Assessment of the safety and efficacy of an additive of *Quillaja saponaria* and *Yucca schidigera* (Magni-Phi®) as a feed additive for use in all avian species (excluding laying and breeding birds)

Reference number RP1047

Regulated Products Risk Assessment Unit
Science, Evidence and Research Division, FSA

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Regulated Product Dossier Assessment
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Abbreviations

Acronym	Definition
ACAF	Advisory Committee on Animal Feedingstuffs
ADFI	Average daily feed intake
ADG	Average daily gain
BCOP	Bovine corneal opacity and permeability
BW	Body weight
CFU	Colony forming units
EFSA	European Food Safety Authority
EPEF	European production efficiency factor
EURL	European Reference Laboratory
FCR	Feed conversion ratio
FSA	Food Standards Agency
FSS	Food Standards Scotland
GLP	Good Laboratory Practice
HACCP	Hazard Analysis and Critical Control Points
HPLC	High performance liquid chromatography
HPLC-MS	High performance liquid chromatography-mass spectrometry
MPN	Most probable number
R_{Rec}	Recovery rate
RSD_{ip}	Relative standard deviations for intermediate precision
RSD_r	Relative standard deviations for repeatability
UHPLC-UV	Ultra-high performance liquid chromatography coupled with ultraviolet detection

Summary

An application was submitted to the Food Standards Agency in April 2021 from Phibro Animal Health Corporation ("the applicant") for the new authorisation of an additive (Magni-Phi®), a natural preparation of powdered dry *Quillaja saponaria* and dry *Yucca schidigera*, under the category "zootechnical additives" and functional group "digestibility enhancer and other (performance enhancer)". The additive is proposed to be used in all avian species (excluding laying and breeding birds), with a proposed inclusion rate of 250 mg/kg of complete feed.

The Advisory Committee on Animal Feedingstuffs (ACAF) was asked to review the dossier and the supplementary information submitted by the Applicant, and to advise the Food Standards Agency and Food Standards Scotland (FSA/FSS) in evaluating the dossier.

The Advisory Committee on Animal Feedingstuffs (ACAF) initially evaluated the identity and characterisation of the additive. Upon receiving further information relating to the identity of the product, the manufacturing process, management of potential contaminants and homogeneity, the Committee concluded that the additive was correctly identified and characterised.

The FSA/FSS concluded, based on the ACAF's advice, that the additive can be considered safe for the target species, consumers, and the environment. With regard to user safety, the additive should be considered potentially harmful by inhalation, and as a potential eye irritant and skin sensitiser. The additive is not a skin irritant.

The additive can be considered efficacious in broiler chickens when included in complete feed at a minimum dose of 250 mg/kg. This efficacy data can be extrapolated to other poultry for fattening and ornamental birds.

The views of ACAF have been taken into account in this safety assessment which represents the opinion of the FSA/FSS.

1. Introduction

The FSA/FSS have undertaken a risk assessment for a feed additive (Magni-Phi®, Phibro Animal Health Corporation, 300 Frank W. Burr Blvd., Ste. 21 / Teaneck, NJ) under Assimilated Regulation (EC) No 1831/2003[1] under the category of "zootechnical additives" and functional group "digestibility enhancer and other (performance enhancer)" for its use in all avian species (excluding laying and breeding birds). To support the safety assessment, the ACAF provided advice to the FSA/FSS as outlined in this document.

In line with Article 8 of 1821/2003, the assessment has considered whether the feed additive complies with the conditions laid down in Article 5, including: safety considerations for human, animal and environmental health; efficacy of the additive for its intended effect; potential impairment of the distinctive features of animal products. This, and the guidance put in place by the European Food Safety Authority (EFSA) for the evaluation of feed additive applications, has formed the basis and structure for the assessment.

