafting stage.

12. Draft opinions

Members were presented with draft Committee's Advice documents for applications RP658 and RP1307. Feedback was provided to be reviewed by the Secretariat.

The Committee was also presented with the final draft of Committee's Advice documents for applications RP416, RP420 and RP791. The Committee provided feedback on final corrections and approved the opinions to be finalised and sent to Risk Managers.

13. Efficacy workshop (practical)

The ACAF members were divided into several online groups to evaluate two example applications of contrasting quality of presentation and trial design. The Secretariat was also able to attend and learn from the exercise to support future assessments.

16. Any Other Business

Members agreed on the need to evaluate the different areas of the guidance to help applicants understand the Committee's interpretation of the existing technical documents, but also to inform any future reform. It was noted that for example, in the case of efficacy, there is a disparity in the animal production stages between guidance and legislation, and that neither of these classifications are necessarily optimal within the UK farming context. The Secretariat agreed to start the re-evaluation process of the guidance.

Next ACAF meeting: Friday 15th of September 2023 on Microsoft Teams