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Safety and efficacy of a feed additive consisting of *Saccharomyces cerevisiae* DBVPG 48 SF (BioCell®) for horses, pigs and ruminants (Mazzoleni S.p.A.)

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Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety and efficacy of *Saccharomyces cerevisiae* DBVPG 48 SF (BioCell®) as a zootechnical feed additive for horses, pigs and ruminants. The product, manufactured in three formulations (microsphere, micropellet and powder), is intended for use in complete feed at a minimum inclusion level of 3×10^9 CFU/kg complete feed for horses, 4×10^8 CFU/kg complete feed for dairy cows and minor dairy species, 4×10^9 CFU/kg complete feed for calves, cattle for fattening, minor growing and fattening ruminants, piglets and pigs for fattening and minor porcine species and 6×10^9 CFU/kg complete feed for sows and minor porcine species for reproduction. *Saccharomyces cerevisiae* is considered by EFSA to be suitable for the qualified presumption of safety approach to safety assessment. The identity of the strain was conclusively established and, therefore, the use of the additive in animal nutrition is considered safe for the target species, the consumer and the environment. The additive, in any formulation, is not irritant to the eyes and skin but should be considered a respiratory sensitiser. The Panel cannot conclude on the skin sensitisation potential of the additive. The Panel concluded that the additive has the potential to be efficacious at the proposed conditions of use for horses, dairy ruminants and all pigs. However, the Panel was not in the position to conclude on the efficacy of the additive for calves, and neither for cattle for fattening, minor growing and fattening ruminants.

Keywords: zootechnical additives, digestibility enhancers, other zootechnical additives, BioCell®, *Saccharomyces cerevisiae* DBVPG 48 SF, safety, efficacy

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Question number: EFSA-Q-2021-00343

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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 feed additive shall submit an application in accordance with Article 7.

The European Commission received a request from Mazzoleni S.p.A.[2] for the authorisation of the additive consisting of *Saccharomyces cerevisiae* DBVPG 48 SF (BioCell®), when used as a feed additive for horses (category: zootechnical additives; functional group: digestibility enhancer), pigs and ruminants (category: zootechnical additives; functional group: other zootechnical additives).

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). The particulars and documents in support of the application were considered valid by EFSA as of 25 November 2021.

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 feed additive consisting of *Saccharomyces cerevisiae* DBVPG 48 SF (BioCell®), when used under the proposed conditions of use (see **Section 3.1.5**).

1.2. Additional information

The additive consisting of viable cells of *Saccharomyces cerevisiae* DBVPG 48 SF is not authorised in the European Union.

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[3] in support of the authorisation request for the use of *Saccharomyces cerevisiae* DBVPG 48 SF (BioCell®) as a feed additive. The dossier was received on 19/03/2021 and the general information and supporting documentation are available at https://open.efsa.europa.eu/questions/EFSA-Q-2021-00343.

The confidential version of the technical dossier was subject to a target consultation of the interested Member States from 25 November 2022 to 9 March 2022 for which the received comments were considered for the assessment.

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of the *Saccharomyces cerevisiae* DBVPG 48 SF in animal feed.[4]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of *Saccharomyces cerevisiae* DBVPG 48 SF (BioCell®) is in line with the principles laid down in Regulation (EC) No 429/2008[5] and the relevant guidance documents: Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012), Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017a), Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEEDAP Panel, 2017b), Guidance on

[1] Regulation (EC) No 1831/2003 of the European Parliament and of the council of 22 September 2003 on the additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.
[2] Mazzoleni S.p.A., via dell'Artigianato 77/81, 24055 Cologno al Serio, Italy.
[3] FEED dossier reference: FAD-2021-0040.
[4] Evaluation report received on 22/02/2022 and available on the EU Science Hub: https://joint-research-centre.ec.europa.eu/publications/fad-2021-0040_en.
[5] 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.

the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017c), Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018a), Guidance on the characterisation of microorganisms used as feed additives or as production organisms (EFSA FEEDAP Panel, 2018b), Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019) and EFSA statement on the requirements for whole genome sequence analysis of microorganisms intentionally used in the food chain (EFSA, 2021).

3. Assessment

The additive under assessment, with the tradename BioCell®, consists of viable cells of *Saccharomyces cerevisiae* DBVPG 48 SF and is intended to be used as a zootechnical additive in feed for horses (digestibility enhancer), and for pigs and ruminants (other zootechnical additives: performance enhancer).

3.1. Characterisation

3.1.1. Characterisation of the active agent

The active agent is a non-genetically modified strain of *Saccharomyces cerevisiae* deposited in the Industrial Yeasts Collection of the Department of Agricultural, Food and Environmental Sciences, University of Perugia, with the accession number DBVPG 48 SF.[6]

The taxonomic identification of the active agent as *S. cerevisiae* was confirmed [redacted].[7]

The antimycotic susceptibility testing was performed using a broth microdilution method. The minimum inhibitory concentration (MIC) values obtained for the antimycotics tested [including anidulafungin (0.12 mg/L), caspofungin (2 mg/L), fluconazole (4 mg/L), 5-flucytosine (< 0.06 mg/L), itraconazole (0.12 mg/L), micafungin (0.06 mg/L) and voriconazole (0.25 mg/L)] were considered low.[8]