With thanks to the members of the ACAF during the course of the assessment, who were: Professor Nicholas Jonsson, Martin Briggs, Professor Emily Burton, Professor Katrina Campbell, Professor Matthew Fisher, Hannah Kane, Susan MacDonald, Dr. Oonagh Markey, Christine McAlinden, Dr. Donald Morrison, Derek Renshaw, Dr. Michael Salter, Dr. Adam Smith, Dr. Helen Warren and Dr. Nick Wheelhouse.

The dossier was initially evaluated by the ACAF at their April 2023 meeting, after which a request for further information was communicated to the applicant. The applicant's response to this request by the FSA was reviewed by ACAF at their September 2023 meeting.

This document sets out the findings of the Committee's assessment on the safety and efficacy of the feed additive, on which the FSA/FSS have made their opinion for the request of a new authorisation.

2. Assessment

2.1. Section II: Identity, characterisation and conditions of use

The additive, Magni-Phi®, is a natural preparation of powdered dry *Quillaja saponaria* (85% w/w) and dry *Yucca schidigera* (15% w/w) with a minimum saponin content of 3.5% (w/w). *Quillaja* saponins are the main active substance and are the primary markers for traceability and stability.

The applicant provided data from five batches supporting the specification values and three batches supporting the physico-chemical properties and purity given below in Table 1.

Table 1: Identity table Magni-Phi®

Parameter	
Moisture	<7 % w/w
Granulometry (< 60 µm mesh)	>90 % w/w
Extractable solids	>15 % w/w
Quillaja saponins	>3.5 % w/w
Ammonium binding capacity or B50	<6 g
Appearance	
Solid beige powder	
Physico-chemical properties	
Dusting potential	2,248.3 mg/m^3
Particle size (measured by laser diffraction)	8.39 µm – 638.2 µm ~ 50 % < 100 µm
Impurities	
Enterobacteriaceae (MPN)	<3
Escherichia coli	Absence/10 g
Salmonella spp.	Absence/25 g
Bacillus cereus	Not tested
Mould	<10 CFU/g
Yeast	<10 CFU/g
Arsenic	<2 mg/kg
Lead	<5 mg/kg
Cadmium	<0.5 mg/kg
Mercury	<0.1 mg/kg
Aflatoxin B1	<5 µg/kg
Aflatoxin B2	<5 µg/kg

Aflatoxin G1	<5 µg/kg
Aflatoxin G2	<5 µg/kg
Total aflatoxins	<5 µg/kg
Fumonisin	<30 µg/kg
HT-2 Toxin	<10 µg/kg
Ochratoxin A	<5 µg/kg
T-2 Toxin	<1 µg/kg
Deoxynivalenol	<10 µg/kg
Zearalenone	<25 µg/kg

The Committee evaluated the identity and characterisation of the additive and determined there was uncertainty surrounding the identity of the product and the comparisons the applicant had made to other substances throughout the literature. Following the request of a more detailed description and analytical characterisation of Magni-Phi® from the applicant, the Committee was able to conclude that the product had been fully identified and characterised. Other queries were satisfactorily addressed by the applicant though provision of additional information on the manufacturing process, particularly relating to the blending and drying phases, as well as further detail on Hazard Analysis and Critical Control Points (HACCP).

The Committee discussed the potential for issues with contaminants given the variable growing environments and the possibility of differing levels of heavy metals and other contaminants, therefore the applicant was asked to provide further information on how this risk is managed. The Committee also requested an explanation for the range of coefficients of variation for homogeneity.

The proposed conditions of use of the additive are described in Table 2.

