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Assessment of the application for renewal of the authorisation of PHYZYME® XP 10000 TPT/L (6-phytase) as a feed additive for all avian species and all swine species

EFSA Panel on Additives and Products or Substances used in Animal Feed (EFSA FEEDAP Panel),
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Abstract

PHYZYME® XP 10000 TPT/L is a feed additive that contains 6-phytase produced by a genetically modified strain of *Schizosaccharomyces pombe.* The applicant requested for the renewal of the authorisation for PHYZYME® XP 10000 TPT and L to be used as a feed additive for avian species for fattening/laying, weaned piglets, pigs for fattening and sows and for an extension of use to avian species reared for laying/breeding, suckling piglets and minor porcine species. To support the request or the renewal of the authorisation, the applicant provided evidence that the additive in the market complies with the conditions of the authorisation. According to the information provided by the applicant, no new evidence has been identified that would make the FEEDAP Panel reconsider the previous conclusions regarding the safety for the target species, consumer, user and environment. The application for renewal of the authorisation did not include a proposal for amending the conditions of use in those species for which an authorisation exists that would have an impact on the efficacy of the additive. Therefore, there was no need for assessing the efficacy of the additive in the context of the renewal of the authorisation. Regarding the new species/categories, the Panel concluded that the additive is safe and has a potential to be efficacious in avian species reared for laying/breeding at 250 FTU/kg feed and for suckling piglets and minor porcine species at 500 FTU/kg feed.

Keywords: zootechnical additives, digestibility enhancers, phytase, safety, efficacy, poultry, pigs

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1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 4(1) of that Regulation lays down that any person seeking authorisation for a feed additive or for a new use of a feed additive shall submit an application in accordance with Article 7. In addition, Article 14(1) of that Regulation lays down that an application for renewal shall be sent to the Commission at the latest one year before the expiry date of the authorisation.

The European Commission received a request from Danisco Animal Nutrition[2] for renewal of the authorisation of the product PHYZYME® XP 10000 TPT/L (6-phytase), when used as a feed additive for all avian species for fattening and for laying, weaned piglets, pigs for fattening and sows (category: zootechnical additives; functional group: digestibility enhancers). Moreover, this request proposes new uses, including avian species reared for breeding or reared for laying, suckling piglets and all relevant minor porcine species.

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 4(1) (authorisation of a feed additive or new use of a feed additive) and under Article 14(1) (renewal of the authorisation). The particulars and documents in support of the application were considered valid by EFSA as of 7 August 2018.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and on the efficacy of the product PHYZYME® XP 10000 TPT and L (6-phytase), when used under the proposed conditions of use (see Section 3.1.1).

1.2. Additional information

The additive PHYZYME® XP 10000 TPT/L is a preparation of 6-phytase produced by a genetically modified strain of *Schizosaccharomyces pombe* (ATCC 5233). EFSA issued two opinions which considered the safety and efficacy of the additive in a less concentrated forms, PHYZYME® XP 5000 XP G/L, when used in chickens for fattening, laying hens, turkeys for fattening, ducks for fattening, piglets (weaned), pigs for fattening and sows, which included the assessment of the safety for the consumer, the user and the environment, as well as the safety aspects of the genetic modification (EFSA, 2006a, b). A third opinion was adopted regarding the use of PHYZYME® XP 10000 TPT/L (EFSA, 2008), and a fourth opinion on the extension of use of the additive for minor poultry species was adopted in 2012 (EFSA FEEDAP Panel, 2012a).

This additive is currently authorised for use in chickens for fattening, laying hens, turkeys for fattening, ducks for fattening, piglets (weaned), pigs for fattening and sows and all avian species for fattening or laying.[3,4]

The applicant requested for the renewal of the authorisation for PHYZYME® XP 10000 TPT/L to be used as a feed additive for chickens for fattening, laying hens, turkeys for fattening, ducks for fattening, piglets (weaned), pigs for fattening and sows and all avian species for fattening or laying. Moreover, the applicant requests the extension of the use to all avian species reared for breeding and reared for laying, suckling piglets and all relevant minor porcine species.