3.1.2. Characterisation of the additive

The additive contains viable cells of the strain *S. cerevisiae* DBVPG 48 SF [redacted].[9]

The additive is marketed in three formulations, namely microsphere (BioCell® S12), micropellet (BioCell® M16) and powder (BioCell® P), with a guaranteed minimum content of 1.2×10^{10}, 1.6×10^{10} and 1.0×10^{9} colony forming units (CFU)/g, respectively. Compliance with the specifications was confirmed by analysis of the active agent in six batches of the microsphere formulation (average 1.5×10^{10} CFU/g, range $1.5–1.6 \times 10^{10}$),[10] in eight batches of the micropellet formulation (average 2.0×10^{10} CFU/g, range $2.0–2.1 \times 10^{10}$)[11] and in five batches of the powder formulation (average 5.3×10^{9} CFU/g, range $5.0–5.7 \times 10^{9}$).[12]

Three batches of each formulation of the additive were analysed for microbiological contamination, aflatoxin B1, lead, mercury, cadmium and arsenic contents. The applicant has specifications for total coliforms (1,000 CFU/g), β-glucuronidase-positive *Escherichia coli* (10 CFU/g), coagulase-positive staphylococci (including *Staphylococcus aureus*; 10 CFU/g), sulfite-reducing bacteria (100 CFU/g), *Listeria monocytogenes* (100 CFU/g) and *Salmonella* spp. (no detection in 25 g). Analytical data

[6] Technical dossier/Section II/Annex II.2.2.1.1.
[7] Technical dossier/Section II/Annex II.2.2.1.2.2a and Supplementary information August 2022/Annex_1Q2_1_ITS.
[8] Technical dossier/Section II/Annex II.2.2.2.2.1.
[9] Technical dossier/Section II/Annex II.2.3.1.1. and Annex II.2.3.1.2.
[10] Technical dossier/Section II/Annex II.2.1.3.2.
[11] Technical dossier/Section II/Annex II.2.1.3.1.
[12] Technical dossier/Section II/Annex II.2.1.3.3.

showed compliance with these limits.[13] In addition, the applicant provided data for filamentous fungi, *Enterobacteriaceae* and contaminant yeasts, with results below the limit of quantification (LOQ) (10 CFU/g).[14] Analytical data for cadmium, lead, mercury, arsenic and aflatoxin B1 concentration showed that arsenic was present in all three batches of the micropellet formulation (average 0.06 mg/kg) and in one batch of the powder formulation 0.04 mg/kg[15] while in the other samples, it was below the respective LOQ (< 0.04 mg/kg); cadmium concentration averaged 0.04 mg/kg in the micropellet and powder formulations and was below the LOQ (0.02 mg/kg) in the three batches tested of the microsphere formulation; lead was present in the microsphere (average 0.2 mg/kg) and powder (average 0.3 mg/kg) formulations of the additive; results for mercury (< 0.04 mg/kg) and aflatoxin B1 (< 0.1 μg/kg) were below the respective LOQ.[14,16]

Nine batches of the additive were analysed for the presence of potential residues from the antifoaming used in the manufacturing of the additive (mono- and diglycerides of fatty acids – E 471). All results were below the LOQ (0.02 g/100 g).[17]

The FEEDAP Panel considers that the microbial contamination and the amounts of the detected impurities do not raise safety concerns.

3.1.3. Physical properties of the additive

The three additive formulations (microsphere,[18] micropellet[19] and powder[20]) appear as dry variable-sized particles. The microsphere formulation of the additive has an average density of 663 kg/m^3 (range 647–685 kg/m^3) and an average bulk density of 688 kg/m^3 (range 679–700 kg/m^3).[21] The micropellet formulation of the additive has an average density of 723 kg/m^3 (range 720–725 kg/m^3) and an average bulk density of 707 kg/m^3 (range 702–710 kg/m^3).[22] The powder formulation of the additive has an average density of 754 kg/m^3 (range 753–756 kg/m^3) and an average bulk density of 525 kg/m^3 (range 517–535 kg/m^3).[23]

The dusting potential of three batches of each formulation of the additive was determined using the Stauber-Heubach method. Values expressed in mg airborne dust per m^3 of air for the microsphere[24] and micropellet[25] were equal to zero, while for the powder formulation[26] averaged 2,292 mg/m^3 (range 2,170–2,390 mg/m^3).

The particle size distribution measured by sieving of three batches of the microsphere formulation of the additive showed that most (between 72% and 80%) of the particles had a size between 750 and 2,000 μm and between 0.06% and 0.29% below 125 μm.[27] The particle size distribution of three batches of the micropellet[28] and powder[29] formulations of the additive was analysed by the laser diffraction method. Results for the micropellet formulation showed an average (v/v) 0.7% of particles below 250 μm and no particles below 200 μm.[28] The particle fractions for the powder formulation below 100, 50 and 10 μm were 44%, 32% and 7% (v/v), respectively.[29]

