ORIGINAL SUBMISSION

GENERALLY RECOGNIZED AS SAFE
GRAS ASSOCIATES, LLC

GRAS Associates, LLC
27499 Riverview Center Blvd.
Bonita Springs, FL 34134
T: 239.444.1724 | F: 239.444.1723
www.gras-associates.com

#644
GRN 000644

3/15/2016

Food and Drug Administration
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety (HFS-255)
5100 Paint Branch Parkway
College Park, MD 20740-3835

Attention: Dr. Paulette Gaynor
Re: GRAS Notification – Nonfat Dry Goats' Milk and Goat Whey Protein

Dear Dr. Gaynor:

On behalf of Ausnutria Hyproca B.V. of The Netherlands, we are submitting for FDA review Form 3667 and the enclosed CD, free of viruses, containing a GRAS notification for *Nonfat Dry Goats' Milk and Goat Whey Protein Concentrate in Infant Formula*. An Expert Panel of qualified persons was assembled to assess the composite safety information of the subject substance with the intended use in infant formula. The attached documentation contains the specific information that addresses the safe human food uses for the subject notified substance as discussed in the GRAS guidance document.

If additional information or clarification is needed as you and your colleagues proceed with the review, please feel free to contact me via telephone or email.

We look forward to your feedback.

Sincerely,

(b) (6)

Cheryl R. Dicks, MS, RAC
Director of Regulatory Affairs
GRAS Associates, LLC
27499 Riverview Center Blvd., Suite 212
Bonita Springs, FL 34134
540-272-3254
dicks@gras-associates.com

Enclosure: GRAS Notification for Ausnutria Hyproca B.V. – *Nonfat Dry Goats' Milk and Goat Whey Protein Concentrate in Infant Formula*

CD

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3/15/2016

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Enclosure: GRAS Notification for Ausnutria Hyproca B.V. – *Nonfat Dry Goats' Milk and Goat Whey Protein Concentrate in Infant Formula*

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

GENERALLY RECOGNIZED AS SAFE *(GRAS)* NOTICE

Form Approved: OMB No. 0910-0342; Expiration Date: 02/29/2016
(See last page for OMB Statement)

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
000644	Mar 15, 2016
ESTIMATED DAILY INTAKE	INTENDED USE FOR INTERNET
NAME FOR INTERNET	
KEYWORDS	

Transmit completed form and attachments electronically via the Electronic Submission Gateway *(see Instructions)*; OR Transmit completed form and attachments in paper format or on physical media to: Office of Food Additive Safety *(HFS-200)*, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740-3835.

PART I – INTRODUCTORY INFORMATION ABOUT THE SUBMISSION

1. Type of Submission *(Check one)*

☒ New ☐ Amendment to GRN No._____ ☐ Supplement to GRN No. _____

2. ☒ All electronic files included in this submission have been checked and found to be virus free. *(Check box to verify)*

3a. For New Submissions Only: Most recent presubmission meeting *(if any)* with FDA on the subject substance *(yyyy/mm/dd)*: _____

3b. For Amendments or Supplements: Is your amendment or supplement submitted in response to a communication from FDA? *(Check one)* ☐ Yes ☐ No If yes, enter the date of communication *(yyyy/mm/dd)*: _____

PART II – INFORMATION ABOUT THE NOTIFIER

1a. Notifier

Name of Contact Person	Position
Leoniek Robroch	Manager Regulatory Affairs

Company *(if applicable)*: Ausnutria Hyproca

Mailing Address *(number and street)*: Dokter van Deenweg 150 Postbus 50078

City	State or Province	Zip Code/Postal Code	Country
LB Zwolle	Overijssel	8002	Netherlands

Telephone Number	Fax Number	E-Mail Address
+31 (0)88 1163631		

1b. Agent or Attorney *(if applicable)*

Name of Contact Person	Position
Cheryl R. Dicks	Director of Regulatory Affairs

Company *(if applicable)*: GRAS Associates, LLC

Mailing Address *(number and street)*: 27499 Riverview Center Blvd.

City	State or Province	Zip Code/Postal Code	Country
Bonita Springs	Florida	34134	United States of America

Telephone Number	Fax Number	E-Mail Address
239-444-1724	239-444-1723	dicks@gras-associates.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

GENERALLY RECOGNIZED AS SAFE *(GRAS)* NOTICE

Form Approved: OMB No. 0910-0342; Expiration Date: 02/29/2016
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+31 (0)88 1163631		

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Cheryl R. Dicks	Director of Regulatory Affairs

Company *(if applicable)*: GRAS Associates, LLC

Mailing Address *(number and street)*: 27499 Riverview Center Blvd.

City	State or Province	Zip Code/Postal Code	Country
Bonita Springs	Florida	34134	United States of America

Telephone Number	Fax Number	E-Mail Address
239-444-1724	239-444-1723	dicks@gras-associates.com

PART III – GENERAL ADMINISTRATIVE INFORMATION

1. Name of Substance

Nonfat dry goat milk (CBM®NFDGM) and goat whey protein concentrate (CBM®GWPC)

2. Submission Format: *(Check appropriate box(es))*

☐ Electronic Submission Gateway

☒ Electronic files on physical media with paper signature page

☐ Paper

If applicable give number and type of physical media

_____

3. For paper submissions only:

Number of volumes _____

Total number of pages _____

4. Does this submission incorporate any information in FDA's files by reference? *(Check one)*

☐ Yes *(Proceed to Item 5)* ☒ No *(Proceed to Item 6)*

5. The submission incorporates by reference information from a previous submission to FDA as indicated below *(Check all that apply)*

☐ a) GRAS Notice No. GRN _____

☐ b) GRAS Affirmation Petition No. GRP _____

☐ c) Food Additive Petition No. FAP _____

☐ d) Food Master File No. FMF _____

☐ e) Other or Additional *(describe or enter information as above)* _____

6. Statutory basis for determination of GRAS status *(Check one)*

☒ Scientific Procedures *(21 CFR 170.30(b))* ☐ Experience based on common use in food *(21 CFR 170.30(c))*

7. Does the submission (including information that you are incorporating by reference) contain information that you view as trade secret or as confidential commercial or financial information?

☐ Yes *(Proceed to Item 8)*

☒ No *(Proceed to Part IV)*

8. Have you designated information in your submission that you view as trade secret or as confidential commercial or financial information *(Check all that apply)*

☐ Yes, see attached Designation of Confidential Information

☐ Yes, information is designated at the place where it occurs in the submission

☐ No

9. Have you attached a redacted copy of some or all of the submission? *(Check one)*

☐ Yes, a redacted copy of the complete submission

☐ Yes, a redacted copy of part(s) of the submission

☐ No

PART IV – INTENDED USE OF THE NOTIFIED SUBSTANCE

1. Describe the intended use of the notified substance including the foods in which the substance will be used, the levels of use in such foods, the purpose for which the substance will be used, and any special population that will consume the substance *(e.g., when a substance would be an ingredient in infant formula, identify infants as a special population).*

Intended use as the combination of CBM®NFDGM and CBM®GWPC in the prescribed ratio as a source of protein in full-term infant formula. See Section V.

2. Does the intended use of the notified substance include any use in meat, meat food product, poultry product, or egg product? *(Check one)*

☐ Yes ☒ No

PART V – IDENTITY

1. Information about the Identity of the Substance

	Name of Substance[1]	Registry Used *(CAS, EC)*	Registry No.[2]	Biological Source *(if applicable)*	Substance Category *(FOR FDA USE ONLY)*
1	Nonfat dry goat milk (CBM®NFDGM)				
2	Goat whey protein concentrate (CBM®GWPC)				
3					

[1] Include chemical name or common name. Put synonyms *(whether chemical name, other scientific name, or common name)* for each respective item (1 - 3) in Item 3 of Part V *(synonyms)*

[2] Registry used e.g., CAS *(Chemical Abstracts Service)* and EC *(Refers to Enzyme Commission of the International Union of Biochemistry (IUB), now carried out by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (IUBMB))*

2. Description

Provide additional information to identify the notified substance*(s)*, which may include chemical formula*(s)*, empirical formula*(s)*, structural formula*(s)*, quantitative composition, characteristic properties *(such as molecular weight(s)),* and general composition of the substance. For substances from biological sources, you should include scientific information sufficient to identify the source *(e.g., genus, species, variety, strain, part of a plant source (such as roots or leaves), and organ or tissue of an animal source)*, and include any known toxicants that could be in the source.

Nonfat Dry Goat Milk (CBM®NFDGM) and Goat Whey Protein Concentrate (CBM®GWPC), produced from whole fresh goats' milk as per the specifications as described in Section III (C).

Detailed description of the composition of the combination appear in Section III.

3. Synonyms

Provide as available or relevant:

1	Nonfat dry goat milk also referred to as CBM®NFDGM
2	Goat whey protein concentrate also referred to as CBM®GWPC
3	

PART VI – OTHER ELEMENTS IN YOUR GRAS NOTICE

(check list to help ensure your submission is complete – check all that apply)

- ☐ Any additional information about identity not covered in Part V of this form
- ☒ Method of Manufacture
- ☒ Specifications for food-grade material
- ☒ Information about dietary exposure
- ☐ Information about any self-limiting levels of use *(which may include a statement that the intended use of the notified substance is not-self-limiting)*
- ☒ Use in food before 1958 *(which may include a statement that there is no information about use of the notified substance in food prior to 1958)*
- ☒ Comprehensive discussion of the basis for the determination of GRAS status
- ☒ Bibliography

Other Information

Did you include any other information that you want FDA to consider in evaluating your GRAS notice?

☒ Yes ☐ No

Did you include this other information in the list of attachments?

☒ Yes ☐ No

PART VII – SIGNATURE

1. The undersigned is informing FDA that Ausnutria Hyproca B.V.
(name of notifier)

has concluded that the intended use*(s)* of Nonfat dry goat milk (CBM®NFDGM) and goat whey protein concentrate (CBM®GWPC)
(name of notified substance)

described on this form, as discussed in the attached notice, is (are) exempt from the premarket approval requirements of section 409 of the Federal Food, Drug, and Cosmetic Act because the intended use(s) is (are) generally recognized as safe.

2. ☒ Ausnutria Hyproca B.V. *(name of notifier)* agrees to make the data and information that are the basis for the determination of GRAS status available to FDA if FDA asks to see them.

Ausnutria Hyproca B.V. *(name of notifier)* agrees to allow FDA to review and copy these data and information during customary business hours at the following location if FDA asks to do so.

Dokter van Deenweg 150 8025 BM Zwolle, The Netherlands
(address of notifier or other location)

Ausnutria Hyproca B.V. *(name of notifier)* agrees to send these data and information to FDA if FDA asks to do so.

OR

☐ The complete record that supports the determination of GRAS status is available to FDA in the submitted notice and in GRP No. ----------
(GRAS Affirmation Petition No.)

3. Signature of Responsible Official, Agent, or Attorney	**Printed Name and Title**	**Date (mm/dd/yyyy)**
Cheryl Dicks MS,RAC Digitally signed by Cheryl Dicks MS,RAC DN: cn=Cheryl Dicks MS,RAC, o=GRAS Associates, ou=Director of Regulatory Affairs, email=dicks@gras-associates.com, c=US Date: 2016.03.15 15:27:55 -04'00'	Cheryl R. Dicks, MS,RAC, Director of Regulatory Affairs	03/15/2016

PART VIII – LIST OF ATTACHMENTS

List your attached files or documents containing your submission, forms, amendments or supplements, and other pertinent information. Clearly identify the attachment with appropriate descriptive file names (or titles for paper documents), preferably as suggested in the guidance associated with this form. Number your attachments consecutively. When submitting paper documents, enter the inclusive page numbers of each portion of the document below.

Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	Multiple appendices---Appendices A through C	

OMB Statement: Public reporting burden for this collection of information is estimated to average 150 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services,Food and Drug Administration, Office of Chief Information Officer, 1350 Piccard Drive, Room 400, Rockville, MD 20850. (Please do NOT return the form to this address.). An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

GRAS Assessment

of

Nonfat Dry Goats' Milk and Goat Whey Protein Concentrate in Infant Formula

Food Usage Conditions for General Recognition of Safety

for

Ausnutria Hyproca B.V.
The Netherlands

CONFIDENTIAL

Evaluation By

Richard C. Kraska, Ph.D., DABT
Robert S. McQuate, Ph.D.
Bo Lonnerdal, Ph.D.

March 15, 2016

TABLE OF CONTENTS

List of Tables

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I. GRAS EXEMPTION CLAIM

A. Claim of Exemption from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR 170.36(c)(1)[1]

Ausnutria Hyproca B.V. has determined that use of its combination of manufactured ingredients consisting of nonfat dry goats' milk and goats' whey protein concentrate, as the sole source of protein for use in formula for full-term gestation infants to 12 months of age, is Generally Recognized As Safe (GRAS) in accordance with Section 201(s) of the Federal Food, Drug, and Cosmetic Act. This GRAS determination was made by experts qualified by scientific training and experience; it is based on generally available and accepted scientific data, information, methods and principles, and this finding is corroborated by the lack of adverse effects reported in countries where goats' milk protein is permitted for use in infant formulas. The evaluation accurately reflects the intended use of this combination substance as a protein source for use in formula for full-term gestation infants to 12 months of age.

Signed:
(b) (6)

Cheryl Dicks, MS, RAC
Director Regulatory Affairs
GRAS Associates, LLC
27499 Riverview Center Blvd.
Suite 212
Bonita Springs, FL 34134

Date: March 15, 2016

B. Name and Address of Notifier

Ausnutria Hyproca B.V.
Dokter van Deenweg 150
8025 BM Zwolle
The Netherlands
+31 (0) 88 11 63 600

As the Notifier, Ausnutria Hyproca B.V. (hereinafter referred to as "Hyproca") accepts responsibility for the GRAS determination that has been made for nonfat dry goats' milk (hereinafter referred to as "NFDGM") combined with goat whey protein concentrate (hereinafter referred to as "GWPC") as described in the subject notification; consequently, the combination of NFDGM and GWPC, meeting the conditions described herein, is exempt from pre-market approval requirements for use as a food ingredient in full-term gestation infants to 12 months of age.