Table 2: Conditions of use of Magni-Phi®

Proposed mode of use in animal nutrition	
Additive	Magni-Phi®
Registration number/ EC No/No	Not available
Category(-ies) of additive	4. Zootechnical feed additive
Functional group(s) of additive	a. Digestibility enhancer and d. Other (performance enhancer)

Description				
Description		**Purity criteria**		**Method of analysis**
A preparation of *Quillaja saponaria* 85% and *Yucca schidigera* 15%		Complies with EU feed hygiene law		HPLC
Trade name (if appropriate)			Magni-Phi®	
Name of the holder of authorisation (if appropriate)			Phibro Animal Health Corporation	
Conditions of use				
Species or category of animal	**Maximum Age**	**Min. content**	**Max. content**	**Withdrawal period**
		mg/kg of complete feedingstuffs		
Chickens for fattening	To slaughter age & weight	250	-	-
Chickens reared for laying/breeding	To point of lay	250	-	-
Turkeys for fattening	To slaughter age & weight	250	-	-
Turkeys reared for breeding	To point of breeding	250	-	-
Minor poultry species	To slaughter age & weight/To point of lay/breeding	250	-	-
Ornamental birds	No max. age	250	-	-

2.1.1. Conclusions on Section II

Upon receiving further information, the ACAF was able to conclude on the complete identification and characterisation of the additive.

No further concerns were raised for Section II of this dossier.

2.2. Section III: Safety

2.2.1. Safety for the target species

The applicant provided a tolerance study in chickens for fattening, intending for the safety of Magni-Phi® to be extrapolated to all avian species (excluding laying and breeding birds). The Committee evaluated the tolerance studies provided, determining

that the studies were not carried out to Good Laboratory Practice (GLP). However, the methods were found to be well described, and the study conducted and monitored by persons with appropriate experience. The Committee requested further details on the collection, storage and analysis of samples, as well as certificates for assurance of quality for this tolerance study. Upon receiving this additional information, the Committee was able to conclude that the additive could be tolerated by the target species up to a 5000 mg/kg inclusion rate.

A literature review was provided by the applicant to support the safety evaluation of Magni-Phi® for the target species. In this review, the applicant considered the individual safety of *Quillaja* saponins and *Yucca* powder in avian species. Given the study performed by the applicant and the supporting literature, the applicant considered Magni-Phi® to be safe for all avian species (excluding laying and breeding birds) at the proposed dose.

2.2.2. Safety for the consumer

No data was provided relating to safety of use for consumers. Alternatively, the applicant used existing literature to demonstrate that *Quillaja* and *Yucca* are present in human food. The Committee was satisfied that Magni-Phi® would not present a risk for the consumer.

2.2.3. Safety for the user

The effects of Magni-Phi® on the skin and eyes were demonstrated through three studies:

- In vitro skin corrosion (EPISKIN™ model)
- Bovine corneal opacity and permeability (BCOP)
- In vitro skin irritation (EPISKIN™/MTT method)

The results of the EPISKIN tests showed that the additive did not have the potential to be corrosive or irritant to skin. The Committee noted that the results of the in vitro test for eye irritation were strongly positive, indicating the potential to cause serious eye damage. The additive must also be considered a potential skin sensitiser as the applicant did not provide a study of this end-point. The Committee concluded that Magni-Phi® must be regarded as potentially harmful by inhalation due to a lack of

inhalation toxicity data. Members therefore requested that the applicant revise the safety data sheet taking into consideration the potential for eye damage and the need for respiratory protection. The Committee also highlighted the need to minimise contact with skin to avoid dermal sensitisation.

2.2.4. Safety for the environment

The components of Magni-Phi® (*Quillaja* and *Yucca*) occur widely in nature, therefore the Committee was satisfied that the use of the additive at the recommended dose of 250 mg/kg feed is unlikely to make any significant additional contribution to or to have adverse effects on the environment.

2.2.5. Conclusions on safety

The ACAF concluded that the additive can be considered safe for the target species, consumers and the environment.

The additive should be considered potentially harmful by inhalation, and as a potential eye irritant and skin sensitiser. The additive is not a skin irritant.

2.3. Section IV: Efficacy

The Committee assessed section IV of the dossier, containing four efficacy studies carried out in three different locations in broiler chickens, as well as a peer-reviewed scientific article presenting the results of a meta-analysis of 15 floor pen trials to demonstrate the effects of Magni-Phi® on animal performance.