[1] Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.

[2] Danisco (UK) Ltd., trading as Danisco Animal Nutrition, PO Box 777, SN8 1XN Marlborough, UK.

[3] Commission Regulation (EC) No 379/2009 of 8 May 2009 concerning the authorisation of a new use of 6-phytase EC 3.1.3.26 as a feed additive for chickens for fattening, turkeys for fattening, laying hens, ducks for fattening, piglets (weaned), pigs for fattening and sows (holder of the authorisation Danisco Animal Nutrition, Legal Entity Danisco (UK) Limited). OJ L 116, 09.05.2009, p.6. Holder of the Authorisation modified to 'Danisco (UK) Ltd, trading as Danisco Animal Nutrition and represented by Genencor International B.V.' by Commission Implementing Regulation (EU) 2019/221 of 6 February 2019.

[4] COMMISSION IMPLEMENTING REGULATION (EU) No 840/2012 of 18 September 2012 concerning the authorisation of 6-phytase (EC 3.1.3.26) produced by *Schizosaccharomyces pombe* (ATCC 5233) as a feed additive for all avian species for fattening other than chickens for fattening, turkeys for fattening and ducks for fattening and all avian species for laying other than laying hens (holder of authorisation Danisco Animal Nutrition). OJ L 252, 19.09.2012, p.14. Holder of the Authorisation modified to 'Danisco (UK) Ltd, trading as Danisco Animal Nutrition and represented by Genencor International B.V.' by Commission Implementing Regulation (EU) 2019/221 of 6 February 2019.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier[5] in support of the authorisation request for the use of PHYZYME® XP 10000 TPT/L (6-phytase) as a feed additive.

The European Union Reference Laboratory (EURL) considered that the conclusions and recommendations reached in the previous assessment regarding the methods used for the control of the active substance are valid and applicable for the current application.[6]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of PHYZYME® XP 10000 TPT/L (6-phytase) is in line with the principles laid down in Regulation (EC) No 429/2008[7] and the relevant guidance documents: Guidance on the renewal of the authorisation of feed additives (EFSA FEEDAP Panel, 2013), Guidance on zootechnical additives (EFSA FEEDAP Panel, 2012b) and Guidance on the risk assessment of genetically modified microorganisms and their products intended for food and feed use (EFSA GMO Panel, 2011).

3. Assessment

The additive PHYZYME® XP 10000 TPT/L is a feed additive that contains 6-phytase produced by a genetically modified strain of *S. pombe*. This additive is authorised for use in all avian species for fattening and laying, weaned piglets, pigs for fattening and sows. This opinion deals with the renewal of the authorisation of PHYZYME® XP 10000 TPT/L as a zootechnical additive (functional group of digestibility enhancers) for the target species for which there is an authorisation and its extension of use to all avian species reared for breeding and reared for laying, suckling piglets and all relevant minor porcine species.

3.1. Characterisation of the additive

The additive is authorised in solid, PHYZYME® XP 10000 TPT, and liquid, PHYZYME® XP 10000 L, forms.

The information submitted regarding the manufacturing process lists a series of modifications applied during the last years to the fermentation and the enzyme recovery process.[8] [redacted]. The Panel considers that these modifications do not have an impact on the final product and data regarding the characterisation supports this conclusion. The applicant declared that no antibiotics are used during the manufacturing process.[9]

PHYZYME® XP 10000 TPT contains the phytase [redacted]. PHYZYME® XP 10000 L consists of active enzyme concentrate of 6-phytase [redacted].

The two formulations ensure a minimum guaranteed enzyme activity of 10,000 FTU[10]/g. The batch-to-batch variation was studied in three recent batches of each formulation. The enzyme activities measured in three recent batches showed in PHYZYME® XP 10000 TPT a mean value of 13,417 FTU/g

[5] FEED dossier reference: FAD-2018-0034.
[6] The full report is available on the EURL website: https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2011-0015.pdf.
[7] Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.
[8] Technical dossier/Section II/Annex II.18.
[9] Technical dossier/Section II/Annex II.22.
[10] FTU: one unit of phytase is defined as the amount of enzyme which liberates one micromole of inorganic phosphate per minute from a sodium phytate substrate at 37° C and pH 5.5.