[13] Technical dossier/Section II/Annex II.2.1.4.2, Annex II.2.1.4.3, Annex II.2.1.4.5, Annex II.2.1.4.6, Annex II.2.1.4.8, Annex II.2.1.4.9, Annex II.2.1.4.11, Annex II.2.1.4.12, Annex II.2.1.4.14a and b, Annex II.2.1.4.15, Annex II.2.1.4.17, Annex II.2.1.4.18, Annex II.2.1.4.20, Annex II.2.1.4.21, Annex II.2.1.4.23, Annex II.2.1.4.24, Annex II.2.1.4.26 and Annex II.2.1.4.27.
[14] Technical dossier/Section II/Annex II.2.1.4.28.
[15] Technical dossier/Section II/Annex II.2.1.4.25.
[16] Technical dossier/Section II/Annex II.2.1.4.1, Annex II.2.1.4.4, Annex II.2.1.4.7, Annex II.2.1.4.10, Annex II.2.1.4.13, Annex II.2.1.4.16, Annex II.2.1.4.19, Annex II.2.1.4.22 and Annex II.2.1.4.25.
[17] Technical dossier/Supplementary information August 2022/Annex_1Q1_2_CoA.
[18] Technical dossier/Section II/Annex II.2.5.2.1.3.
[19] Technical dossier/Section II/Annex II.2.5.2.1.2.
[20] Technical dossier/Section II/Annex II.2.5.2.1.1.
[21] Technical dossier/Section II/Annex II.2.1.5.18, Annex II.2.1.5.19 and Annex II.2.1.5.20.
[22] Technical dossier/Section II/Annex II.2.1.5.11, Annex II.2.1.5.12 and Annex II.2.1.5.13.
[23] Technical dossier/Section II/Annex II.2.1.5.4, Annex II.2.1.5.5 and Annex II.2.1.5.6.
[24] Technical dossier/Section II/Annex II.2.1.5.21.
[25] Technical dossier/Section II/Annex II.2.1.5.14.
[26] Technical dossier/Section II/Annex II.2.1.5.7.
[27] Technical dossier/Section II/Annex II.2.1.5.15, Annex II.2.1.5.16 and Annex II.2.1.5.17.
[28] Technical dossier/Section II/Annex II.2.1.5.8, Annex II.2.1.5.9 and Annex II.2.1.5.10.
[29] Technical dossier/Section II/Annex II.2.1.5.1, Annex II.2.1.5.2 and Annex II.2.1.5.3.

3.1.4. Stability and homogeneity

3.1.4.1. Shelf-life

The shelf-life of three batches of each formulation was studied when stored in vacuum aluminium bags at variable room temperature (ranging between −2.8 and 32.8°C for 12 months (powder))[30] or 24 months (micropellet and microsphere).[30] Negligible losses in yeast counts (≤ 0.5 log) were observed at the end of the respective storage periods.

3.1.4.2. Stability

One batch of the micropellet and one batch of microsphere formulations of the additive were mixed into three different standard vitamin/mineral premixture (two for dairy cows and one for piglets). Samples were stored in paper bags for 6 months at 20–25°C/50%RH. No reduction in the yeast counts (< 0.5 log) was observed.[30]

Three batches of the micropellet formulation of the additive were incorporated either in mash feed for piglets (based on maize, barley and soybean), feed for pigs for fattening (based on maize and wheat) or feed for calves (based on maize and soybean) following the respective conditions of use. Samples of the mash feeds were stored in paper bags for 3 months at 20–25°C. No reduction in the yeast counts (< 0.5 log) was observed after 3-month storage.[30]

Two batches of the microsphere formulation of the additive were incorporated in a standard mash feed for pigs for fattening based on maize, wheat and sunflower meal and tested for stability during pelleting at 70°C. Mash and pelleted feeds were stored in paper bags at 20–25°C/50% relative humidity (RH) for 3 months. Pelleting caused a loss of 0.5 log in the yeast count. No reduction in the yeast count (< 0.5 log) was observed after 3-month storage.[30]

Two batches of the powder formulation of the additive were incorporated in three samples of mash feed for piglets (based on sweet whey, soy protein concentrate and wheat middlings), for dairy cows (based on distiller grain, sucrose and wheat middlings) and for pigs fattening (based on maize, wheat and sunflower meal). Mash feeds were stored in paper bags at 20–25°C/50% RH for 3 months.[31] No reduction in the yeast count (< 0.5 log) was observed after 3-month storage.[30]

3.1.4.3. Homogeneity

The homogeneous distribution of the formulations of the additive micropellet, microsphere and powder was studied in 10 subsamples of starter feed for calves,[32] mash feed for pigs for fattening[33] and mash feed for dairy cows,[34] respectively. The coefficients of variation were 4.9%, 3.3% and 4.7%, respectively.[35]

3.1.5. Conditions of use

The additive is intended to be used at the following proposed minimum use levels for:

- Horses: 3.0×10^9 CFU/kg complete feed
- Dairy cows and minor dairy species: 4.0×10^8 CFU/kg complete feed
- Calves, cattle for fattening and minor growing and fattening ruminants: 4.0×10^9 CFU/kg complete feed
- Piglets and pigs for fattening and minor porcine species: 4.0×10^9 CFU/kg complete feed
- Sows and minor porcine species for reproduction: 6.0×10^9 CFU/kg complete feed