[1] See 62 FR 18938 (17 April 1997): Accessible at www.gpo.gov/fdsys/pkg/FR-1997-04-17/pdf/97-9706.pdf.

All communications on this matter are to be sent to the representative of the Notifier:

Cheryl R. Dicks, MS, RAC
GRAS Associates, LLC (Division of Nutrasource Diagnostics Inc.)
27499 Riverview Center Blvd.
Suite 212 Bonita Springs, FL 34134
Office: 239-444-1724
Business Cell: 540-272-3254
Email:dicks@gras-associates.com

C. Common Name and Identity of the Notified Substance

The common name for the combination substance of interest is "Nonfat dry goat milk" (NFDGM) and "goat whey protein concentrate" (GWPC). The trade name of each component ingredient is CBM®NFDGM and CBM®GWPC, respectively.

"Nonfat dry goat milk," which is synonymous with "skimmed goat milk powder", is a homogeneous off-white, free flowing powder which is obtained by the removal of water from fresh nonfat goat milk. It is characterized by a maximum milkfat content of 1.5%, maximum 5% moisture and a minimum milk protein in milk solids (non-fat) of 34%.

"Goat whey protein concentrate" is also a homogeneous off-white, free flowing powder, containing 25-75% protein and less than 6% moisture by weight. It is obtained from processing pasteurized goat whey by means of ultrafiltration.

D. Conditions of Intended Use in Food

CBM®NFDGM and CBM®GWPC are intended to be used in combination as a source of protein in infant formula for full-term gestation infants to 12 months of age. CBM®NFDGM will be added at 57% (±5%) of the protein blend. The remaining 43% (±5%) of total protein will be provided by CBM®GWPC. The whey-to-casein ratio in infant formulas for term infants will be 60-65% whey protein and 35-40% casein.

The resultant infant formula will provide the levels of protein and amino acids required for compliance with 21 CFR 107.100, the recommendations of the Expert Panel of the Life Sciences Research Office (LSRO) of the American Society of Nutritional Sciences (Raiten, Talbot, & Waters, 1998) and Codex Standard 72-198 (CODEX, Amended 2011).

E. Basis for the GRAS Determination

Pursuant to 21 CFR 170.30, CBM®NFDGM combined with CBM®GWPC as the protein source in infant formula has been determined to be GRAS on the basis of scientific procedures in accordance with Section 201(s) of the Federal Food, Drug, and Cosmetic Act and on a consensus among a panel of experts (Bo Lonnerdal, Ph.D., Robert S. McQuate, Ph.D. and Richard Kraska, Ph.D., DABT) who are qualified by scientific training and experience to

evaluate the safety of CBM®NFDGM and CBM®GWPC as a protein source for use in infant formula.

F. Availability of Information

The data and information that serve as the basis for this GRAS evaluation are available for review in response to a direct request placed to the offices of:

Ausnutria Hyproca B.V.
Dokter van Deenweg 150
8025 BM Zwolle, The Netherlands
+31 (0) 88 11 63 600

II. INTRODUCTION

A. Objective

At the request of Ausnutria Hyproca B.V. (hereinafter referred to as "Hyproca"), GRAS Associates, LLC ("GA") has undertaken an independent safety review of the combination of CBM®NFDGM and CBM®GWPC as a protein source for use in formula for full-term gestation infants to 12 months of age. An Expert Panel of independent scientists, qualified by their relevant experience and scientific training to evaluate the safety of food ingredients, was convened in order to conduct a critical and comprehensive evaluation of all available pertinent data and information and to ascertain whether the intended food uses of the combination of CBM®NFDGM and CBM®GWPC as a protein source for use in formula for full-term gestation infants to 12 months of age are generally recognized as safe (GRAS)

B. Foreword

Cows' milk protein sources, with modification of the 20 / 80, whey:casein ratio to better reflect that of human milk, have a long history of use in infant formulas. Furthermore, the impact of cows' milk protein on the first year of infant growth is well known and documented (Dewey, 1998; Ziegler, 2006). Hyproca's goat milk protein source, composed of non-fat dry goat milk (CBM®NFDGM) and goat whey protein concentrate (CBM®GWPC), has also been modified meet infant formula protein requirements and compares favorably with cows' milk protein sources currently used in infant formulas.

Hyproca provided detailed information about the identity, manufacturing, and specifications of CBM®NFDGM and CBM®GWPC. A summary regarding the safety of and exposure to CBM®NFDGM and CBM®GWPC is provided, along with how the blended composition compares to cows' milk protein. This information was augmented with an independent search of the scientific and regulatory literature and the long history of goat milk consumption to support the safety of the combination of CBM®NFDGM and CBM®GWPC for the intended use.

C. Regulatory Framework of Goats' Milk

1. United States (U.S.) Current Regulatory Status of Goats' Milk

Per the United States Department of Agriculture (USDA), use of goats' milk as a food ingredient is allowable in the form of cheese, milk, ice cream and yoghurts (United States Department of Agriculture (USDA), 2012). Per the U.S. Code of Federal Regulations (CFR), goats' skim milk, goats' milk, and goats' cream may be used in liquid, concentrated, and/or dry form as an ingredient in ice cream (21 CFR 135) or for production of cheeses (21 CFR 133).

In 2013, the Dairy Practices Council updated their regulatory standards guidelines for the production and regulation of quality goats' milk, thus setting revised standards for determination and publication for production of goats' milk so as to be marketed as Grade A dairy product in the U.S. (Dairy Practices Council, 2013).

Goats' milk is also recognized as a supplemental food via 7 CFR 246.10 WIC (Women, Infants and Children). The WIC food package regulatory requirements define the types of milk, and at the State's discretion, goats' milk may be substituted for cows' milk. WIC-authorized goats' milk must meet the same requirements and specifications as cows' milk for supplemental foods (7 CFR 246.10).

2. Global Regulatory Status of Goats' Milk for use in Infant Formula

Worldwide, approximately 4.8 million tons of goats' milk are consumed either in the form of "milk" or cheese (G. Heinlein & R. Caccese, 2003), and this comprises approximately 2% of the world's dairy milk supply. In the U.S., approximately one million goats are in active milk production for use in various food forms such as cheese, liquid milk, yogurt and ice cream.

While current U.S. FDA regulations do not permit the use of goats' milk as a source of protein in infant formula, there are many countries such as Australia, New Zealand, and Taiwan that have over a ten-year history of such use in infant formula (Grant et al., 2005) . Goats' milk, is also used in Korea, Russia, and China also use goats' milk as a sole protein source in both infant formula and follow-on formulas, making up approximately 5% of all formula sales (Prosser et al., 2008).

In March 2012, the European Food Safety Authority (EFSA) published their "Scientific Opinion on the suitability of goats' milk protein as a source of protein in infant formulae and in follow-on formulae". In this opinion paper, EFSA concluded "that protein from goats' milk can be suitable as a protein source for infant and follow-on formulae, provided the final product complies with the compositional criteria laid down in Directive 2006/141/EC. For goats' milk protein to be used in infant and follow-on formulae, particular attention has to be given to the protein content and composition of the milk proteins, and to the amino acid content, which should in the final product be in compliance with Directive 2006/141/EC, if necessary by the addition of free amino acids in appropriate amounts."

The United Kingdom (UK) Department of Health, in 2013, published "Draft Statutory Instrument – The Infant Formula and Follow-on Formula (England) (Amendment) Regulations 2014." This directive allows for the use of goats' milk protein in infant formulas.

Currently, Hyproca's CBM®NFDGM and CBM®GWPC ingredients are being used as a sole source of protein in infant formula products in international markets such as The Netherlands, United Kingdom (UK), China, Macao, Hong Kong, Vietnam, Russia, Latvia, Kazakhstan, Moldova, Israel, Turkey, South Africa, Trinidad & Tobago, Taiwan, Saudi Arabia, United Arab Emirates, Yemen, Qatar, Bahrain and other Middle Eastern countries. Table 1 summarizes the regulatory status for goats' milk in the U.S., UK and European Union (EU).

Table 1. Regulatory Status for Goats' Milk U.S, UK and EU

Country	Regulation Citation	Description
U.S.	21 CFR 135.115	Goats' Milk Ice Cream
U.S.	21 CFR 133.150	Hard cheeses
U.S.	21 CFR 133.182	Soft ripened cheeses
U.S.	21 CFR 133.190	Spiced cheeses
U.S.	21 CFR 133.183	Romano cheese;
U.S.	21 CFR 133.148	Hard grating cheeses
U.S.	21 CFR 133.111	Caciocavallo siciliano cheese
U.S.	21 CFR 133.188	Semisoft part-skim cheeses
UK	2013 No. 3243 FOOD, ENGLAND, The Infant Formula and Follow-on Formula (England) (Amendment) Regulations 2013.enforcement 28th February, 2014 [1]	Amendment of compositional criteria for infant formula and follow – on formula to include goats' milk proteins
EU	European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies (NDA), Scientific Opinion,2012 [2]	Scientific Opinion on the suitability of goats' milk protein as a source of protein in infant formulae and in follow-on formulae

[1] Accessed via web: http://www.legislation.gov.uk/uksi/2013/3243/pdfs/uksi_20133243_en.pdf)
[2] Accessed via web: http://www.efsa.europa.eu/en/efsajournal/pub/2603

D. Rationale for Pursuing a GRAS Determination for Use of Blends of CBM®NFDGM and CBM®GWPC

There has been an increase in the use of goats' milk-based infant formulas both globally and in the U.S. In the U.S., this rise in goats' milk-based infant formula use occurs with consumers who are currently preparing homemade goats' milk infant formula in the absence of a regulated and safe alternative (Basnet, Schneider, Gazit, Mander, & Doctor, 2010; Baur & Allen, 2005; Taitz, 1984; D. Ziegler, Russell,SJ, Rozenberg, James, Trahair, & O'Brien, 2005)

Several factors are driving this increase in use including increased consumer access to information on digestive and health benefits of goats' milk *via* the internet, global growth of marketed goats' milk infant formulas as an additional option to cows' milk and soy protein based infant formulas, as well as an increasing number of domestic (U.S.) ethnic populations who are very familiar with and use goats' milk. In the U.S., the current infant formula market offers both cows' milk protein, with modification of the 20/80 whey:casein ratio, to better reflect that of human milk, as well as soy protein based formulas. The impact of these protein sources on

infant growth, as compared to breast-fed infants, is well-known (Dewey, Heinig, Nommsen, Peerson, & Lönnerdal, 1992; Gross, 1983; L. Kohler, Meeuwisse, G. and Mortensson, W. , 1984; Steichen & Tsang, 1987). There are several scientific studies comparing the composition of goats' milk protein to cows' milk protein (see Section III.A), as well as its impact on growth of full-term infants to 12 months of age compared with cows' milk (EFSA, 2012; Grant et al., 2005; Razafindrakoto, 1994; Zhou et al., 2014).

Hyproca proposes to use their blend of CBM®NFDGM and CBM®GWPC as an alternative source of protein in infant formula for full-term infants to 12 months of age, and it is anticipated that it will become available for consumption in the U.S. market. Hyproca's goal upon establishing GRAS status is to provide a regulated and safe option beyond cows' milk and soy protein-based infant formula.

III. INGREDIENT IDENTITY, CHEMICAL CHARACTERIZATION, PURITY AND MANUFACTURING PROCESS

A. Background Information on Composition of Goats' Milk with Comparison to Cows' Milk and Human Milk

1. Nutritional Composition Comparison between Goats' Milk, Cows' Milk and Human Milk

Much research has been conducted on the similarities between goats' milk and cows' milk in overall composition and nutritional adequacy (G. Heinlein & R. Caccese, 2003; Kumar, 2012; Park, 1994; C. G. Prosser & McLaren, 2008). According to the Food and Nutrition Board of the National Academy of Sciences (NRC, 1968), the daily dietary nutrient recommendations are met equally by goats' milk when compared to an equal amount of cows' milk. The compositional and nutritional similarities are demonstrated in Table 2.

Table 2. Overall Composition of Goats' Milk and Cows' Milk[a]

Nutrient	Units	Goats' Milk	Cows' Milk
Fat	%	3.8	3.6
Solids-non-fat	%	8.9	9.0
Lactose	%	4.1	4.7
Nitrogen component x 6.38%	%	3.4	3.2
Protein	%	3.0	3.0
Casein	%	2.4	2.6
Albumin, globulin	%	0.6	0.6
Non-Nitrogen component x 6.38%	%	0.4	0.2
Ash	%	0.8	0.7
Calcium (CaO)	%	0.19	0.18
Phosphorous (P_2O_5)	%	0.27	0.23
P_2O_5 / CaO	ratio	1.4	1.3
Chloride	%	0.15	0.10
Iron	p/100,000	0.07	0.08
Copper	p/1,000,000	0.05	0.06
Vitamin A	i.u./g fat	39	21
Riboflavin	µg/100 mL	210	1569

Nutrient	Units	Goats' Milk	Cows' Milk
Thiamin	mg	0.068	0.045
Folic Acid	µg	1.0	5.0
Biotin	µg	1.5	2.0
Vitamin B12	µg	0.065	0.357
Pantothenic acid	mg	0.31	0.32
Niacin	mg	0.27	0.08
Vitamin C	mg/mL	2	2
Vitamin D	i.u./g fat	0.7	0.7
Calories	100 mL	70	69

[a] Data from Heinlein, et al, 2014: Kumar, et al, 2012, Park, et al., 2007.