6-phytase (range 13,165–13,576 FTU/g) and in PHYZYME® XP 10000 L 12,509 FTU/g 6-phytase (range 11,710–12,917 FTU/g).[11]

Chemical and microbiological impurities were analysed for the two formulations.[12] The chemical contamination included lead (< 0.05 mg/kg for solid and < 0.09 mg/kg for the liquid), cadmium (< 0.01 mg/kg), mercury (< 0.01 mg/kg for solid and < 0.005 mg/kg for the liquid) and arsenic (< 0.1 mg/kg); aflatoxins (< 1 μg/kg), deoxynivalenol (< 20 μg/kg), fumonisins (< 20 μg/kg), ochratoxin A (< 2 μg/kg) and zearalenone (< 10 μg/kg). Microbial contamination analysis included total viable count (< 1,000 colony forming units (CFU)/g for the solid and < 1 CFU/mL for the liquid), total coliforms (< 10 CFU/g or mL), *Salmonella* spp. (absent in 25 g or mL) and *Escherichia coli* (absent in 25 g or mL). In the liquid formulation, it was also measured the content of polychlorinated dibenzo-*p*-dioxins and furans (upper-bound WHO-TEQ ≤ 0.0630 ng/kg), dioxin-like polychlorinated biphenyls (upper-bound WHO-TEQ ≤ 0.0381 ng/kg) and non-dioxin-like polychlorinated biphenyls (≤ 0.367 μg/kg). No antimicrobial activity was found in three batches of either formulation.[13]

The 6-phytase present in the additive is obtained by fermentation with a genetically modified strain of *S. pombe* which is deposited at the American Type Culture Collection under deposition number SD-5233.[14] [redacted] The assessment of the genetic modification was performed in a previous opinion (EFSA, 2006a) and the Panel concluded that the genetic modification does not raise any safety concern. The production strain has not been subject to any further genetic modification.

The presence of viable cells of the production strain was investigated in three batches of the liquid formulation and three of the solid formulation.[16] The samples of the liquid formulation were plated (1 mL) in yeast glucose chloramphenicol agar in duplicate and incubated at 30°C for 72 h. The samples of the solid formulation were first dissolved (approximately 1:10) and then 1 mL aliquots were plated on the same type of agar and incubated as those of the liquid samples. No cells were detected.

The presence of recombinant DNA was tested [redacted] The analyses showed no amplification in any of the samples from the three batches (while positive PCR control gave amplification). [redacted]

3.1.1. Conditions of use

PHYZYME® XP 10000 TPT/L is currently authorised for use in feed for all avian species for fattening and all porcine species (except sows and suckling piglets) at 250 FTU/kg complete feed, in feed for sows at 500 FTU/kg and in feed for avian species for laying at 150 FTU/kg The applicant has not modified these conditions of use. In addition, the applicant proposes the extension of use to all avian species reared for breeding and reared for laying, suckling piglets and all relevant minor porcine species at a recommended dose of 250 FTU/kg.

3.2. Safety

3.2.1. Safety for the target species, consumers, users and environment

The safety of PHYZYME® XP 10000 TPT/L for the target species, consumers, users and the environment, including the safety of the production strain, has been evaluated in previous opinions (EFSA, 2006a,b, 2008; EFSA FEEDAP Panel 2012a). The Panel concluded that the genetic modification of the production strain is of no concern, that the additive is safe for the target species evaluated, and the use of the product as a feed additive would be of no concern for the consumers of products

[11] Technical dossier/Section II/Annex II.3 and II.4.
[12] Technical dossier/Section II/Annex II.5 and II.6.
[13] Technical dossier/Section II/Annex II.5 and II.6 and Supplementary information March 2019.
[14] Technical dossier/Section II/Annex II.13.
[redacted]
[16] Technical dossier/Section II/Annexes II.5 and II.6 and Supplementary information March 2019/Main response.
[redacted]

derived from animals fed with the additive, or for the environment. Concerns for the user were limited to its potential as a respiratory sensitiser.