3.2. Safety

3.2.1. Safety for the target species, consumer and environment

The species *S. cerevisiae* is considered by EFSA to be suitable for the qualified presumption of safety (QPS) approach to safety assessment (EFSA, 2007; EFSA BIOHAZ Panel, 2020). The identity of the active agent was confirmed as *S. cerevisiae* and the MIC values resulting from the antimycotic

[30] Technical dossier/Section II/Annex II.2.4.1.2.
[31] Technical dossier/Supplementary information August 2022/Annex_1Q3_II.2.4.1.2_Stability_BioCell_updated.
[32] Technical dossier/Section II/Annex II.2.4.2.2.
[33] Technical dossier/Section II/Annex II.2.4.2.3.
[34] Technical dossier/Section II/Annex II.2.4.2.4.
[35] Technical dossier/Section II/Annex II.2.4.2.2, Annex II.2.4.2.3. and Annex II.2.4.2.4.

susceptibility testing were considered to be low. Therefore, it is presumed safe for the target species, the consumer and the environment.

3.2.2. Safety for the user

3.2.2.1. Effect on respiratory system

The dusting potential reported for the powder formulation of the additive (up to 2,390 mg/m^3 air) indicated that exposure by inhalation is likely, whereas the dusting potential analytical data for the micropellet and microsphere formulations of the additive indicate that the exposure by inhalation is unlikely. Considering the proteinaceous nature of the additive, BioCell® should be considered a respiratory sensitiser.

3.2.2.2. Effect on eyes and skin

For each formulation of the additive (microsphere,[36] micropellet[37] and powder[38]), an *in vitro* study for skin irritation was performed following OECD Test Guideline 439. The results of these studies showed that all the test items are not skin irritants.

For each formulation of the additive (microsphere,[39] micropellet[40] and powder[41]), an *in vitro* study for eye irritation was performed according to OECD Test Guideline 492. The results of these studies showed that all the test items are not eye irritants.

For each formulation of the additive (microsphere,[42] micropellet[43] and powder[44]), an *in vitro* study for skin sensitisation was performed according to OECD Guideline 442E. The Panel notes that the OECD test guidelines available at present are designed to assess the skin sensitisation potential of chemical substances only and that currently no validated assays for assessing the sensitisation potential of microorganisms are available.[45] Thus, no conclusion can be drawn on the skin sensitising potential of the additive.

3.2.2.3. Conclusions on safety for the user

The additive, in any formulation, is not irritant to the eyes and skin, but should be considered a respiratory sensitiser. However, exposure by inhalation to the microsphere and micropellet formulations is unlikely. No conclusions could be drawn on the skin sensitisation potential of the additive.

3.3. Efficacy

Saccharomyces cerevisiae DBVPG 48 SF (BioCell®) is intended for use as digestibility enhancer for horses and as 'other zootechnical additives' (to improve productive performance) for pigs and ruminants. The applicant submitted a total of 15 studies in horses, veal calves, dairy cows, piglets and sows to support the efficacy of the target species.

3.3.1. Efficacy for horses

Three short-term digestibility trials sharing a similar design were submitted aiming at assessing the effect of the additive on the nutrient digestibility in horses. The details on the experimental design are shown in Table 1 and the main results in Table 2.

[36] Technical dossier/Section II/Annex III.3.3.1.2.3., Supplementary Information August 2022/Annex_1Q6_III.3.3.1.2.3a_Skin_Irritation_Microsphere and Supplementary Information August 2022/Annex_1Q4_1_CoAs.
[37] Technical dossier/Section II/Annex III.3.3.1.2.2., Supplementary Information August 2022/Annex_1Q6_III.3.3.1.2.2a_Skin_Irritation_Micropellet and Supplementary Information August 2022/Annex_1Q4_1_CoAs.
[38] Technical dossier/Section II/Annex III.3.3.1.2.1., Supplementary Information August 2022/Annex_1Q4_1_CoAs and Supplementary Information August 2022/Annex_1Q6_III.3.3.1.2.1a_Skin_Irritation_Powder.
[39] Technical dossier/Section II/Annex III.3.3.1.2.9. and Supplementary Information August 2022/Annex_1Q4_1_CoAs.
[40] Technical dossier/Section II/Annex III.3.3.1.2.10. and Supplementary Information August 2022/Annex_1Q4_1_CoAs.
[41] Technical dossier/Section II/Annex III.3.3.1.2.8. and Supplementary Information August 2022/Annex_1Q4_1_CoAs.
[42] Technical dossier/Section II/Annex III.3.3.1.2.5. and Supplementary Information August 2022/Annex_1Q6_III.3.3.1.2.6a_Skin_Sensitization_Microsphere.
[43] Technical dossier/Section II/Annex III.3.3.1.2.6. and Supplementary Information August 2022/Annex_1Q6_III.3.3.1.2.5a_Skin_Sensitization_Micropellet.
[44] Technical dossier/Section II/Annex III.3.3.1.2.4., Supplementary Information August 2022/Annex_1Q6_III.3.3.1.2.4a_Skin_Sensitization_Powder and Supplementary Information August 2022/Annex_1Q4_1_CoAs.
[45] https://www.efsa.europa.eu/sites/default/files/2022-07/feedap20220629-30_m.pdf.