Heinlein et al., 2003, also demonstrated the similarities between goats', cows' and human milk in nutrient values. While the protein in goats' and cows' milk is higher than in human milk, fat content is similar. Goats' milk has a higher mineral content than either cows' or human milk. The vitamin A, C and D profiles of goats' milk are similar to that of cows' milk and human milk. The overall nutrient composition of goats', cows' and human milk is represented in Table 3.

Table 3. Comparison of Goats' Milk, Cows' Milk and Human Milk—Average Contents of Nutrient's[a]

Nutrient	Units	Goats' Milk	Cows' Milk	Human Milk
Fat	%	3.8	3.6	4.0
Solids-non-fat	%	8.9	9.0	8.0
Lactose	%	4.1	4.7	6.9
Nitrogen component x 6.38% [1]	%	3.4	3.2	1.2
Protein	%	3.0	3.0	1.1
Casein	%	2.4	2.6	0.4
Albumin, globulin	%	0.6	0.6	0.7
Non-protein nitrogen component x 6.38% [2]	%	0.4	0.2	0.1
Ash	%	0.8	0.7	0.3
Calcium (CaO)	%	0.19	0.18	0.04
Phosphorous (P_2O_5)	%	0.27	0.23	0.06
P_2O_5 / CaO	ratio	1.4	1.3	1.4
Chloride	%	0.15	0.10	0.06
Iron	p/100,000	0.07	0.08	0.2
Copper	P/1,000,000	0.05	0.06	0.06
Vitamin A	i.u./g fat	39	21	32
Riboflavin	µg/100 mL	210	1569	26
Vitamin C	mg/mL	2	2	3
Vitamin D	i.u./g fat	0.7	0.7	0.3
Calories	100 mL	70	69	68

[a] from Heinlein, G. et al, 2014.

[1] Nitrogen component of milk is composed of Protein and non-protein nitrogen (Prosser et al., 2008).

[2] Non-protein nitrogen component of milk is composed of urea, free amino acids, nucleotides, creatinine, other nitrogen containing moieties (Prosser et al., 2008).

2. Fatty Acid Comparison Between Goats' Milk and Cows' Milk

Cows' milk and goats' milk also have similar fatty acid profiles. Goats' milk lipid content is found to be higher in monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), and medium chain triglycerides (MCT) than cows' milk but lower in stearic and oleic acid (Kumar et al., 2012). Table 4 demonstrates the fatty acid composition of goats' and cows' milk.

Table 4. Goats' Milk and Cows' Milk Fatty Acid Profiles[a]

Fatty Acid	Goats' Milk (g/100g) milk)	Cows' Milk (g/100g) milk)
C4:0 butyric	0.13	0.11
C6:0 caproic	0.09	0.06
C8:0 caprylic	0.10	0.04
C10:0 capric	0.26	0.08
C12:0 lauric	0.12	0.09
C14:0 myristic	0.32	0.34
C16:0 palmitic	0.91	0.88
C18:0 stearic	0.44	0.40
C6-14 total MCT	0.89	0.61
C4-18 total SAFA	2.67	2.08
C16:1 palmitoleic	0.08	0.08
C18:1 oleic	0.98	0.84
C16:1-22:1 total MUFA	1.11	0.96
C18:2 linoleic	0.11	0.08
C18:3 linolenic	0.04	0.05
C18:2-18:3 total PUFA	0.15	0.12

[a] Kumar et al., 2012.
MCT: medium chain triglycerides
SAFA: saturated fatty acids
MUFA: monounsaturated fatty acids
PUFA: polyunsaturated fatty acids

3. Protein and Amino Acid Comparison Between Goats' Milk and Cows' Milk

In addition to fat, vitamins, minerals, and lactose, protein is a major constituent of goats' milk. Goats' milk protein content and amino acid profiles are similar to those of cows' milk protein (Kumar et al., 2012). These similarities are summarized in Table 2 and Table 5, respectively.

The two major categories of ruminant milk protein are insoluble proteins, which contain the casein family (α_{s1}-casein, α_{s2}- casein, β-casein and κ-casein), and soluble proteins found in whey protein (β-lactoglobulin and α-lactalbumin) (Kumar, 2012; Selvaggi, Laudadio, Dario, & Tufarelli, 2014). In goats' milk, as in cows' milk, there is a natural whey protein to casein protein ratio of approximately 20:80 respectively. As the major protein fraction in the milk of many species, casein proteins carry calcium phosphate in milk, providing newborns with a source of calcium and phosphorus for bone formation. Casein proteins also contribute to the requirement for amino acids (Stewart et al., 1987).

Whey proteins are globular molecules with a substantial content of α-helix motifs. In these α-helix motifs, the acidic/basic and hydrophobic/hydrophilic amino acids are distributed in a balanced way along their polypeptide chains (Selvaggi et al., 2014). Milk whey proteins have a

more favorable amino acid profile for infants than casein proteins. Therefore, whey proteins are typically recommended for the formulation of milk products used for replacement of cows' milk in infant nutrition (Hambraeus, 1982). For example, whey proteins are characterized by a comparatively high content of sulfur-containing amino acids. This is important for newborns because they need 4-6% sulfur-containing amino acids (in the context of total amino acids) to support adequate growth (Foldager, Huber, & Bergen, 1977; Oftedal, 2012).

Furthermore, the overall amino acid composition is similar for cows' and goats' milk in these proteins with a homology of 84-95% (European Food Safety Authority (EFSA), 2012). Goats' milk is higher in essential amino acid levels for threonine, isoleucine, lysine, cysteine, tyrosine and valine (Kumar et al., 2012). Prosser et al., 2008, found that alanine, arginine, glutamic acid, histidine, lysine and tyrosine were all comparable between whole goats' milk powder and whole cows' milk powder when expressed in mg/100 mL.

Table 5. Amino Acid Content of Goats' Milk and Cows' Milk (mg/g protein)

Amino acid	Goats' milk[1,2]	Goats' milk sweet whey[1]	Cows' milk[2]	Cows' milk sweet whey[3]
Alanine	31	59	N/A	46
Arginine	30	24	N/A	29
Aspartic acid + Asparagine	73	109	N/A	98
Cysteine*	11	25	8	20
Glutamic acid + Glutamine	199	165	N/A	174
Proline	116	54	N/A	61
Glycine	17	19	N/A	22
Histidine*	25	21	27	18
Isoleucine*	46	58	51	56
Leucine*	92	96	100	92
Lysine	78	94	85	80
Methionine*	24	18	27	19
Methionine + Cysteine	35	43	35	39
Phenylalanine*	45	32	50	32
Phenylalanine + Tyrosine	85	61	101	60
Tryptophan*	12	19	15	16
Tyrosine	40	29	51	28
Valine*	65	58	63	54

*Essential Free Amino Acids

1. Analyses for Hyproca, method of analysis according to EP 2.2.56 from powdered goats' milk and whey.
2. The EFSA Journal (2004) 30, 1-15 Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission relating to the evaluation of goats' milk protein as a protein source for infant formulae and follow-on formulae.
3. Agricultural Research Service United States Department of Agriculture. National Nutrient Database for Standard Reference Release 26. NDB No. 01115.

In order to meet minimum amino acid requirements for infant formula marketed in the United States (per Codex Standard 72-1981(72, 1981)), the essential and semi-essential amino acid profile of the combination of CBM®NFDGM and CBM®GWPC is monitored and verified to be in line with the expected amino acid profile on various occasions during the finished product manufacturing.

4. Comparison of CBM®NFDGM to FDA and Codex Standards for Nonfat Dry Cows' Milk Powder

Nonfat dry milk from bovine sources is included in FDA's food standards for milk and cream products (21 CFR 131.125), being described as the product obtained by removal of water only from pasteurized skim milk. Nonfat dry milk contains not more than 5 percent by weight of moisture and not more than 1.5 percent by weight of milkfat unless otherwise indicated. Information presented in Table 6 demonstrates how CBM®NFDGM produced by Hyproca complies with the specifications for nonfat dry milk sourced from bovine milk, as well as with additional parameters described in Codex Standard 207-1999 for milk powders and cream powder (CODEX, 2011). This compliance is represented in Table 6.

Table 6. Comparison of CBM®NFDGM to FDA and Codex Standards for Nonfat Dry Cows' Milk Powder

Parameter	Official Specification (reference)	CBM® NFDGM		Method
		Typical	Maximum	
Milkfat (% w/w)	Max 1.5 (21 CFR 131.125)	1.3	1.5	ISO 1736 (IDF 9:2008)
Moisture (% w/w)	Max 5 (21 CFR 131.125)	3.9	5	ISO 5537(IDF 26:2004)
Milk protein in milk solids-non-fat (%	Min 34 (Codex Standard 207-1999)	38	Min 34	ISO 8968-1:2014 (IDF20-1:2014) / AOAC 991.20
Titratable acidity (mL-0.1 N NaOH / 10 g-solids-not-fat)	Max 18 (Codex Standard 2007-1999)	14.4	18	ISO 6091 (IDF 86:2010)
Scorched particles	Max Disc B(Codex Standard 207-1999)	A	B	ISO 5739 (IDF 107:2003)
Solubility index (mL)	Max 1 (Codex Standard 207-1999)	0.1	1	ISO 8156
Heavy metals				
Lead (mg/kg)	< 0.15 (Codex Standard 193-1995)	< 0.1	< 0.15	Accredited method using ICP-MS
Cadmium (µg/kg)	< 10 (EU Reg. No 488/2014)	<5	<10	Accredited method using ICP-MS
Arsenic (µg/kg)	< 100 Internal standard	<100	<100	Accredited method using ICP-MS
Mycotoxins				
Aflatoxin M_1 (µg /kg)	< 0.15 (Codex Standard 193-1995)	< 0.15	< 0.15	NEN-EN-ISO 14501
Others				
Nitrate (mg/kg)	< 50 (Dutch legislation on dairy: Warenwetbesluit Zuivel)	5	< 50	ISO 14673-2
Nitrite (mg/kg)	< 2 (Dutch legislation on dairy: Warenwetbesluit Zuivel)	<0.2	< 2	ISO 14673-2
Melamine (mg/kg)	< 1 (EU Reg No 1881/2006, CODEX STAN 193-1995)	<0.5	< 1	ISO/TS15495 (IDF/RM 230:2010)

5. Comparison of CBM®GWPC to FDA and Codex Standards for Cows' Milk Whey Protein Concentrate

Whey protein concentrate is affirmed as GRAS by FDA, as seen in 21 CFR 184.1979c, where it is noted that the substance is obtained by the removal of sufficient nonprotein constituents from whey so that the finished dry product contains not less than 25 percent protein. Specifications for whey protein concentrate are published in Food Chemicals Codex (FCC 8 2013). The specifications for the composition of CBM®GWPC are very similar to the food grade specifications outlined in the FCC 2013 monograph for whey protein concentrate as demonstrated in Table 7.

Table 7. Comparison of CBM®GWPC to FDA and Codex Standards for Cows' Milk Whey Protein Concentrate

Parameter	FCC 8 2013 whey protein concentrate	Ausnutria Hyproca GWPC	Method
Loss on drying	<6	< 6	ISO 12779
Protein[1]	25 - 89.9	35 – 80	ISO 8968-1
Fat	0.2 - 10	0.2 – 10	NEN-ISO 1736
Minerals (Ash)	2.0 - 15	2.0 – 6	NEN 6810
Carbohydrate	<60	< 50	NEN-ISO 5765
pH	6.0 – 7.2	6.0 – 7.2	Internal method

Unmodified cows' and goats' milk do not meet nutritional requirements of infants, and early introduction of unmodified milk is a strong negative determinant of, for example, iron status (Turck, 2013; United States Department of Agriculture (USDA), 2014). Consequently, while CBM®NFDGM and CBM®GWPC will be used as the source of protein in infant formula, the finished product will be manufactured to comply with overall nutrient requirements defined in 21 CFR 107.100, the recommendations of the Expert Panel of the Life Sciences Research Office (LSRO) of the American Society of Nutritional Sciences (Raiten et al., 1998), and Codex Standard 72-198.

B. Supply Chain and Manufacturing Process for CBM®NFDGM and CBM®GWPC

CBM®NFDGM and CBM®GWPC are manufactured as separate ingredients prior to their combination as the source of protein in infant formula products. Hyproca's final finished infant formula product will be manufactured according to FDA current Good Manufacturing Practices (cGMPs) 21 CFR 110 and all other applicable FDA manufacturing regulations and guidance for infant formula.

The following section provides an overall synopsis of the goats' milk supply chain, as well as a description of manufacturing processes for CBM®NFDGM and CBM®GWPC.

1. Supply Chain

Over 55 Dutch dairy goat farms supply raw goats' milk to Ausnutria Hyproca's subsidiary Hyproca Goat Milk (HGM); all farms mainly use goats of the Swiss breed Saanen. The Saanen breed is recognized as a high-yielding breed in addition to three other breeds: Alpine, Toggenburg, and Nubian (Gall, 1996). The Saanen breed can be classified morphologically into the group of goats with short ears and sabre-like horns (Mason, 1991).

Goats' milk is delivered to Hyproca's manufacturing facility according to European Union (EU) legislation specific to raw milk. Milk and milk products must fulfill the basic animal and public health requirements as outlined in Regulation (EC) No 853/2004 of the European Parliament and the Council of 29 April 2004, which lays down specific hygiene rules for food of animal origin.

With regard to primary production of raw goats' milk, the specific health requirements are as follows:

- Raw milk must come from female goats, which are in a good general state of health that do not show any symptoms of infectious diseases communicable to humans through the milk or colostrum and which are not suffering from any infection of the genital tract with discharge, enteritis with diarrhea and fever, or a recognizable inflammation of the udder. The animals must not have any udder wound likely to affect the milk;
- Subject to further, more specific provisions, raw milk must comply with microbiological criteria and standards for plate count; and
- Milking, collection and transport of raw milk must comply with clearly-defined hygiene rules in order to avoid any contamination. The same applies to persons involved, premises, equipment and utensils used in production.