The current application requests for an extension of use of the additive to avian species reared for laying/breeding, suckling piglets and minor porcine species. The FEEDAP Panel evaluated in the past tolerance trials which showed that chickens and turkeys for fattening, weaned piglets and sows, tolerated well at least 10 times the maximum recommended dosages proposed in previous assessments; 750 FTU/kg feed in chickens for fattening, 1,000 FTU/kg feed in turkeys for fattening, 1,000 FTU/kg feed in weaned piglets and 500 FTU/kg feed in sows. Therefore, the Panel considers that the conclusions from chickens and turkeys for fattening can be extended to minor avian species reared for laying/breeding (1,000 FTU/kg feed) and those reached in weaned piglets can be extended to suckling piglets (1,000 FTU/kg feed). Similarly, the conclusions reached in weaned piglets can be extrapolated to minor porcine species for growing (1,000 FTU/kg feed) and those reached in sows can be extrapolated to reproductive minor porcine species (500 FTU/kg feed). Consequently, the additive is safe for the new species/categories at the recommended use level of 250 FTU/kg feed and up to 1,000 FTU/kg feed.

3.2.2. Further evidence

In 2007, EFSA established the Qualified Presumption of Safety (QPS) approach to safety assessment for microorganisms (EFSA, 2007). The production strain of the additive belongs to a species, *Schizosaccharomyces pombe,* that is considered to qualify for the QPS approach to safety assessment (EFSA, 2007; EFSA BIOHAZ Panel, 2017). The taxonomic classification of the strain has been unambiguously established and the genetic modification raised no concerns. Therefore, the fermentation product obtained from the production strain does not raise any safety concerns for the consumer and the environment.

In line with the requirements established in the EFSA guidance on the renewal (EFSA FEEDAP Panel, 2013), the applicant performed a literature search in order to provide evidence that in the light of the current knowledge the additive remains safe under the approved conditions for target species, consumers, users and the environment. [redacted] The literature search retrieved 97 publications out of which most of them were excluded from the assessment because the product was not the one under assessment. The other publications found did not report any safety issues.

The applicant claims that no adverse effects have been reported in the framework of its global monitoring plan.[19]

3.3. Efficacy

The present application for renewal of the authorisation does not include a proposal for amending or supplementing the conditions of use for those species/categories for which there is an authorisation. Therefore, there is no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

However, the current application includes the extension of use to avian species reared for laying/breeding, suckling piglets and minor porcine species at 250 FTU/kg feed. The FEEDAP Panel has concluded in previous opinions (EFSA 2006a,b, 2008; EFSA FEEDAP Panel 2012a) that the additive is efficacious in chickens for fattening at 500 FTU/kg feed, in turkeys for fattening at 250 FTU/kg feed and in weaned piglets and sows at 500 FTU/kg feed. The Panel considers that the conclusions reached in turkeys for fattening can be extended to avian species reared for laying/breeding and those reached in piglets can be extended to suckling piglets. Similarly, the conclusions reached in weaned piglets and sows can be extrapolated to minor porcine species. Therefore, the additive has a potential to be efficacious in avian species reared for laying/breeding at 250 FTU/kg feed, and in suckling piglets and minor porcine species at 500 FTU/kg feed.

[redacted]
[19] Technical dossier/Section III/Annex III.1.

3.4. Post-market monitoring

The FEEDAP Panel considers that there is no need for specific requirements for a post-market monitoring plan other than those established in the Feed Hygiene Regulation[20] and Good Manufacturing Practice.

4. Conclusions

The additive currently in the market complies with the existing conditions of authorisation.