Table 1: Trial design of the efficacy trials performed in horses

Trial	No. of replicates (duration) Cycle(1)	Breed (Gender) Age Body weight	Basal diet (% of feed offered)	Test item concentration in feed (CFU/kg)	
				Intended	Analysed
1[46]	6 (48 days) 20:8:20	Gidran (♀) 7.6 ± 5.0 years 443–540 kg	Meadow hay (80%) and concentrate(2) (20%)	0 3.0×10^9	0 3.8×10^9
2[47]	6 (48 days) 20:8:20	Gidran (♀) 8.7 ± 4.3 years 478–554 kg	Meadow hay (80%) and concentrate(3) (20%)	0 3.0×10^9	0 4.0×10^9
3[48]	8 (71 days) 28:15:28	Quarter 5♂ 3♀ 8.0 ± 1.8 years 420–511 kg	Mix hay (80%), concentrate(4) (7%), fibrous mixture(5) (6%) and cracked maize (6%)	0 3.0×10^9	0 4.8×10^9

(1): Phase I:Washout:Phase II.
(2): Rolled oat (2/3) and barley (1/3).
(3): 80% rolled oat (2/3) and barley (1/3) and 20% commercial concentrate (based on barley, wheat bran, maize).
(4): Based on wheat bran, alfalfa and barley.
(5): Based on grass hay, ryegrass and barley.

In all trials, the horses were randomly allocated into two groups, balanced by initial body weight and were kept in individual pens throughout the whole experimental period. All trials followed a crossover design, acting each horse as its own control. The trials lasted 48 (trials 1 and 2) or 71 (trial 3) days distributed in three phases: phase I – half of the horses received a basal diet, whereas the other half received the same basal diet supplemented with the additive for 20 (trials 1 and 2) or 28 (trial 3) days; washout phase – all horses received the basal diet for 8 (trials 1 and 2) or 15 (trial 3) days; phase II – the horses previously receiving the basal diet were supplemented with the additive for 20 (trials 1 and 2) or 28 (trial 3) days and vice versa.

In trials 1 and 2, the horses were fed three times per day, with hay and concentrate offered separately (see Table 1). The first and last concentrate of the day were top-dressed either with 3 g of wheat flour (control) or the same amount of BioCell® S12 per horse and day (equivalent to 3.0×10^9 CFU/kg complete feed). Horses were weighed at the beginning and at the end of each phase, and the feed intake daily recorded. On days 17–20 of each phase, feed (both hay and concentrate) and rectal faecal samples were collected from each horse, and analysed for dry matter, neutral detergent fibre (NDF), acid detergent fibre (ADF), acid detergent lignin (ADL), crude ash and AIA (acid insoluble ash; as internal marker). The organic matter, hemicellulose (NDF-ADF) and cellulose (ADF-ADL) contents were calculated, and the apparent total tract digestibility (ATTD) of all parameters determined.

In trial 3, the horses were fed twice a day, with a mixture of hay, concentrate, fibrous mixture and cracked corn (see Table 1). The morning feed was either not supplemented (control) or top-dressed with 3 g of BioCell® S12 per horse and day (equivalent to 3.0×10^9 CFU/kg complete feed). The horses were weighed on days 1, 15, 23 and 28 of each phase. From day 23 to 28, feed intake was daily recorded, and feed and rectal faecal samples were collected from each horse and analysed for dry matter, NDF, ADF, ADL, crude ash and AIA. The organic matter, hemicellulose and cellulose contents were calculated, and the ATTD of all parameters determined.

The experimental data of the three trials were analysed using the mixed procedure for repeated measurements, accounting for the effects of treatment, phase and their interactions, and the horse as a random factor. Significance was set at 0.10. The interaction phase × treatment was not significant in any trial.

[46] Technical dossier/Section IV/Annex IV.4.2.1.
[47] Technical dossier/Section IV/Annex IV.4.2.2.
[48] Technical dossier/Section IV/Annex IV.4.2.3.

Table 2: Effects of BioCell® on the apparent total tract digestibility in horses

Trial	Groups	Apparent total tract digestibility (%)					
	CFU/kg feed	Dry matter (DM)	Organic matter (OM)	Neutral detergent fibre (NDF)	Acid detergent fibre (ADF)	Hemicellulose	Cellulose
1	0	40.2	41.4[b]	26.7[b]	10.5	52.1[b]	14.3
	3.0×10^9	41.1	42.9[a]	29.0[a]	11.3	59.1[a]	12.9
2	0	43.2	43.9	25.3[b]	17.8[b]	39.7	26.5
	3.0×10^9	43.6	44.3	31.5[a]	26.8[a]	43.5	29.7
3	0	54.0[b]	55.4[b]	46.7[b]	41.0[b]	52.9[b]	53.6[b]
	3.0×10^9	58.2[a]	59.9[a]	52.5[a]	48.0[a]	57.6[a]	59.4[a]

[a,b]: Mean values within a trial and within a column with a different superscript are significantly different $p < 0.10$.