Regulation (EC) No 853/2004 further sets out the general hygiene requirements for heat-treated drinking milk and other milk products, dealing mainly with the preparation of pasteurized milk and Ultra High Temperature (UHT) milk. Wrapping and packaging must be designed to protect milk and/or milk products from harmful effects of external origin.

HGM is a member of the Dutch Goat Dairy Organization (Nederlandse GeitenZuivel Organization (NGZO)). The quality department of NGZO has set up a program to assure the quality of the goats' milk by applying the QualiGoat ('KwaliGeit') program. This program was compiled in close collaboration with the Dairy Goat Farming Department of the Dutch Agricultural and Horticultural Organization which takes into account the European hygienic legislations applicable to goats' milk and goats' milk farms as established in (Regulation (EC) No. 178/2002, 852/2004, 853/2004, 882/2004 and 854/2004). The QualiGoat quality assurance program consists of five modules:

1. Business Hygiene

This module comprises general business hygiene, pest control, handling crop herbicides, and manure, waste and hazardous substances.

2. Veterinary Medicines

This module comprises the purchase, the storage, the administering and the administration of veterinary medicines and the procedures for milking treated goats and handling of the milk.

3. Animal Health and Well-Being

This module comprises the approach to animal health, the administration of animal sicknesses, the housing and level of care of the goats, and the sales of slaughter kids.

4. Feed and Drinking Water

This module comprises the purchase of feeds, their storage and the quality of feed and drinking water.

5. Milk Production and Cooling

This module comprises the milking shed and/or milking table, the milk room, the hygiene for milking the goats, matters concerning milk quality and the milk collection loading point.

Correct implementation of the QualiGoat program by the farmers supplying HGM is controlled by Qlip, which is an organization that controls quality assurance in the agrifood chain, and is accredited to visit, criticize and certify goats' milk farms according ISO/IEC 17020 (RvA reg.no. I121). The QualiGoat program is complemented with milk quality parameters set by HGM which are more stringent than EU legislation requirements.

The U.S. Dairy Practices Council's Guidelines for the Production and Regulation of Quality Dairy Goat Milk (Dairy Practices Council, 2013) lists the regulatory standards and laboratory methods that have been identified as appropriate by the National Conference on Interstate Milk Shipments (NCIMS) in the U.S. The guideline deals with production systems and procedures, as well as management practices that are essential for producing high quality goats' milk. Although methods may vary somewhat, the U.S. Guidelines and the EU legislation as a part of the QualiGoat program and the specific quality requirements set by HGM are similar (as summarized in Table 8).

Table 8. Summary of the Parameters in U.S. Dairy Practices Council's Guidelines for QualiGoat Program

Parameter	U.S. Dairy Practices Council's Guidelines for the Production and Regulation of Quality Dairy Goats' Milk	QualiGoat and HGM Quality requirements
Somatic cell count[1]	< 1,500,000 cells/mL	2 times/month tested for each farm (guidelines) Ok: <1,400,000 cells/mL Reasonable: 1,400,000 – 2,000,000 cells/mL Requires attention: >2,000,000 cells/mL
Bacteria	< 100,000 /mL	<100,000 /mL, 4 times/month tested for each farm
Preliminary Incubation Count	< 100,000 /mL	Not specified
Antibiotic Residues	Not allowed	Not allowed, Each farm milk delivery is tested
Butyric acid bacteria	Not specified	4 times/month tested for each farm
Cleanliness milk	Not specified	Once per month tested for each farm
Freezing point	Not specified	3 times/year tested for each farm
Flavor and odor	Specific to goats' milk	Specific to goats' milk
Cleaning of milk contact surfaces description	Yes	Yes
Milking systems description	Yes	Yes
Milking parlors description	Yes	Yes
Udder preparation	Yes	Yes
Post milking disinfection	Optional	Optional
Cleaning milking equipment	Yes	Yes
Milk room requirements	Yes	Yes
Farm hygiene	Not specified	Yes
Veterinary medicines	Not specified	Yes
Animal health and well-being	Not specified	Yes
Feed and drinking water	Not specified	Yes

[1] Goats' produce milk differently than cattle. The goat's milk secretion system is apocrine; the system in cattle is merocrine. Apocrine secretion results in the presence of cytoplasmic particles in the milk, making a true somatic cell count challenging. According to The Dairy Practices Council's Guidelines for the Production and Regulation of Quality Dairy Goat Milk (Dairy Practices Council, 2013), the use of a dichromatic, differential stain (Pyronin Y-methyl green) that stains nuclear material differently than cytoplasmic particles should be used. However, this stain is only used in combination with a microscopic, manual cell count (Direct Microscopic Somatic Cell Count). In The Netherlands, the somatic cell count is tested in the same way for both cows' and goats' milk, using the Fossomatic according ISO 13366-2 (Flow cytometry using ethidium bromide as a coloring agent). The Fossomatic is calibrated to Direct Microscopic Somatic Cell Count according ISO 13366-1 with ethidium bromide as a coloring agent. Due to differences in analytical methods, the cell counts for goats' milk are not comparable for the U.S. and The Netherlands. Similar in both countries is that an elevated cell count in goats' milk can be found in the fall since seasonal breeding results in many in the goat herd approaching late lactation at the same time and late lactation often results in an elevated count. Goats' milk bulk tank somatic cell counts show a distinct seasonal variation with in The Netherlands the lowest in May and June and the highest in December to February.

2. CBM®NFDGM Manufacturing

a. Introduction

CBM®NFDGM is manufactured from nonfat goats' milk in Hyproca's factory practicing Hazard Analysis Critical Control Point (HACCP) plans (see Appendix A for HACCP Certificate). The manufacturing process also has received food safety certification from the British Retail Consortium (BRC).

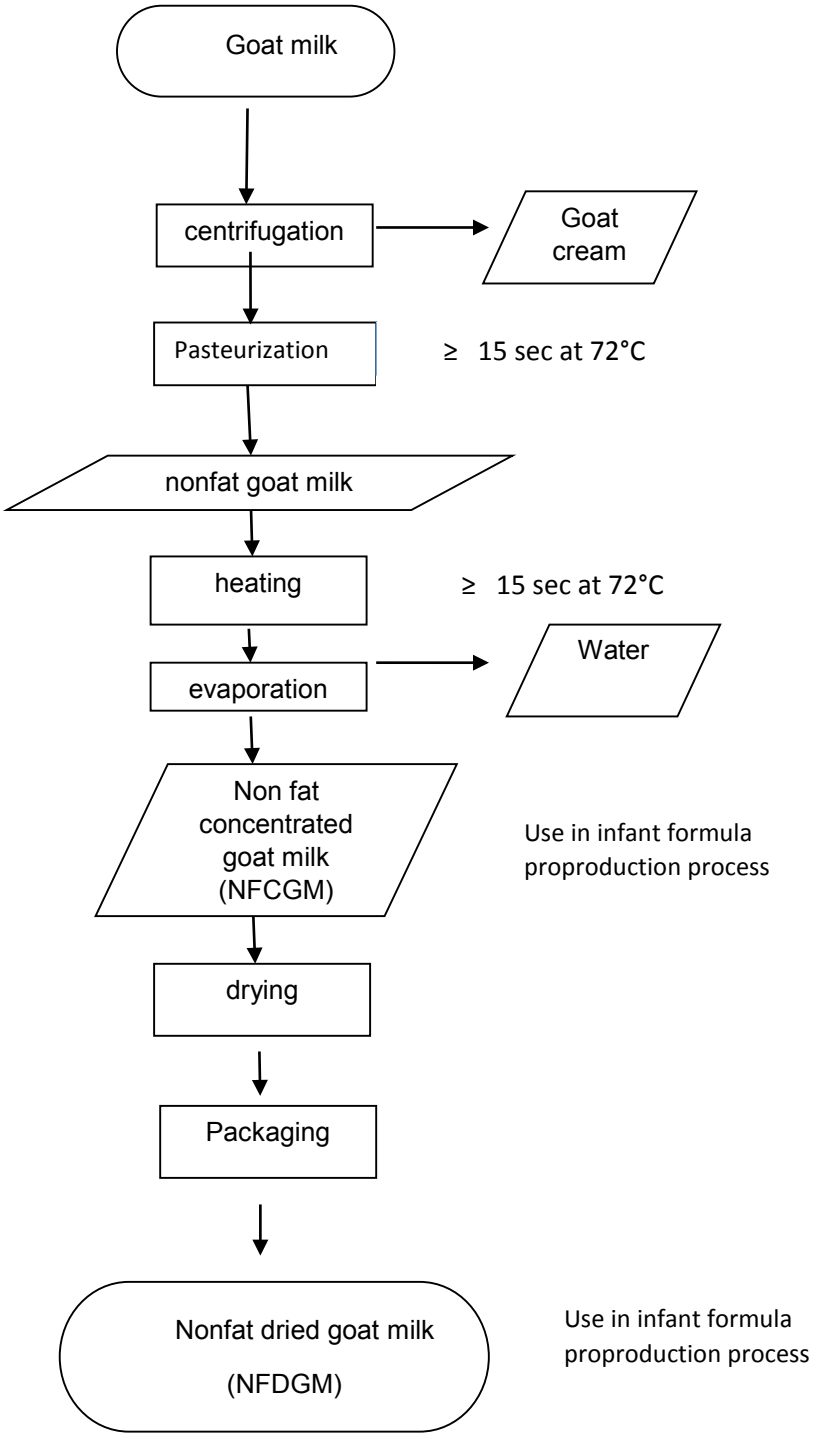
b. Manufacturing Process

CBM®NFDGM powder is obtained *via* standardized, well-described processes which are identical to the processes used by Hyproca to manufacture nonfat dry cows' milk powder. Figure 1 provides a step-by-step illustration of the manufacturing process for CBM®NFDGM production which is also described in detail below.

Before processing, the raw goats' milk is analyzed for absence of antibiotics. The milk is then centrifuged to remove the fat; consequently, the skimmed milk is pasteurized (≥ 72°C, 15 seconds), cooled to 4°C and stored at 7°C until further processing (maximum of 48 h). Following storage, a second pasteurization takes place, where the skimmed milk is heated to 102°C for 15 seconds. An evaporator is then used to concentrate the skimmed goats' milk to approximately 42% dry matter. The goats' milk concentrate is further dried *via* a spray dryer. The water content of the goats' milk is then reduced to ± 4%, rendering the product a powder. This dried goats' milk powder is directly filled in bags and packed. All bags are passed through a metal detector. The end product is extensively checked to ensure compliance with specifications. Standard chemical analyses include moisture, fat, lactose, protein, ash, titratable acid, insolubility and absence of cow casein. Moisture is tested before the powder is packaged (every half hour). Standard microbiological analyses include total plate count, *Bacillus cereus*, yeast and molds, thermophilic spores, coliforms, S*taphylococcus aureus*, S*almonella* and cronobacter.

To confirm pasteurization, the temperature logs of the pasteurizer and extended heater are monitored. The pasteurization is a Critical Control Point (CCP), and confirmation is performed by the process operator. When any irregularities are found, the production manager is notified, product batches are blocked, and the malfunction is investigated.

Figure 1. Manufacturing Process Flow for CBM®NFDGM



3. CBM®GWPC Manufacturing

a. Introduction

The pasteurized whey is obtained *via* standardized, well-described cheese-making procedures from pasteurized goats' milk and may be concentrated by standard membrane filtration techniques and/or treated with a centrifugal separator for the removal of (microbial) solids from the whey.

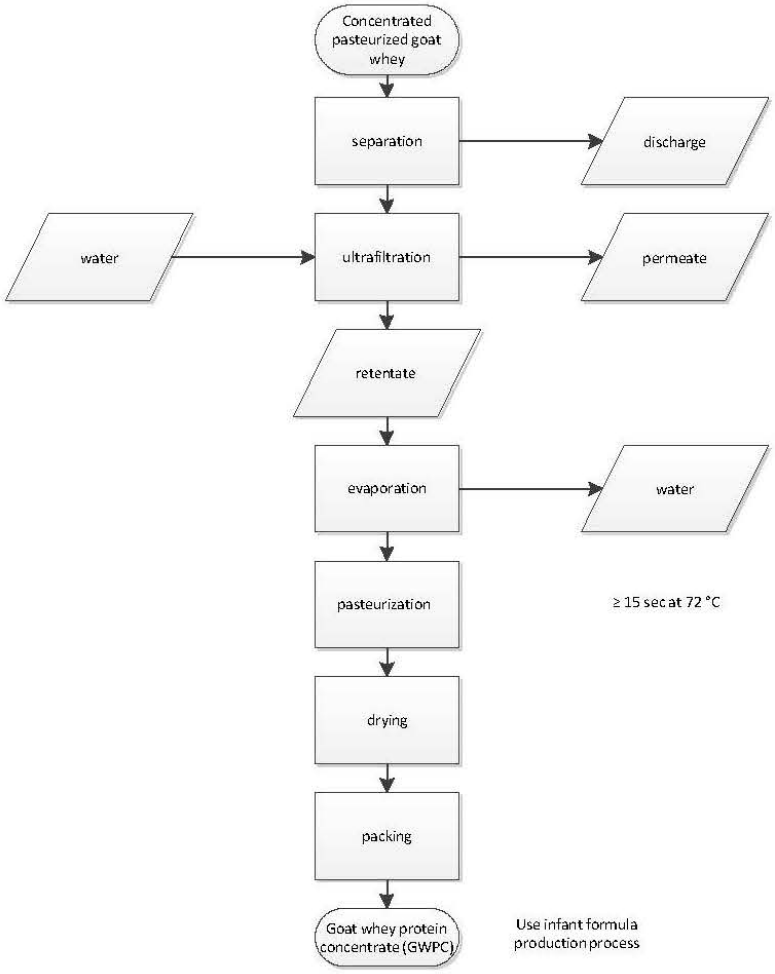
b. Manufacturing Process

The manufacturing techniques employed to concentrate protein into the thick whey and to remove non-protein constituents from it are based primarily on the use of membrane filtration technologies (All equipment used in the manufacturing process complies with FDA cGMP regulations). The raw material (thick whey) is circulated along a semi-permeable membrane in a pressure-driven process. The membrane is permeable to low molecular weight constituents (sugars, minerals, and other low molecular weight components) that pass through and form a permeate stream. High molecular weight constituents (protein and fat) are preferentially retained by the membrane and become components of the retentate stream. Sufficient lactose and minerals are removed from the permeate until the desired protein content is reached in the retentate stream. A diafiltration step may be included, wherein water is added to dilute the retentate in order to facilitate the removal of further quantities of minerals and lactose.