The FEEDAP Panel concludes that PHYZYME® 10000 TPT/L remains safe for avian species for fattening/laying, weaned piglets, pigs for fattening and sows, consumers of products from animals fed the additive and the environment under the approved conditions of authorisation. The additive is a potential respiratory sensitiser. There is no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

The FEEDAP Panel concludes that PHYZYME® 10000 TPT/L is safe and has a potential to be efficacious at 250 FTU/kg feed for avian species reared for laying/breeding and at 500 FTU/kg feed in suckling piglets and minor porcine species.

Documentation provided to EFSA/Chronology

Date	Event
04/06/2018	Dossier received by EFSA. PHYZYME® 10000 TPT/L. Submitted by Danisco Animal Nutrition.
26/06/2018	Reception mandate from the European Commission
07/08/2018	Application validated by EFSA – Start of the scientific assessment
18/12/2018	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: characterisation, safety*
01/03/2019	Reception of supplementary information from the applicant - Scientific assessment re-started
04/04/2019	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

References

EFSA (European Food Safety Authority), 2006a. Opinion of the Scientific Panel on Additives and Products or Substances used in Animal Feed and the Scientific Panel on Genetically Modified Organisms on the safety and efficacy of Phyzyme XP 5000 (G/L), 6-phytase) as a feed additive for chickens for fattening. EFSA Journal 2006;4(5):350, 14 pp. http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2006.350/epdf

EFSA (European Food Safety Authority), 2006b. Opinion of the Scientific Panel on Additives and Products or Substances used in Animal Feed and the Scientific Panel on Genetically Modified Organisms on the safety and efficacy of Phyzyme XP 5000 (G/L), 6-phytase) as a feed additive for chickens for fattening, laying hens, turkeys for fattening, ducks for fattening, piglets (weaned), pigs for fattening and sows. EFSA Journal 2006;4 (10):404, 20 pp. https://www.efsa.europa.eu/en/efsajournal/pub/404

EFSA (European Food Safety Authority), 2007. Opinion of the Scientific Committee on a request from EFSA on the introduction of a Qualified Presumption of Safety (QPS) approach for assessment of selected microorganisms referred to EFSA. EFSA Journal 2007;5(12):587, 16 pp. https://doi.org/10.2903/j.efsa.2007.587

EFSA (European Food Safety Authority), 2008. Safety and efficacy of Phyzyme XP 10000 (TPT/L), 6-phytase as a feed additive for chickens for fattening, laying hens, turkeys for fattening, ducks for fattening, piglets (weaned), pigs for fattening and sows. EFSA Journal 2008;6(12):915, 10 pp. https://doi.org/10.2903/j.efsa.2008.915

EFSA BIOHAZ Panel (EFSA Panel on Biological Hazards), 2017. Scientific Opinion on the update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA. EFSA Journal 2017;15 (3):4664, 177 pp. https://doi.org/10.2903/j.efsa.2017.4664

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012a. Scientific Opinion on the safety and efficacy of Phyzyme XP (6-phytase) as a feed additive for minor poultry species. EFSA Journal 2012;10(3):2619, 9 pp. https://doi.org/10.2903/j.efsa.2012.2619

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012b. Guidance for the preparation of dossiers for zootechnical additives. EFSA Journal 2012;10(1):2536, 19 pp. https://doi.org/10.2903/j.efsa.2012.2536

[20] Regulation (EC) No 183/2005 of the European Parliament and of the Council of 12 January 2005 laying down requirements for feed hygiene. OJ L 35, 8.2.2005, p. 1.

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2013. Guidance on the renewal of the authorisation of feed additives. EFSA Journal 2013;11(10):3431, 8 pp. https://doi.org/10.2903/j.efsa.2013.3431

EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), 2011. Scientific Opinion on Guidance on the risk assessment of genetically modified microorganisms and their products intended for food and feed use. EFSA Journal 2011;9(6):2193, 54 pp. https://doi.org/10.2903/j.efsa.2011.2193

Abbreviations

CFU	colony forming unit
EURL	European Union Reference Laboratory
QPS	Qualified Presumption of Safety
TEQ	toxic equivalent
WHO	World Health Organization

Appendix A – List of references retrieved from the literature search provided by the applicant to support the safety of the additive