The horses fed with BioCell® S12 at the use level showed higher ATTD of NDF in all trials compared with the control group. Moreover, compared to the control, the supplemented group showed higher ATTD of organic matter and hemicellulose in trial 1; of ADF in trial 2; and of dry matter, organic matter, ADF, hemicellulose and cellulose in trial 3. No differences were observed in the final body weight and feed intake in any trial.

3.3.2. Efficacy for veal calves

Three long-term efficacy studies were performed with Holstein calves (range of age in days: trial 1: 17–71; trial 2: 13–40; trial 3: 10–69).[49] However, none could be further considered to support the efficacy of the additive due to the high number of veterinary medical treatments administered (ranging 20%–45% of total animals) and the high mortality rates (6%–7% in the control groups).

3.3.3. Efficacy for dairy cows

Three long-term trials sharing a common design were submitted aiming at assessing the effect of the additive on the productive performance of dairy cows. The details on the study design are provided in Table 3 and the main results in Table 4. The duration of all the trials was 84 days and the cows were randomly allocated into two treatments, balanced according to lactation number, lactation stage and average milk yield.

The Panel noted that in trials 2 and 3, several cows were at ≥ 100 days in milk (DIM)[50] at start, instead of 4–8 weeks after calving as stated in the Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018a). Despite that, the Panel considered these trials in the assessment, as the average milk yield was higher than 30 kg/day.

In all trials, the cows were housed in collective barns equipped with automatic feed bins, allowing for individual feed intake monitoring. In trials 1 and 2, the basal feed was offered ad libitum as a total mixed ration (see Table 3). Twice daily, at the milking parlour, each cow received 25 g of sucrose either not supplemented (control) or supplemented with 0.5 g BioCell® M16/head/day (equivalent to an intended dose of 4.0×10^8 CFU/kg complete feed).[51] In trial 3, the cows received a partial mixed ration ad libitum, complemented with a concentrate offered separately. The concentrate was daily top-dressed with 50 g of maize gluten which was either not supplemented (control) or supplemented with 0.5 g BioCell® M16/head/day (equivalent to an intended dose of 4.0×10^8 CFU/kg complete feed). In all cases, it was reported that all the cows consumed the supplement, and, thus, no leftovers were detected.[52]

[49] Technical dossier/Section IV/Annex IV.4.3.7-Annex IV.4.3.9.
[50] Supplementary information August 2022/Annex_2Q2g_DIM_parity_stats_Trial1_cows, Supplementary information August 2022/Annex_2Q2g_DIM_parity_stats_Trial2_cows and Supplementary information August 2022/Annex_2Q2g_DIM_parity_stats_Trial3_cows.
[51] Supplementary information August 2022/0_EFSA_SIn_03Mar2020_add18May2022_reply_AUG22 and Supplementary information August 2022/Annex_2Q2_UM_Summary_cows.
[52] Supplementary Information August 2022/0_EFSA_SIn_03Mar2020_add18May2022_reply_AUG22.

Table 3: Trial design and use level of the efficacy trials performed in dairy cows

Trial	Total N (cows/rep) Reps/treat	Breed Av. body weight Days in milk (Lactation number)	Feeding method (Composition)	Groups (CFU/kg complete feed)	
				Intended	Calculated
1[53]	42 (1) 21	Holstein Friesian 655 kg 60 (2–3)	Total mixed ration (maize silage and meal, wheat silage and soybean meal)	0 4.0×10^8	0 3.6×10^8
2[54]	42 (1) 21	Holstein Friesian 654 kg 100 (2–3)	Total mixed ration (based on maize silage and meal, lucerne hay, ryegrass hay and soybean meal)	0 4.0×10^8	0 3.8×10^8
3[55]	44 (1) 22	Holstein Friesian 693 kg 137 (1–10)	Partial mixed ration (based on maize silage and ryegrass silage) plus concentrate (based on maize meal, soybean hulls and rapeseed meal)	0 4.0×10^8	0 3.4×10^8

The health status of the animals in all trials was monitored daily and any administered treatment recorded. In trials 1 and 2, the cows were weighed at the start (day 1) and at the end (day 84) of the trial, and the individual feed intake and milk yield were daily recorded. Milk samples were collected from each cow twice a week to determine total solids, fat, protein, lactose, urea and somatic cell counts. The average body weight change, daily dry matter intake and feed efficiency (kg of milk production per kg of dry matter consumed) calculated per week and for whole experimental period. In trial 3, individual body weight, feed intake and milk production were recorded daily. Milk samples were collected from each cow twice a week to determine total solids, fat, protein, lactose, urea and somatic cell counts. The average body weight change, daily dry matter intake and feed efficiency (kg of milk production per kg of dry matter consumed) calculated per week and for the whole experimental period.

In all trials, the data for performance parameters and milk composition were analysed with a mixed model, considering the treatment and week as fixed effects, and including cow as random effect. Significance level was set at 0.10.