When the retentate has reached its target protein content, it is removed from the filtration system. Further processing steps include an optional evaporative concentration stage in which moisture is removed to increase the solid content of the product stream. Following evaporation (or without this processing step, depending on the particular manufacturing circumstance), the product stream may be dried and packaged using normal dairy drying techniques. During these processes, pasteurization of the product will take place.

Concentrated whey protein finished products may be obtained by removing the product stream from the process at the completion of various stages, such as the filtration stage, concentration stage, or drying stage. The resulting products may be identified as fluid, concentrate, or dried versions of concentrated milk protein, respectively. For use in infant formula, the CBM®GWPC is obtained after the drying stage in dry form. Figure 2 provides a step-by-step illustration of the manufacturing process.

Figure 2. Manufacturing Process for CBM®GWPC



4. CBM®NFDGM and CBM®GWPC Blending Process

CBM®NFDGM is combined with CBM®GWPC to achieve the desired protein whey to casein ratio during the production of formula base powder. The two products are diluted or dissolved in water, and other ingredients (e.g., vegetable oils and lactose) are added before evaporation and drying of formula base. The formula base is consequently dry-blended with other ingredients, thereby rendering a complete infant formula with the desired amount of protein and amino acid profile.

C. Ingredient Specifications

1. CBM®NFDGM Nutritional and Microbiological Specifications

Table 9 and Table 10 outline the nutritional and microbiological specifications, respectively, for CBM®NFDGM, being used as a dry blended ingredient in goats' milk protein based infant formula.

Table 9. Average Nutritional Specifications for CBM®NFDGM

Average nutritional composition NFDGM		
Parameters	Specifications (per 100 gram)	Units
energy	1504	kJ
energy	360	kcal
protein (Nx6.25)	37.9	g
carbohydrates	49.4	g
lactose	45.3	g
fat	1.2	g
moisture	≤ 5	g
ash	9.1	g
vitamins		
vitamin C	1.1	mg
vitamin B1	244	µg
vitamin B2	0.66	mg
vitamin B6	290	µg
vitamin B12	0.59	µg
niacin	2.4	mg
folic acid	5.3	µg
pantothenic acid	1.9	mg
biotin	7.4	µg
minerals		
calcium	1260	mg
phosphorus	1000	mg
magnesium	154	mg
iron	0.15	mg
zinc	2.5	mg
manganese	43	µg
copper	90	µg
iodine	220	µg

Average nutritional composition NFDGM		
Parameters	Specifications (per 100 gram)	Units
minerals		
sodium	375	mg
potassium	2172	mg
chloride	1500	mg
selenium	15	µg
others		
choline	40	mg
inositol	75	mg
taurine	47	mg
L-carnitine	21	mg

Table 10. Microbiological Specifications for CBM®NFDGM

Parameter	n	c	m	M	Method
Total plate count 30°C (cfu/g)	5	2	1,000	10,000	ISO 4833
Yeast and Molds (cfu/g)	5	2	50	100	ISO 7954
Enterobacteriaceae (/10 g)	10	0	absent		ISO 21528-1
Coagulase positive staphylococci (/g)	5	0	absent		ISO 6888-3
Bacillus cereus spores (cfu/g)	5	1	50	100	ISO 7932
Salmonella (/25 g[1])	60	0	absent		ISO 6579
Cronobacter (/10 g[2])	30	0	absent		ISO/DTS 22964
Listeria monocytogenes (/25 g)	5	0	absent		ISO 11290-1
Sulfite red. Clostridia spores (cfu/g[3])	5	2	10	30	Based on NEN-ISO 15213, 2003

n = number of samples representing the batch
c = maximum number of results between m and M
m = a count which separates good quality from marginal quality and which most test samples should not exceed
M = a count which if exceeded by any of the test samples would lead to rejection of the lot
[1] *Salmonella* shall be tested in 1500 grams/24h production samples, preferably using an automatic sampler.
[2] Cronobacter shall be tested in 300 grams/24h production samples preferably using an automatic sampler.
[3] If SRC's are within specification, *Clostridium perfringens* does not need to be tested.

2. CBM®NFDGM Summary of Analyses of 3 Non-Consecutive Lots

Table 11 is a summary of the analyses of 3 non-consecutive lots of CBM®NFDGM that demonstrates a consistent manufacturing process and that the resulting product is in compliance with product specifications. Note that CBM®NFDGM is also tested for melamine. Furthermore, all equipment used in the manufacture of CBM®NFDGM and its packaging materials is melamine free and complies with FDA cGMP regulations.

Table 11. Summary of Three Non-consecutive Batch Analyses for CBM®NFDGM

Parameter	Specification	CBM®NFDGM			Method
		Batch 1	Batch 2	Batch 3	
Milkfat (% w/w)	< 1.5	1.1	1.1	1.2	NEN-ISO 1736 (IDF 9:2008)
Moisture (% w/w)	< 5	4.1	4.2	3.8	ISO 5537 (IDF26:2004)
Protein in milk solids-non-fat [1] (% w/w)	>34	39.5	37.3	37.2	ISO 8968-1:2014 (IDF20-1:2014) / AOAC 991.20
Titratable acidity (mL-0.1 N NaOH/ 10 g-solids-not-fat)	< 18	16.8	14.4	14.4	ISO 6091 / IDF 86:2010
Scorched particles	Max Disc B	A	A	A	ISO 5739 (IDF 107:2003)
Solubility index (mL)	< 1	0.05	0.05	0.05	ISO 8156 (IDF 129:2005)
Microbial					
Total aerobic count (cfu/g)	n=5 c=2 m=1,000 M=10,000	<400 <100 <400 <400 <400	1,200 <400 <400 500 500	<400 <400 <400 <400 <400	ISO 4833-1
Yeasts and molds (cfu/g)	n=5 c=2 m=50 M=100	<10 <10 <10 <10 <10	<10 <10 <10 <10 <10	<10 <10 <10 <10 <10	ISO 6611
Enterobacteriaceae (/10x10g)	absent	absent	absent	absent	ISO 21528-1
Salmonella spp (/30x25g)	absent	absent	absent	absent	ISO 6579
Coagulase positive staphylococci (/5x1g)	absent	absent absent absent absent absent	absent absent absent absent absent	absent absent absent absent absent	NEN-ISO 6888-2
Bacillus cereus spores (cfu/g)	n=5 c=2 m=50 M=100	<10 <10 <10 <10 <10	<10 <10 <10 <10 <10	<10 <10 <10 <10 <10	ISO 7932
Cronobacter (/30x10g)	absent	absent	absent	absent	ISO/DTS 22964
Listeria monocytogenes (/5x25g)	absent	absent	absent	absent	ISO 11290-1
Sulfite red. Clostridia spores (cfu/g)	n=5 c=2 m=10 M=30	<1 <1 <1 <1 <1	<1 <1 <1 <1 <1	<4 <4 <1 <1 <1	Based on NEN-ISO 15213, 2003
Residues & contaminants					
Lead (mg/kg)	< 0.15	< 0.1	< 0.1	< 0.1	Accredited method using ICP-MS
Cadmium (µg/kg)	< 10	< 5	< 5	< 5	Accredited method using ICP-MS
Arsenic (µg/kg)	< 100	< 100	< 100	< 100	Accredited method using ICP-MS
Aflatoxin M_1 (mg/kg)	< 0.15	< 0.1	< 0.1	< 0.1	NEN-EN-ISO 14501
Nitrite (mg/kg)	< 2	< 0.2	< 0.2	< 0.2	ISO 14673-2
Nitrate (mg/kg)	< 50	4.9	5.2	5.2	ISO 14673-2
Melamine (mg/kg)	< 1	< 0.5	< 0.5	< 0.5	ISO/TS15495 (IDF/RM 230:2010)

[1] Nx6.38

3. CBM®GWPC Specifications and Summary of Analyses of 3 Non-Consecutive Lots

As demonstrated in Section III.A.5),Table 7, CBM®GWPC is very similar to the food grade specifications for whey protein concentrate as outlined in the FCC 2013 monograph (FCC 8 2013). Table 12 provides both the specifications for the composition of CBM®GWPC and summarizes the analyses of 3 non-consecutive batches.

Table 12. Summary of Three Non-consecutive Batch Analyses for CBM®GWPC

Parameter	Specification	GWPC			Method
		Batch 1	Batch 2	Batch 3	
Dry Matter (%)	> 95	95.9	95.5	97.1	ISO 12779
Protein * ° (% w/w)	35-80	60.9	58.9	58.3	ISO 8968-1
Ash (%)	< 6	4.4	4.5	4.7	NEN 6810
Fat (%)	< 10	9.4	9.8	8.9	NEN-ISO 1736
Carbohydrates (%)	< 50	23.7	26.3	26.9	NEN-ISO 5765
pH	6.0 – 7.2	6.3	6.0	6.1	Internal method
Residues & contaminants					
Lead (mg/kg)	<0.5	<0.1	<0.1	<0.1	Accredited method using ICP-MS
Cadmium (ug/kg)	<10	<5	<5	<5	Accredited method using ICP-MS
Arsenic (ug/kg)	<100	<100	<100	<0.1	Accredited method using ICP-MS
Microbial					
Total aerobic count (cfu/g)	n=5 c=2 m=1,000 M=10,000	780 2000 810 1600 1900	<40 <10 <10 <10 <40	<40 91 8000 740 75	ISO 4833-1
Yeasts and molds (cfu/g)	n=5 c=2 m=50 M=100	<40 <10 <10 <10 <10	<40 <10 <10 <10 <40	<40 <10 <40 <40 <40	ISO 6611
Enterobacteriaceae (/10x10g)	absent	absent	present	Absent	ISO 21528-1
Salmonella (/60x25g)	absent	absent	absent	absent	ISO 6579

Parameter	Specification	GWPC			Method
		Batch 1	Batch 2	Batch 3	
Coagulase positive *staphylococci* (/5x1g)	absent	absent absent absent absent absent	absent absent absent absent absent	absent absent absent absent absent	NEN-ISO 6888-3
Bacillus cereus spores (cfu/g)	n=5 c=1 m=50 M=100	55 <40 <40 <40 <40	<10 <10 <10 <10 <40	<10 <10 <10 <10 <10	ISO 7932
Cronobacter (/30x10g)	absent	absent	absent	absent	ISO/DTS 22964
Listeria monocytogenes	absent	absent	absent	absent	ISO 11290-1
Sulfite red. *Clostridia* spores (cfu/g)	n=5 c=2 m=10 M=30	<10 <10 <10 <10 <10	<10 <10 <10 <10 <10	<10 <40 <40 <10 <40	Based on NEN-ISO 15213, 2003
Residues & contaminants					
Aflatoxin M_1 (µg/kg)	< 0.15	<0.1	<0.1	<0.1	NEN-EN-ISO 14501
Nitrite (mg/kg)	< 2	<0.2	<0.2	<0.2	ISO 14673-2
Nitrate (mg/kg)	< 50	42	6.7	6.6	ISO 14673-2
Melamine (mg/kg)	< 1	<0.5	<0.5	<0.5	ISO/TS15495 (IDF/RM 230:2010)

*Nx6.38
o in dry matter

D. Stability

1. CBM®NFDGM Stability

Shelf-life studies for CBM®NFDGM were conducted using material sampled during production. The sample bags (200 g), non-gas flushed, were stored at ambient conditions (15-25°C). Material of each batch underwent sensory analysis according to Hyproca's internal procedures (Table 13).

Table 13. Shelf-Life Testing: Sensory Analyses of CBM®NFDGM

Post-Production (months)	Production Date NFDGM	Sensory evaluation (-, ±, +)				
		Overall (1 – 10)	Sweet	Salty	Goaty	Boiled milk
2	2014-08-21	reference	±	±	±	±
4	2014-06-18	8.6	-	±	±	±
6	2014-04-26	8.1	±	±	±	±
8	2014-02-06	8.8	±	±	±	±
10	2013-12-13	8.4	±	±	±	±
12	2013-10-03	8.5	-	±	±	±
14	2013-08-13	7.3	-	±	±	-
16	2013-06-13	7.7	-	±	±	±
18	2013-04-19	7.9	±	±	±	-
20	2013-03-02	7.9	-	+	+	+

* TPC: Total Plate Count
** Y&M: yeasts and molds

The organoleptic properties of the CBM®NFDGM do not change significantly during the shelf life of the product during 18 months and stays well within acceptable ranges.

2. CBM®GWPC Stability

Shelf-life studies performed on CBM®GWPC were conducted using material sampled during production. The sample bags (200 g), non-gas flushed, were stored at ambient conditions (15-25°C). Material of each batch underwent sensory analysis according to Hyproca's internal procedures (Table 14).

Table 14. Shelf-Life Testing: Sensory Analyses of CBM®GWPC

Post-Production (months)	Production Date GWPC	Sensory evaluation (-, ±, +)						Microbial analysis	
		Overall (1 – 10)	Sweet	Salty	Goaty	Cheesy	Soapy	TPC* (cfu/g)	Y&M** (cfu/g)
2	2014-08-29	reference	±	±	±	±	±	<400	<40
3	2014-07-25	8.3	±	±	±	±	-	<100	<40
4	2014-06-23	8.1	±	±	±	±	±	<100	<10
6	2014-04-23	8.0	±	±	±	±	-	<100	<40
9	2014-01-27	8.3	±	±	±	±	-	<100	<10
12	2013-10-25	8.6	±	±	±	±	±	430	<10
14	2013-08-30	7.7	±	±	±	±	±	<400	<40

*TPC: Total Plate Count
**Y&M: yeasts and molds

The organoleptic properties of the GWPC do not change significantly during the shelf life of the product; the overall evaluation of the product during 12 months (using linear regression on all available data) stays well within acceptable ranges.