2.3.1. Efficacy studies in broiler chickens

- Study 1 was carried out on 480 one-day old male broiler chickens for 42 days, with targeted dosages of 250 and 500 mg/kg feed.
- Study 2 was carried out on 480 one-day old male broiler chickens for 35 days, with targeted dosages of 250 and 500 mg/kg feed.
- Study 3 was carried out on 480 one-day old male broiler chickens for 35 days, with targeted dosages of 250 and 500 mg/kg feed.
- Study 4 was carried out on 2496 one-day old male and female broiler chickens for 42 days, with targeted dosages of 250 and 500 mg/kg feed.

The zootechnical performance results from the four efficacy studies in broiler chickens are summarised in table 3.

Table 3. Effect of Magni-Phi® on overall growth performance in growing poultry

Study	Dosage (mg/kg complete feed)	BW (g)	ADG (g)	ADFI (g)	FCR	EPEF
1	0	3019^{a}	70.8^{a}	112.6	1.590^{a}	417.5^{a}
	250	3077^{b}	72.2^{b}	112.7	1.561^{ab}	439.5^{ab}
	500	3092^{b}	72.6^{b}	112.4	1.549^{b}	448.2^{b}
2	0	2282^{a}	64.0^{a}	89.1	1.393^{a}	439.6^{a}
	250	2301^{a}	64.5^{a}	89.0	1.379^{ab}	462.3^{b}
	500	2340^{b}	65.6^{b}	88.9	1.355^{b}	475.6^{b}
3	0	2300^{a}	64.5^{a}	88.0	1.364^{a}	455.3^{a}
	250	2333^{a}	65.4^{a}	87.3	1.335^{a}	475.1^{a}
	500	2388^{b}	67.1^{b}	86.7	1.294^{b}	508.9^{b}
4	0	2667^{a}	63.5^{a}	118.7	1.83^{a}	312.2^{a}
	250	2772^{b}	66.0^{b}	120.2	1.79^{ab}	347.0^{b}
	500	2842^{c}	67.7^{c}	121.5	1.77^{b}	365.6^{c}

Notes: BW: average body weight, ADG: average daily gain, ADFI: average daily feed intake, FCR: feed conversion ratio, EPEF: European Production Efficiency Factor.
Means with different letters in superscript within the same column are significantly different (P≤0.05).

The results of the studies (studies 1-3) that assessed total-tract digestibility are summarised in Table 4.

Table 4. Effect of Magni-Phi® on apparent total-tract digestibility of growing poultry

Study	Dosage (mg/kg complete feed)	Crude ash (%)	Organic matter (%)	Dry matter (%)	Crude protein (%)	Crude fat (%)	Crude fibre (%)	Ca (%)	P (%)
1	0	17.09^{a}	75.90	-	51.50^{a}	85.74^{a}	-	40.38^{a}	35.94
	250	20.88^{b}	76.37		60.87^{b}	88.48^{b}		43.03^{ab}	38.38
	500	21.52^{b}	78.09		65.14^{b}	87.88^{b}		43.52^{c}	38.76
2	0	19.40^{a}	69.91^{a}	66.78^{a}	53.88^{a}	79.43^{a}	13.49	-	-
	250	20.57^{ab}	72.71^{b}	69.82^{b}	57.25^{ab}	81.26^{ab}	13.06		
	500	22.05^{b}	76.45^{c}	73.95^{c}	59.78^{b}	83.32^{b}	15.04		
3	0	16.98^{a}	70.94^{a}	67.56^{a}	53.85^{a}	82.51^{a}	15.32^{x}	-	-
	250	20.45^{b}	73.53^{b}	70.40^{b}	56.85^{b}	82.40^{a}	16.07^{xy}		
	500	23.71^{c}	76.77^{c}	74.23^{c}	60.23^{b}	84.84^{b}	17.59^{y}		

Notes: study one results are from days 22-25, studies two and three are from days 21-25. Ca: calcium, P: phosphorus.
Means with different superscripts within the same column are significantly different or show a trend (^{a,b}P ≤ 0.05; ^{x,y}0.05 < P ≤ 0.10.