Table 4: Effects of BioCell® on the performance of dairy cows

Trial	Groups	Average daily dry matter intake	Milk yield	Feed efficiency	Milk fat content	Milk protein content	Milk total solids content
	(CFU/kg complete feed)	(kg DM)	(kg)	(kg milk/kg DM intake)	(%)	(%)	(%)
1	0 4.0×10^8	25.28 25.47	40.19^b 42.56^a	1.59^b 1.67^a	3.77 3.77	3.24^b 3.30^a	12.67 12.66
2	0 4.0×10^8	24.27 24.42	37.33^b 39.25^a	1.54^b 1.61^a	3.77 3.78	3.28 3.27	12.68 12.67
3	0 4.0×10^8	25.03 25.10	30.35 32.97	1.21^b 1.35^a	4.61 4.64	3.84 3.95	13.60 13.70

[a,b]: Mean values within a trial and within a column with a different superscript are significantly different $p < 0.1$.

The supplementation of dairy cows with the additive at the use level showed higher milk yield (trials 1 and 2), improved feed efficiency (trials 1, 2 and 3) and milk protein content (trial 1) in comparison with the control.

[53] Technical dossier/Section IV/Annex IV.4.3.10 and Supplementary information August 2022/Annex_2Q2_UM_Summary_cows.
[54] Technical dossier/Section IV/Annex IV.4.2.11 and Supplementary information August 2022/Annex_2Q2_UM_Summary_cows.
[55] Technical dossier/Section IV/Annex IV.4.2.12 and Supplementary information August 2022/Annex_2Q2_UM_Summary_cows.

3.3.4. Efficacy for piglets

Three long-term trials sharing a common design were submitted aiming at evaluating the effect of the additive on the zootechnical performance of weaned piglets. The details on the study design are provided in Table 5 and the main results in Table 6.

Table 5: Trial design and use level of the efficacy trials performed in weaned piglets

Trial	Total n° of animals (animals × replicate) Replicates × treatment	Breed Gender (duration) Initial BW (kg)	Composition feed (form)	Groups (CFU/kg complete feed)	
				Intended	Analysed*
1[56]	240 (10) 12	Topigs 50:50 ♀♂ (42 days) 6.93	Maize, barley and soybean meal (mash)	0 4.0×10^9	0 4.1×10^9
2[57]	192 (8) 12	Hypor 50:50 ♀♂ (42 days) 8.11	Maize, wheat and soybean meal (mash)	0 4.0×10^9	0 4.1×10^9
3[58]	450 (15) 15	Duroc × Large White 40:60 ♀♂ (42 days) 7.42	Maize and soybean meal (mash)	0 4.0×10^9	0 4.0×10^9

*: Average analysed values for the pre-starter and starter diets.

In all trials, the piglets (28 days of age) were distributed in pens balanced by initial body weight and randomly allocated into two treatments. Two basal diets (pre-starter, from day 1 to 14; starter, from day 15 to 42) were either non-supplemented (control) or supplemented with BioCell® M16 at 4.0×10^9 CFU/kg feed (confirmed by analysis).

Health status and mortality of the animals were monitored daily and the cause of death, reason for culling and veterinary medicinal interventions recorded. Animals were weighed at the start of the trial (day 1) and body weight and feed intake recorded at the end (day 42). The average daily feed intake, average daily gain and feed to gain ratio were calculated and corrected for mortality for the whole experimental period. Data were analysed by mixed model, accounting for the fixed effect of dietary treatment and the random effect of the pen. Significance was set at 0.05.

Table 6: Effects of BioCell® on the performance of weaned piglets (from 28 to 70 days of life)

Trial	Groups	Daily feed intake	Final body weight	Average daily gain	Feed to gain ratio	Mortality and culling
	(CFU/kg complete feed)	kg/day	kg	g		(%)
1	0 4.0×10^9	1.05 1.04	27.0^b 28.7^a	475^b 519^a	2.22^a 2.02^b	2.5 0.8
2	0 4.0×10^9	1.11 1.09	29.4^b 31.0^a	506^b 545^a	2.20^a 2.02^b	2.1 0
3	0 4.0×10^9	0.98 0.99	28.4^b 30.8^a	500^b 556^a	1.96^a 1.79^b	3.6 2.7

^{a,b}: Mean values within a trial and within a column with a different superscript are significantly different $p < 0.05$.

Mortality and culling were low and not affected by treatment in any trial. In the three trials, the animals receiving the additive at the use level showed higher final body weight, average daily gain and improved feed to gain ratio.

[56] Technical dossier/Section IV/Annex IV.4.3.1.
[57] Technical dossier/Section IV/Annex IV.4.3.2.
[58] Technical dossier/Section IV/Annex IV.4.3.3.

3.3.5. Efficacy for sows

Three trials sharing a common design were submitted in order to assess the effect of the additive on the productive performance of sows and their litter. The details on the study design are provided in Table 7 and the main results in Table 8 and Table 9.