3. Consideration of Potential Contaminating Materials

Levels of all residues and contaminants, such as aflatoxin, heavy metals, radioactivity, pesticides, chloroform, PCBs, dioxins and anthelmintics, are measured in raw milk and in milk products by The Netherlands Controlling Authority for Milk and Milk Products (COKZ). The results of the monitoring program consistently demonstrate that goats' milk used by Hyproca for manufacture of NFDGM and GWPC is in compliance with the hygiene requirements of The Netherlands and the European Union with an adequate monitoring program based on risk analysis.

IV. NUTRITIONAL ASPECTS OF PROTEIN SOURCES IN INFANT FORMULA

A. Compositional Standards for Protein and Amino Acids in Infant Formula

The purpose of the Infant Formula Act of 1980 is to ensure the safety and nutrition of infant formula, including minimum and maximum levels of specified nutrients. 21 CFR 107.100 outlines these nutrients specifications, including a requirement for 1.8 (minimum) - 4.5 g (maximum) protein per 100 kcal of infant formula. The amino acid profile of infant formula available in the U.S. should align with the essential and semi-essential amino acid profile outlined in the Codex Standard for Infant Formulas and Formulas for Special Medical Purposes Intended for Infants (CODEX, 1981). Table 15 presents a summary of the Codex Standard for essential and semi-essential amino acids, per 100 kcal of an infant formula, with a minimum protein content of 1.8 g/100 kcal.

Table 15. Requirements for Essential and Semi-Essential Amino Acids in Infant Formula[a]

Amino Acid	Minimum content per 100 kcal infant formula (mg/1.8 g protein)	Content per 1.8 g protein in NFDGM	Content per 1.8 g protein in GWPC	Content per 1.8 g protein in 60:40 mix whey protein: casein	Content per 2.5 g protein/100 kcal (intended for Kabrita US)
Cysteine	38	20	45	33	46
Histidine	41	45	38	41	57
Isoleucine	92	83	104	94	131
Leucine	169	166	173	169	235
Lysine	114	140	169	155	216
Methionine	24	43	32	38	52
Phenylalanine	81	81	58	69	96
Threonine	77	88	121	105	146
Tryptophan	33	22	34	28	39
Tyrosine	75	72	52	62	86
Valine	90	117	104	110	153

[a] (CODEX, Amended 2011).

The values listed in Table 15 are averages of the essential and semi-essential amino acids in human milk derived from published studies (Bindels & Harzer, 1985; Darragh & Moughan, 1998; Janas, Picciano, & Hatch, 1987; L. Kohler, Meeuwisse, & Mortensson, 1984; Lönnerdal & Forsum, 1985) which reported measurements of the total nitrogen content and/or the calculation method of the protein content. The average level of a given amino acid (mg per g of nitrogen)

from each study was used to calculate the corresponding amino acid content per 100 kcal of infant formula with a minimum protein content of 1.8 g/100 kcal.

Research has shown that goats' milk infant formulas have amino acids in amounts similar to human milk reference values, on a per-energy basis, and that the casein composition in human milk, particularly the level of alphas1-casein, is more similar to goats' milk than to cows' milk (Rutherfurd, Moughan, Lowry, & Prosser, 2008).

In the infant formula manufactured by Hyproca, CBM®NFDGM and CBM®GWPC will be used in combination as the sole source of protein. Hyproca will ensure that the finished product complies with protein requirements as outlined in 21 CFR 107.100, as well as the standard for essential and semi-essential amino acid composition as defined in Codex Standard for Infant Formulas and Formulas for Special Medical Purposes Intended for Infants. In order to meet minimum amino acid requirements for infant formula marketed in the United States (CODEX 1981), CBM®GWPC is used to improve the amino acid profile of CBM®NFDGM, to ensure compliance with this CODEX standard. This process is similar to the manufacture of cows' milk formula, where the addition of whey proteins is also used to improve the essential and semi-essential amino acid profile of cows' milk proteins from skimmed milk (Hernell, 2011; Räihä et al., 2002).

B. Suitability of CBM®NFDGM & CBM®GWPC as a Source of Protein in Infant Formula

All infant formulas must contain protein, which provides essential and semi-essential amino acids for normal growth and maintenance of health in infants. The most commonly consumed infant formulas are made from modified cows' milk with added carbohydrate (e.g., lactose), vegetable oils, and vitamins and minerals (United States Department of Agriculture (USDA), 2014). As mentioned previously, modified goats' milk, however, is used in many countries around the world as the protein source in infant formula products. Similar to cows' milk, the predominant protein in goats' milk is casein, while the primary protein in breast milk is whey protein (United States Department of Agriculture (USDA), 2014). As a result of this difference, infant formula based on cows' milk proteins from skimmed milk typically have extra whey proteins added to improve the essential and semi-essential amino acid profile (Hernell, 2011; Räihä et al., 2002). The premise for the addition of CBM®GWPC to CBM®NFDGM in goats' milk protein-based infant formula is the same as that for cows' milk formula – to improve the amino acid profile and make the formula as similar as possible to human milk.

A review by the European Food Safety Authority (European Food Safety Authority (EFSA), 2012) supports the suitability of goats' milk as a source of protein in infant formula. EFSA reviewed several studies in the literature, but the most definitive study was a randomized, double-blind trial comparing the growth rates and nutritional status of infants exclusively fed goats' milk formula. Overall, the EFSA Panel concluded that protein from goats' milk can be a suitable protein source for infant and follow-on formulas, provided the final product complies with the compositional criteria in Directive 2006/141/EC (European Food Safety Authority (EFSA), 2012).

Zhou et al. (2014), conducted a double-blind, randomized controlled clinical trial with 200 formula fed term-infants, in order to compare the growth and nutritional status of infants fed a goats' milk infant formula with those of infants fed a typical whey-based cows' milk infant formula. The infants fed goats' milk formula (n=101) were compared to infants fed cows' milk formula (n=99) and infants breast-fed (n=101) exclusively for four months, with continuous feeding up to 12 months in addition to complementary food. Markers of nutritional status in blood at the age of four months (hemoglobin, hematocrit, creatinine, urea nitrogen, folate, albumin, ferritin, blood amino acids) did not significantly differ between the formula-fed groups. There were no statistically significant or clinically relevant differences in the weight, length or head circumference development in the infants in the formula-fed groups. They also examined a range of health- and allergy-related outcomes as secondary endpoints. Infants received either a goats' milk or cows' milk formula from 2 weeks to 4 months of age. At 4 months, nutritional status as well as the Z-scores for weight, body length, head circumference and weight to length were assessed. Zhou et al. (2014) reported that there was no diffidence in Z-scores between the two formula groups. Differences between the two formula-fed groups were noted for amino acids and blood biomarkers; however, the mean values for biomarkers were within the normal reference range. The researchers concluded that there was no difference between the goats' milk formula fed group and the whey-based cows' milk group with respect to growth and nutritional outcomes.

V. INTENDED DIETARY USE

Hyproca intends to use the combination of CBM®NFDGM and CBM®GWPC in the prescribed ratio as a source of protein in full-term infant formula. The ratio of whey to casein is approximately 60:40, and total protein content is 2.5 g/100 kcal. This ratio is similar to the ratio of whey to casein found in mature human milk (Kunz & Lönnerdal, 1992). To achieve this protein content, the proposed use level for CBM®NFDGM in reconstituted infant formula is 22.95 g/L formula. The proposed use level for CBM®GWPC in reconstituted infant formula is 19 g/L.

A. Intended Levels of Use of Protein from CBM®NFDGM and CBM®GWPC in Infant Formula

In the powdered infant formula manufactured by Hyproca, total protein content is 2.5 g per 100 kcal. CBM®NFDGM contributes approximately 57% (±5%) of the total protein content, or approximately 1.42 g protein/100 kcal. CBM®GWPC contributes approximately 43% (±5%) of the total protein content, or approximately 1.08 g protein/100 kcal. Combined, these ingredients yield a whey: casein ratio of approximately 60:40. Using these ingredients, Hyproca is able to produce infant formula that meet requirements for protein content per 21 CFR 107.100, as well as essential and semi-essential amino acids per Codex Standard 72-1981 as shown in Table 15.

In assessing the impact of the exposure of infants to goats' milk protein-containing infant formula, typical intakes of protein from goats' milk have been estimated. These estimates have been made for a typical consumer (taken as a 6-month-old infant consuming infant formula as a

sole source of nutrition) and an extreme consumer (taken as a younger infant aged 3 months who requires additional energy to support catch-up growth and whose intakes, because of the lower body weight, are greater per unit of weight than an older infant). All estimates of energy requirements for boys and girls are taken from the Institute of Medicine, National Academy of Sciences, 2002/2005, U.S. Dietary Reference Intakes, Tables 5-16 and 5-17 (Institute of Medicine Panel on Micronutrients, 2005).

A typical consumer is considered to be a 6-month-old infant with a daily energy requirement of 645 kcal/day (male) or 593 kcal/day (female). Based on a protein content of 2.5 g protein/100 kcal formula, the 6-month old male infant is anticipated to consume 16.1 g protein from NFDGM and GWPC daily. The 6-month-old female infant is anticipated to consume 14.8 g protein from CBM®NFDGM and CBM®GWPC daily.

The extreme consumer is taken as an infant born with a birth weight on the 50th percentile. This infant experiences subsequent growth failure and is on the 3rd centile for weight at 3 months of age, resulting in increased energy requirements to facilitate catch-up growth. Calculations are based on a 3 month male infant weighing 4.7 kg (Institute of Medicine Panel on Micronutrients, 2005) and 3 month female infant weighing 4.3 kg (Institute of Medicine Panel on Micronutrients, 2005) with a daily energy requirement of 115 kcal/kg (Great Ormond Street Hospital for Children NHS Trust, 2000). Based on a protein content of 2.5 g/100 kcal, the daily protein intake of the extreme male infant consumer is anticipated to be 13.5 g from CBM®NFDGM and CBM®GWPC. The daily protein intake of the extreme female infant consumer is anticipated to be 12.4 g from CBM®NFDGM and CBM®GWPC.

B. Intakes of CBM®NFDGM and CBM®GWPC by Typical and Extreme Consumers

Estimates for the intake of NFDGM and GWPC were based on the proposed food use and use levels in conjunction with food consumption data included in the U.S. National Health and Nutrition Examination Survey (NHANES) data (Centers for Disease Control and Prevention (CDC), 2011; U.S. Department of Agriculture (USDA), 2011). Calculations for the mean, 90th, 95th and 97.5th percentile all-person and all-user intakes were performed for the proposed food use of CBM®NFDGM and CBM®GWPC, and the percentages of consumers were determined. These estimates were based on the assumption that all formulas in the market contained CBM®NFDGM and CBM®GWPC. Per person and per kilogram body weight intakes were reported for newborns (ages 0 to 6 months) and infants (ages 7 to 11 months) (see Table 16, Table 17, Table 18 and Table 19). A description of how the use levels were calculated and the NHANES database used can be found in Appendix B.

Table 16 summarizes the estimated total intake of CBM®NFDGM (g/person/day) from infant formula in the U.S. population groups. Approximately 74.8% of newborns between the ages of 0 to 6 months were identified as consumers of infant formula, representing the highest percentage of users identified. Within infants, 58.8% of this population reported consumption of infant formula.

Within the all-person consumption, the intake of CBM®NFDGM was observed to be greatest in newborns, ranging from 14.5 g/day at the mean to 31.5 g/day at the 97.5th percentile. When the intake was limited to consumers only (all-user consumption) the estimated intakes of CBM®NFDGM in newborns ranged between 19.3 g/day at the mean and 31.9 g/day at the 97.5th percentile. In infants aged 7 to 12 months, the all-person intake of NFDGM was estimated to be 9.37 g/day at the mean and 27.6 g/day at the 97.5th percentile. Within the all-user designation the intake of CBM®NFDGM was estimated to be 15.9 g/day at the mean and 30.1 g/day at the 97.5th percentile.

Table 16. Summary of the Estimated Daily Intake of CBM®NFDGM from Infant Formula by Population Group [a]

Population Group	Age	All-Person Consumption (g/day)				% Users	Actual # of Total Users	All-User Consumption (g/day)			
		Mean	P90	P95	P97.5			Mean	P90	P95	P97.5
Newborns	0 to 6 months	14.5	26.1	30.5	31.5	74.8	161	19.3	27.8	30.8	31.9
Infants	7 to 12 months	9.37	21.7	25.2	27.6	58.8	117	15.9	25.2	26.9	30.1

[a] NHANES 2009-2010.

Table 17 presents these data on a per kilogram body weight basis (g/kg body weight/day) for newborns (0-6 months) and infants (7-12 months). On a body weight basis, newborns remained the population group with the greatest intakes of CBM®NFDGM based on the proposed uses. When all respondents were considered (all-person), the mean and 97.5th percentile intakes of goats' milk powder were estimated to be 2.38 and 5.95 g/kg body weight/day, respectively, in this age group. Within the all-user designation, the mean and 97.5th percentile intakes were equivalent to 3.18 and 6.10 g/kg body weight/day, respectively. Within infants the all-person estimates intakes of NFDGM were equivalent to 1.05 g/kg body weight/day at the mean and 3.33 g/kg body weight/day at the 97.5th percentile. Within consumers of infant formula the estimated mean intake of CBM®NFDGM increased to 1.78 g/kg body weight/day while the estimated 97.5th percentile increased to 3.43 g/kg body weight/day.