The Committee evaluated the reports presented concluding that Magni-Phi® can be considered efficacious in broiler chickens when included in feed at a minimum dose of 250 mg/kg feed.

The Committee had queries regarding the extrapolation of trials in broilers to all avian species excluding layers and breeders, noting that the animal categories listed by the applicant for authorisation were not clear. Following clarification by the applicant, the Committee was able to conclude positively on extrapolation to other poultry for fattening and ornamental birds.

3. Analytical methods evaluation

Conclusions on the analytical methods are presented here as an extract from the Evaluation Report of the European Union Reference Laboratory (EURL) for Feed Additives on the Method(s) of the Analysis of *Quillaja saponaria* and *Yucca schidigera*[2]:

> "For the determination of saponins in the feed additive the Applicant submitted a single-laboratory validated and further verified analytical method based on reversed-phase ultra-high performance liquid chromatography coupled with ultraviolet detection (UHPLC-UV). The following method performance characteristics were derived from the validation and verification studies (partially re-calculated by the EURL): a relative standard deviation for repeatability (RSD_r) ranging from 1.3 to 6.5%; a relative standard deviation for intermediate precision (RSD_{ip}) ranging from 2.3 to 6.3%; and a recovery rate (R_{Rec}) ranging from 84 to 109%. Based on the satisfactory performance characteristics presented, the EURL recommends for official control the single-laboratory validated and further verified analytical method based on reversed-phase ultra-high performance liquid chromatography coupled with ultraviolet detection (UHPLC-UV) for the determination of saponins in the feed additive.
>
> In the frame of supplementary information to the original dossier, the Applicant submitted for the determination of saponins in the feed additive and in feedingstuffs two similar single-laboratory validated and further verified analytical methods based on reversed-phase high performance liquid

chromatography coupled with a mass spectrometry detector (HPLC-MS). However, due to incomplete supporting studies provided, the EURL cannot recommend for official control the HPLC-MS methods for the quantification of saponins in the feed additive and feedingstuffs.

Further testing or validation of the methods to be performed through the consortium of National Reference Laboratories as specified by Article 10 (Commission Regulation (EC) No 378/2005, as last amended by Regulation (EU) 2015/1761) is not considered necessary."

FSA/FSS accepts the EURL analytical method evaluation reports. FSA/FSS determined the analytical method as appropriate for official controls for this feed additive.

4. Conclusions

The FSA/FSS have considered and agree with the conclusions reached by the ACAF on the safety and efficacy of the feed additive.

No causes for concern were identified by the ACAF in the identity, characterisation and manufacturing sections.

The ACAF concluded that the additive can be considered safe for the target animal species, the consumer and the environment. However, with regards to user safety, the additive should be considered potentially harmful by inhalation, and as a potential eye irritant and skin sensitiser. The additive is not a skin irritant.

Upon evaluation of the efficacy studies provided, the ACAF was able to conclude that the additive was expected to be efficacious in chickens for fattening and were also able to conclude positively on extrapolation to other poultry for fattening and ornamental birds for the proposed dose of 250 mg/kg of complete feedingstuffs.

The FSA/FSS agree with the conclusions reached by the ACAF. FSA/FSS accepts the EURL analytical method evaluation reports. FSA/FSS determined the analytical method as appropriate for official controls for this feed additive.

5. References

1. EC (European Commission), 2003. Regulation No 1831/2003 of the European Parliament and of the Council on additives for use in animal nutrition. Available at Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition (Text with EEA relevance) (legislation.gov.uk)

2. EURL-FA (European Reference Laboratory for Feed Additives), 2022. Evaluation Report on the Analytical Methods submitted in connection with the Application for Authorisation of a Feed Additive according to Regulation (EC) No 1831/2003. *Quillaja saponaria* and *Yucca schidigera*. Available at: finrep_fad-2021-0046-Magni-Phi.pdf (europa.eu)

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