Table 7: Trial design and use level of the efficacy trials performed in lactating sows

Trial	Total n° of animals (animals × replicate) Replicates × treatment	Breed (duration) Parity number	Basal diet composition (form)	Groups (CFU/kg complete feed)	
				Intended	Analysed
1[59]	24 (1) 12	Topigs TN60 (43 days) 2–5	Maize, barley, soybean meal (mash)	0 6.0×10^9	0 6.1×10^9
2[60]	24 (1) 12	Hypor (48 days) 2–5	Maize, wheat, canola meal (mash)	0 6.0×10^9	0 6.1×10^9
3[61]	50 (1) 25	Large White (55 days) 2–5	Maize, wheat, sunflower meal (mash)	0 6.0×10^9	0 5.8×10^9

All trials started approximately 3–4 weeks before the expected farrowing date until weaning (piglets at 25 days of age). The animals were blocked by parity and randomly allocated to two dietary treatments. In trials 1 and 2, sows were kept in multiple pens of six sows each until 10 days before the expected farrowing, and then transferred to individual farrowing crates. In trial 3, the animals were kept in individual crates throughout the whole trial. The basal diets were either non-supplemented (control) or supplemented with BioCell® M16 at the recommended use level of 6.0×10^9 CFU /kg feed (confirmed by analysis). The litters were fostered between sows of the same treatment group, within 3 days after birth, to ensure even distribution of piglets per sow. No creep feed was offered to the piglets during lactation in any trial.

The health status and mortality of sows and piglets were monitored daily, and the veterinary medical interventions recorded. Sows were weighed at the beginning and at the end (weaning) of the experimental period, and the individual feed intake daily recorded. Regarding the litters' performance, the number of births, stillbirth and birth alive, the fostered and weaned size of the litter, and the weight of piglets at birth and at weaning were recorded. The sows' body weight loss, total feed intake and feed efficiency[62] and the litter's average fostered weight and piglets' individual average daily weight gain were calculated.

The sows' and litters' performance data were tested with a mixed model, including the treatment as fixed effect and the sow/litter as random effect. Significance was set at 0.05.

No sow died in any trial. Piglets' mortality was on average 4.5%, 4.2% and 5.9% for trials 1, 2 and 3, respectively, and no significant differences were observed among treatments.

Table 8: Effects of BioCell® on the performance of sows

Trial	Groups	Total feed intake	Body weight at farrowing	Body weight at weaning	Body weight loss
	(CFU/kg complete feed)	(kg)	(kg)	(kg)	(g)
1[59]	0 6.0×10^9	130.70^b 133.65^a	274.8 267.7	220.1 232.3	54.66^a 35.42^b
2[60]	0 6.0×10^9	130.84^b 132.80^a	265.0 277.4	207.0^b 235.9^a	58.00^a 41.50^b
3[61]	0 6.0×10^9	163.89 163.88	264.7 267.8	209.4 227.0	55.28^a 40.84^b

[a,b]: Mean values within a trial and within a column with a different superscript are significantly different $p < 0.05$.

[59] Technical dossier/Section IV/Annex IV.4.3.4.
[60] Technical dossier/Section IV/Annex IV.4.3.5.
[61] Technical dossier/Section IV/Annex IV.4.3.6.
[62] kg of feed consumed by sow per kg of weight gained by the litter.

In the three trials, the supplementation of the sows' feed with BioCell® M16 at the recommended level significantly improved the zootechnical performance of the litter (higher individual average daily gain and body weight at weaning). A higher feed intake (trials 1 and 2) and lower back fat loss (all trials) were observed in the sows receiving the additive in comparison with the control.

Table 9: Effect of BioCell® on litter size, piglets' weight and mortality during lactation

Trial	Group	Litter Size		Piglets' weight		Individual average daily gain	Mortality
		Birth	Weaning	Birth	Weaning		
	(CFU/kg complete feed)	(n)	(n)	(kg)	(kg)	(kg)	(%)
1	0	11.2	10.4[b]	1.25	6.70[b]	0.22[b]	6.7
	6.0×10^9	11.8	11.5[a]	1.27	7.47[a]	0.25[a]	2.2
2	0	13.8	11.1	1.25	6.63[b]	0.22[b]	4.9
	6.0×10^9	14.1	11.6	1.24	7.56[a]	0.25[a]	3.4
3	0	11.2	10.6	1.02	7.44[b]	0.20[b]	5.6
	6.0×10^9	11.7	11.0	1.01	7.83[a]	0.24[a]	6.2

[a,b]: Mean values within a trial and within a column with a different superscript are significantly different $p < 0.05$.

3.3.6. Conclusions on efficacy

The additive BioCell® has the potential to be efficacious at the proposed conditions of use as digestibility enhancer for horses and to improve the zootechnical performance of dairy cows, weaned piglets and sows (with an effect on the litter). This conclusion can be extrapolated to all pigs and other dairy ruminants. Due to lack of adequate data, no conclusion can be drawn on the efficacy for veal calves, and, consequently, on other ruminants for fattening or rearing.

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[63] and good manufacturing practice.

4. Conclusions

Saccharomyces cerevisiae DBVPG 48 SF is considered safe for the target species, the consumer and the environment. The additive, in any formulation, is not irritant to the eyes and skin but should be considered a respiratory sensitiser. No conclusions could be drawn on the skin sensitisation potential of the additive. The Panel concluded that the additive has the potential to be efficacious at the proposed conditions of use for horses, dairy ruminants and all pigs. Due to lack of adequate data, no conclusion could be drawn on the efficacy for veal calves, and, consequently, on other ruminants for fattening or rearing.

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[63] 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.

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Abbreviations

BW	body weight
CFU	colony forming unit
DM	dry matter
EURL	European Union Reference Laboratory
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
LOQ	limit of quantification
OECD	Organisation for Economic Co-operation and Development
RH	relative humidity