Table 17. Summary of the Estimated Per Kilogram Body Weight Daily Intake of CBM®NFDGM from Infant Formula by Population Group [a]

	0 to 6 months	2.38	4.56	5.34	5.95	74.8	161	3.18	5.12	5.39	6.10
	7 to 12 months	1.05	2.31	3.03	3.33	58.8	117	1.78	2.96	3.31	3.43

[a] NHANES 2009-2010.

Table 18 summarizes the estimated total intake of CBM®GWPC (g/person/day) from infant formula in the U.S. population group. Approximately 74.8% of newborns between the ages of 0 to 6 months were identified as consumers of infant formula, representing the highest percentage

of users identified. Within infants, 58.8% of this population reported consumption of infant formula.

Within the all-person consumption, the intake of CBM®GWPC was observed to be greatest in newborns, ranging from 8.83 g/day at the mean to 19.2 g/day at the 97.5th percentile. When the intake was limited to consumers only (all-user consumption), the estimated intakes of CBM®GWPC in newborns ranged between 11.8 g/day at the mean and 19.5 g/day at the 97.5th percentile. In infants aged 7 to 12 months, the all-person intake of CBM®GWPC was estimated to be 5.72 g/day at the mean and 16.9 g/day at the 97.5th percentile. Within the all-user designation the intake of CBM®GWPC was estimated to be 9.7 g/day at the mean and 18.4 g/day at the 97.5th percentile.

Table 18. Summary of the Estimated Daily Intake of CBM®GWPC from Infant Formula

Population Group	Age	All-Person Consumption (g/day)				% Users	Actual # of Total Users	All-User Consumption (g/day)			
		Mean	P90	P95	P97.5			Mean	P90	P95	P97.5
Newborns	0 to 6 months	8.83	15.9	18.5	19.2	74.8	161	11.8	17.0	18.8	19.5
Infants	7 to 12 months	5.72	13.2	15.4	16.9	58.8	117	9.7	15.4	16.4	18.4

[a] NHANES 2009-2010.

Table 19 presents these data on a per kilogram body weight basis (g/kg body weight/day). On a body weight basis, newborns remained the population group with the greatest intakes of CBM®GWPC from infant formula. When all respondents were considered (all-person), the mean and 97.5th percentile intakes of CBM®GWPC were estimated to be 1.45 and 3.63 g/kg body weight/day, respectively, in this age group. Within the all-user designation, the mean and 97.5th percentile intakes were equivalent to 1.94 and 3.72 g/kg body weight/day, respectively. Within infants the all-person estimated intakes of GWPC were equivalent to 0.64 g/kg body weight/day at the mean and 2.03 g/kg body weight/day at the 97.5th percentile. Within consumers of infant formula, the estimated mean intake of CBM®GWPC increased to 1.09 g/kg body weight/day while the estimated 97.5th percentile increased to 2.09 g/kg body weight/day.

Table 19. Summary of the Estimate Per Kilogram Body Weight Daily Intake of CBM®GWPC from Infant Formula by Population Group[a]

Population Group	Age	All-Person Consumption (g/kg bw/day)				% Users	Actual # of Total Users	All-User Consumption (g/kg bw/day)			
		Mean	P90	P95	P97.5			Mean	P90	P95	P97.5
Newborns	0 to 6 months	1.45	2.78	3.26	3.63	74.8	161	1.94	3.12	3.29	3.72
Infants	7 to 12 months	0.64	1.41	1.85	2.03	58.8	117	1.09	1.81	2.02	2.09

[a] NHANES 2009-2010.

VI. REVIEW OF SAFETY DATA ON NFDGM & GWPC

A. Common Knowledge of Safe Goats' Milk Consumption

The domestication of goats' is estimated to have originated in the mountains of Iran, approximately 10,000 years ago (G. Haenlein, 2007). The ability of the goats' to provide high quality food in extreme and diverse climates has contributed to its popularity in developing countries, such as those in the Middle East, Eastern Europe, South America and the Mediterranean (Selvaggi et al., 2014). Goats accompanied the early European settlers to the U.S., although breed organization and market development have been stronger among cattle and sheep (G. F. Haenlein, 1996). In addition to the goat meat and fiber industries, there are 6 breeds of dairy goats producing milk in the U.S., including the Saanen, Nubian, Toggenburg, LaMancha, Oberhasli and Alpine (GFW Heinlein & R Caccese, 2003; Selvaggi et al., 2014).

The composition of goats' milk is such that it has a natural whey protein to casein ratio of approximately 20:80, similar to that of cows' milk (Selvaggi et al., 2014). There is subsequently a high presumption of safety for goats' milk and its constituents due to the long history of use in milk and cheese as human food. Worldwide, approximately 4.8 million tons of goats' milk are consumed either in the form of "milk" or cheese, and this comprises approximately 2% of the world's dairy milk supply (FAO, 1997). According to the FAO, the top producers of goats' milk in 2008 were India (4 million metric tons), Bangladesh (2.16 million metric tons) and the Sudan (1.47 million metric tons).

In the U.S., approximately one million goats are in active milk production for use in various food forms such as cheese, liquid milk, yogurt and ice cream. USDA reported that from 1987-1997 production of goats' milk doubled to 9 million gallons per year with the fastest growing market for goats' milk being the production of cheese (United States Department of Agriculture (USDA), 2004). Today, dairy goats are found in every state of the U.S. In addition to domestic production, the US imports more than 50% of the goat cheese consumed, most of which comes from France (Agricultural Marketing Resource Center (AgMRC), 2012).

1. Safety Studies on Goats' Milk

a. Overview

A comprehensive review of the literature was conducted to identify published research on the safety of goats' milk, and by extension, CBM®NFDGM and CBM®GWPC. The search parameters included animal safety and human safety studies.

b. Animal Safety Studies

While no traditional toxicology studies specifically designed to look for safety endpoints on goats' milk in laboratory animals were located, several safety-related studies have been conducted on animals using goats' milk (Alférez et al., 2006; Aliaga, Alferez, Barrionuevo, Lisbona, & Campos, 2000; Barrionuevo, Alferez, Aliaga, Sampelayo, & Campos, 2002; Barrionuevo et al., 2003; Diaz-Castro et al., 2012; Kruger et al., 2008; Murry et al., 1999;

Nestares et al., 2008; S. M. Rutherfurd, A. J. Darragh, W. H. Hendriks, C. G. Prosser, & D. Lowry, 2006), goats' milk protein (Sanz Ceballos, Sanz Sampelayo, Gil Extremera, & Rodriguez Osorio, 2009), and goats' milk infant formula (S. M. Rutherfurd et al., 2006). These studies focused on the comparison of lyophilized goats' milk to cows' milk with regard to the nutritive value and/or bioavailability of specific minerals, but they did not address safety endpoints or adverse events.

c. Studies Investigating Safety and the Effects of Feeding Goats' Milk Infant Formula in Human Infants

The safety of CBM®NFDGM and CBM®GWPC as a source of protein and amino acids in infant formula is dependent not only on potential toxicological effects but also on the nutritional adequacy of the protein source. Several clinical studies have assessed the adequacy of goats' milk as a source of protein and amino acids in infant formula. An overall synopsis of these studies is provided below and in Appendix C while a few key clinical studies are summarized below.

Grant et al. (2005) conducted a goats' milk infant formula growth rate pilot study to investigate whether feeding infant formula manufactured from goats' milk was nutritionally equivalent to feeding infant formula manufactured from cows' milk. Sixty-two of the 72 infants randomized completed the study (goats' milk formula n=30; cows' milk formula n=32). Infant weight, body length, and head circumference were measured at birth and age 14, 28, 56, 84, 112, 140 and 168 days. Additionally, bowel motion frequency and consistency, sleeping and crying patterns and adverse events were also measured. No statistically significant difference was seen in mean weight, body length or head circumference increase between the two formula groups. Median daily bowel motion frequency was greater in the goats' milk formula group, but there were no group differences in bowel motion consistency, duration of crying, ease of settling, or frequency of adverse events (e.g., vomiting, diarrhea, constipation, food refusal or screaming). The results indicate that the tolerability and safety of goats' milk formula did not differ to that of cows' milk formula.

Han et al. (2011) conducted an in-market surveillance of 976 Korean infants from birth to 12 months of age receiving either goats' milk infant formula, cows' milk infant formula, a mix of breast milk and goats' infant formula, a mix of breast milk and cows' infant formula or breast milk alone. The infants fed human milk, goats' or cows' milk infant formulas during the first 4 months showed similar growth outcomes. The infants fed the cows' milk formula had fewer but more solid bowel movements compared to human milk and goats' milk fed infants. The authors, based on the study outcomes, concluded that goats' milk infant formula is suitable for infants less than 12 months of age.

Zhou et al. (2014) conducted a well-powered, double-blind, randomized controlled clinical study to compare the growth of infants fed a goats' milk infant formula with that of infants fed a typical whey-based cows' milk infant formula. A range of health- and allergy-related outcomes was also examined (i.e., nutritional status, general health, tolerance to formula and allergy symptoms). Two hundred formula-fed infants were randomly assigned to either goats' (n=101) or cows' milk

formula (n=99) from 2 weeks to at least 4 months of age, and thereafter with other complementary foods up to 12 months of age. A reference group of 101 breast-fed infants was included for comparison. Infant weight, length and head circumference were measured at enrollment, 2 weeks and 1, 2, 3, 4, 6 and 12 months. Non-fasting blood samples were collected at 4 months to assess blood biomarkers, including Hb, packed cell volume, serum creatinine, urea, albumin, ferritin, folate, and plasma amino acids. There were no differences in the adjusted intention-to-treat analyses of weight, length, and head circumference and weight-for-length Z-scores between the formula-fed groups over the 12 month study period. Interestingly, differences in weight or weight-for-length Z-scores persisted for 12 months between the breast-fed infants and cows' milk formula-fed infants, but there were no differences between goats' milk formula-fed infants and breast-fed infants.

Researchers reported minor differences in blood biomarkers between the formula-fed groups, which were attributed to the compositional differences of the formulas; however, concentrations of these biomarkers at 4 months were within normal reference ranges for infants of this age. There were also no differences in the risk of an adverse health condition (i.e., respiratory illness, gastrointestinal illness, reflux, eye infection, ear, nose and throat conditions, fever, urinary tract infection and thrush) between the two formula-fed groups. The proportion of infants with a medically diagnosed food allergy did not differ between the groups. There were some differences observed in plasma levels of some amino acids between formula- and breast-fed infants; these differences are most likely explained by the higher protein intake of the formula-fed infants compared to breast-fed infants. Overall, goats' milk protein-based formula has shown to provide growth and nutritional outcomes in infants that did not differ from those provided by a standard whey-based cows' milk formula.

Studies have also been conducted on the safety and adequacy of goats' milk versus cows' milk in the malnourished child population. These studies are summarized, respectively, below.

Razafindrakoto et al. (1994) conducted a randomized study to look at the effects of goats' milk based formula versus a cows' milk based formula (referred to in the study as High Energy Milks (HEM)) on weight gain in thirty malnourished children ages one to five years of age with the same inclusion criteria. At inclusion there was no significant difference between the children. Both formulas were well defined. The children were fed an initial serving at 100 kcal/kg leading up to 200 kcal/kg on the tenth day. There was one death due to systematic candidiasis in the goats' milk group. There was no significant difference between the two formula groups with respect to the quantity of the HEM consumed, weight gain, nutritional status improvement or volume of stool and urine extracted. Both groups demonstrated good tolerance of the formulas and no intolerances, diarrhea, vomiting or abdominal swelling. The researchers concluded that there is a beneficial effect of feeding HEM to malnourished children and that goats' milk has a similar nutritional value to that of cows' milk and can be used as a suitable alternative for this population.

Hachelaf et al. (1993) performed a comparative, double - blind digestibility study of goats' and cows' milk fats in 64 children aged 9 to 72 months with intestinal malnutrition or malabsorption due to gluten intolerance. The primary objective was to determine if goat's milk, with 2x the

medium-chain triglycerides (MCTs) content than that of cows' milk, would result in a positive clinical effect with regards to intestinal fat absorption rate (FAR). Of importance here is that the secondary objective assessed the clinical value to using goats' milk as a viable alternative to cows' milk for this purpose. Each group was given standardized food based on either goats' or cows' milk for three days. There was no difference in the two groups upon inclusion. It was observed that there was no significant difference between the two groups with respect to food tolerance, food and caloric intake and body weight changes. The researchers concluded that goats' milk is similar to cows' milk in nutritional value in the malnourished population.

B. Allergenicity of Goats' Milk

1. Introduction

Approximately 6% of the U.S. infant population has an allergic-type response to cows' milk with approximately 14% of this 6% reacting to the cow's milk protein (CMP) (G. Heinlein & R. Caccese, 2003). Many of the cows' milk allergic type responses are to other constituents of cows' milk that may also be found in goats' milk. Camel, mare, soy milks and goats' milk have been reported to be effective alternatives to cows' milk in the case of cows' milk allergy; however, studies have reported cases of allergenicity or intolerance to these milks (El-Agamy, 2007; Hill, Heine, Cameron, Francis, & Bines, 1999). Therefore, the literature suggests that milks from a variety of sources have allergenic potential.

On a molecular level, it appears that casein fractions and beta-lactoglobulins are the components of cows' milk which are the most common causes of cows' milk allergy. An individual's genetic polymorphisms are also thought to have an effect on the allergenicity of milks (El-Agamy, 2007; Koletzko et al., 2012).

There is evidence to suggest a lower allergenic potential of goats' milk compared to cows' milk (Ballabio et al., 2011; Lara-Villoslada et al., 2006; Restani, 2004; Sanz Ceballos et al., 2009) along with many anecdotal reports from consumers. This has led to the belief that goats' milk may be used as an alternative to cows' milk in cases of allergy. The evaluation of several components of cows' and goats' milk has indicated that goats' milk lacking α-s1-casein, the main casein in cows' milk, is less allergenic than goats' milk with α-s1-casein (El-Agamy, 2007). This is supported by a guinea pig study by Bevilacqua et al. (2001) that suggests this variance in the presence of α-s1-casein is due to the high degree of genetic polymorphism in goats. On the other hand, a study in Balb/C mice looked at the cross-reactivity between goats' and cows' milk and concluded that goats' milk "...when used as the first source of protein after a breast feeding period, is less allergenic than cows' milk in mice" but further suitability studies are needed (Lara-Villoslada, Olivares, Jimenez, Boza, & Xaus, 2004). Another study on the cross-reactivity between individuals with cows' milk allergy and goats' milk allergy, noted that the percentage of individuals with cows' milk allergy who tolerated goats' milk ranged from 7.7% to 92.7% (Restani, 2004). Ballabio et al. (2011) further cautioned about the cross-reactivity between these milks when using goats' milk infant formula.

Following their review of the literature, EFSA concluded that there are no convincing data to substantiate the view that the incidence of allergic reactions is lower when feeding goats' milk-based infant formula compared with cows' milk-based infant formula (European Food Safety Authority (EFSA), 2012). As such, the finished product label will indicate that the product is goats' milk-based to inform care-givers of infant consumers who are allergic to cows' milk. Koletzko et al. (2012) have published recommendations for the diagnosis and management of suspected cow's milk protein allergy (CMPA).

Several scientific publications have evaluated the potential allergenicity of goats' milk, particularly in comparison to cows' milk (Ballabio et al., 2011; Restani, 2004; Sanz Ceballos et al., 2009). These studies are summarized below.

2. Allergenicity Study Overview

Sanz Ceballos et al. (2009), looked at the allergenicity of goats' milk versus cows' milk with respect to their whey proteins, by using a guinea pig model. This was a comparative analysis of the allergenicity of goats' milk versus cows' milk using both *in vivo* and *in vitro* analyses. The guinea pigs were put into groups and sensitized to either goats' milk or cows' milk and the corresponding whey proteins. The researchers concluded that the goats' milk is hypoallergenic when compared to cows' milk; however, both the casein and whey proteins may play a role in the allergenicity of each milk.

Ballabio et al. (2011) looked at goats' milk allergenicity as a function of αS1-casein genetic polymorphism. The objective of the study was to evaluate the suitability of goats' milk for children allergic to cows' milk, based on the genetic variation in αs1-CN between goat breeds. Serum samples were collected from six children already identified as allergic to cows' milk with a high sensitization to the α-CN, ranging in ages from 9 months to over 9 years of age. Goats' milk samples were collected from 25 goats with different CSN1S1 genotypes. Nine samples were then selected for use in testing of the sera of the children identified based on the low α-CN content as compared with the abundance of β-CN. The results indicated that, while no serum of either goats' or cows' milk demonstrated a negative reaction pattern *via* SDS-PAGE, 2 of the milk goats' milk samples, with lower amounts of α-CN content, had a lower immunoreaction. The researchers do, however, caution about the risk of cross-reactivity between goats' and cows' milk proteins with use of goats' milk in infant formula but did hypothesize that goats' can be used for select groups of allergic patients.

Lara-Villoslada et al. (2004) looked at the allergenicity of goats' milk compared to cows' milk in a mouse atopy model. The researchers were looking at the probability of cross-reactivity between the two milks. 3-week-old female Balb/C mice (13 in each group) were sensitized to either goats' or cows' milk at 5 doses weekly for six weeks. It was observed that the cows' milk group had a significantly higher number of mice with diarrhea than the goats' milk group along with significantly higher serum cows' milk-specific immunoglobulin G1 and histamine levels in the cows' milk group. The team concluded that goats' milk "...when used as the first source of protein after a breast feeding period, is less allergenic than cows' milk in mice" but further infant formula suitability studies are needed.

VII. DISCUSSION OF REVIEWED INFORMATION AND GRAS CRITERIA

A. GRAS Criteria

The safety standard for GRAS status is "reasonable certainty of no harm under the intended conditions of use." FDA discusses in more detail what is meant by the requirement of general knowledge and acceptance of pertinent information within the scientific community, i.e., the so-called "common knowledge element," in terms of the two following elements[2]:

- Data and information relied upon to establish safety must be generally available, and this is most commonly established by utilizing published, peer-reviewed scientific journals; and
- There must be a basis to conclude that there is consensus (but not unanimity) among qualified scientists about the safety of the substance for its intended use, and this is established by relying upon secondary scientific literature such as published review articles, textbooks, or compendia, or by obtaining opinions of expert panels or opinions from authoritative bodies, such as the National Academy of Sciences.

The subject safety assessment undertaken was to ascertain whether GRAS status for the designated combination of NFDGM and GWPC as the source of protein and amino acids in infant formula with defined use levels meets FDA criteria for reasonable certainty of no harm under the intended use conditions by considering both the technical and common knowledge elements.

B. Summary of Basis for CBM®NFDGM and CBM®GWPC as GRAS for Use in Infant Formula

The first element of common knowledge that is required for a GRAS determination is the general availability of the key information on which the GRAS conclusion is based. Since the majority of the studies and data relied upon in this assessment have been published in the scientific literature, this aspect has been fulfilled. There are many published studies on the amino acid and nutritional composition as well as the nutritional quality of goats' milk (European Food Safety Authority (EFSA), 2012; Mack, 1952; Rutherfurd et al., 2008; Zhou et al., 2014).

European Food Safety Authority's (EFSA) 2012 opinion, *Scientific Opinion on the suitability of goats' milk protein as a source of protein in infant formulae and in follow-on formulae,* is a key document to support the regulatory and scientific consensus of the safety and suitability of goats' milk protein for the use in infant formula. EFSA reviewed the compositional scientific data on infant and follow-on formula using whole goats' milk, retaining its natural whey: casein ratio, as the protein source. This compositional data came from a double-blind, randomized, controlled, three-center trial with 200 Australian infants (fed formula with unmodified goats' milk protein or cows' milk formula for at least four months, then complementary food until 12 months) (Zhou et al., 2014, published after the EFSA opinion finalized) and the re-analysis of the data from a New Zealand clinical trial growth study previously review by the Committee. The

[2] See 62 FR 18938 (17 April 1997): http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafe/ucm083058.htm.

Australian study did not show a significant difference between the goats' milk and cows' milk groups with respect to weight, body length or head circumference development and was found to be supportive of the study previously reviewed by the Committee where the sample size was inadequate. The Committee concluded: "… goat milk can be suitable as a protein source for infant and follow-on formulae, provided the final product complies with the compositional criteria laid down in Directive 2006/141/EC"..

The published studies summarized in Appendix C indicate a low likelihood of adverse effects in infants consuming goats' milk protein in infant formula. These same publications also support the position that a goats' milk protein-based infant formula is able to support growth and nutritional outcomes in infants that do not differ from those provided by a standard whey-based cows' milk formula.

The second critical aspect of fulfilling the common knowledge criteria for GRAS determinations is through the establishment of consensus within the scientific community that is knowledgeable in the subject area. In this regard, the key decisions made by regulatory agencies (e.g., FSANZ, EFSA, 2012 - Scientific Opinion; Department of Health, England, 2013 No. 3243) to accept use of protein from goats' milk in infant formula in various countries supports a consensus opinion of its safety for the designated food use.

C. Summary Assessment by the Expert Panel

A high presumption of safety for the major constituents of goats' milk exists due to the long history of the use of goats' milk and cheese as human food. The production of goats' milk accounts for 2% of world's annual milk supply (FAO, 1997), and it is commonly consumed in whole milk form, cheese, yogurt and ice cream. In the United States, dairy goats are found in every state. As of 2012, the US had a census of 360,000 milk goats (Agricultural Marketing Resource Center (AgMRC), 2012). In a report from the United States Department of Agriculture (USDA), production of goats' milk doubled from 1987-1997 to 9 million gallons per year. USDA indicated the fastest growing market in the US for goat products is cheese (United States Department of Agriculture (USDA), 2004). In addition to domestic production, the US imports more than 50% of the dairy goat cheese consumed, most of which comes from France (Agricultural Marketing Resource Center (AgMRC), 2012).

No traditional toxicology studies in laboratory animals on components of goats' milk were located in the scientific literature. In light of the broad-based documentation of human food usage of goats' milk, this absence of traditional toxicology testing is not surprising. There have been several studies in animals using goats' milk (Alférez et al., 2006; Aliaga et al., 2000; Barrionuevo et al., 2003; Díaz-Castro et al., 2012; Kruger et al., 2008; Lopez-Aliaga et al., 2003; Nestares et al., 2008; S. Rutherfurd, A. Darragh, W. Hendriks, C. Prosser, & D. Lowry, 2006) and goats' milk protein (Ceballos, Sampelayo, Extremera, & Osorio, 2009) to study nutritional aspects and effects on absorption of vitamins and minerals. No adverse effects were identified in these studies.

The nutritional adequacy and the potential benefits of goats' milk as opposed to cows' milk in the diets of humans have been well reviewed (Kumar, 2012; Park, 1994). The protein content of goats' milk can be higher than cows' milk, but the protein concentration depends on the breed, lactation stage, feeding of the goat and season (European Food Safety Authority (EFSA), 2012). A review by Jenness (1980) noted that the 5 principal proteins of goats' milk (α-lactalbumin, β-lactoglobulin, κ-casein, β-casein, and α2-casein) closely resemble their homologs in cows' milk. In addition, the overall amino acid composition is similar for cows' and goats' milk in these proteins with a homology of 84-95% (European Food Safety Authority (EFSA), 2012). Colin G Prosser, McLaren, Frost, Agnew, and Lowry (2008) found that alanine, arginine, glutamic acid, histidine, lysine and tyrosine were all very comparable between whole goats' milk powder and whole cows' milk powder in mg/100 mL.

Safety of goat's milk protein in infant formula is dependent not only on possible frank toxicology effects but also the nutritional adequacy of the protein source. The review by the European Food Safety Authority (European Food Safety Authority (EFSA), 2012) goes a long way in endorsing the suitability of goats' milk protein for use in infant formula. EFSA reviewed several studies in the literature, but the most definitive study was a randomized, double-blind trial comparing the growth rates and nutritional status of infants exclusively fed whole goats' milk formula (Zhou et al., 2014). Infants fed goats' milk formula (n=101) were compared to infants fed cows' milk formula (n=99) and infants being breast-fed (n=101) exclusively for four months, with continued feeding up to 12 months together with complementary food. Markers of nutritional status in blood at the age of four months (hemoglobin, hematocrit, creatinine, urea nitrogen, folate, albumin, ferritin, amino acids) did not significantly differ between the formula-fed groups. Further, concentrations of none of the amino acids were lower in either formula-fed group compared with those in the breast-fed infants. There were no statistically significant or clinically relevant differences in weight, body length or head circumference development between the infants in the two formula-fed groups.

Overall, the EFSA Panel concluded that protein from goats' milk can be a suitable protein source for infant and follow-on formula, provided the final product complies with the compositional criteria in Directive 2006/141/EC (European Food Safety Authority (EFSA), 2012).

In 2011, an additional report was published but not reviewed by EFSA. Han et al. (2011) conducted an in-market surveillance of 976 Korean infants from birth to 12 months of age receiving either goats' infant formula, cows' infant formula, a combination of breast milk and goats' milk infant formula, a mix of breast milk and cows' milk infant formula or breast milk alone. The infants fed goats' or cows' milk infant formula or being breast-fed during the first 4 months showed similar growth outcomes. The authors concluded that goats' infant formula is suitable for infants less than 12 months of age.

While cows' milk protein allergy is uncommon during infancy, it does affect approximately 3-5% of infants in industrialized countries (Infante, Tormo, & Conde, 2003). It should be noted that most cows' milk allergy occurs in toddlers (Infante et al., 2003). Many children that are allergic to cows' milk cannot tolerate goats' or sheep milk either. On rare occasions, goats' and sheep's milk allergies will not be associated with allergic cross-reactivity to cows' milk (Ah-Leung et al.,

2006). There is a high genetic variability in goats' milk proteins which may result in a different allergenicity. This may explain the differences in tolerance to goats' milk by subjects allergic to cows' milk protein (Ballabio et al., 2011; European Food Safety Authority (EFSA), 2012). In the study by Zhou et al. (2014), there were no differences between the groups with regard to medically diagnosed food allergy or parentally reported symptoms related to allergy.

VIII. THE EXPERT PANEL CONCLUDES THAT THE EFSA OPINION OF 2012---AS WELL AS THE COMPANION STUDIES REVIEWED---PROVIDE ADEQUATE SUPPORT TO CONCLUDE THAT GOATS' MILK PROTEIN FULFILLS THE GRAS CRITERIA FOR USE IN INFANT FORMULA. CONCLUSIONS[3]

Hyproca's CBM®NFDGM combined with CBM®GWPC---when produced in accordance with FDA Good Manufacturing Practices requirements---as the protein source in infant formula for full-term gestation infants to 12 months of age and when used at levels as stated in this document has been determined to be GRAS on the basis of scientific procedures in accordance with Section 201(s) of the Federal Food, Drug, and Cosmetic Act. This finding is further based on a consensus among the panel of experts (Bo Lonnerdal, Ph.D., Robert S. McQuate, Ph.D., and Richard Kraska, Ph.D., DABT) who are qualified by scientific training and experience to evaluate the safety of CBM®NFDGM and CBM®GWPC as a protein source for use in formula.

(b) (6)

Bo Lonnerdal, Ph.D.

(b) (6)

Robert S. McQuate, Ph.D.

(b) (6)

Richard Kraska, Ph.D., DABT (Chair)

[3] The detailed educational and professional credentials for Drs. Karaka and McQuate in serving on the Expert Panel can be found on the GRAS Associates website at www.gras-associates.com. Both worked on GRAS and food additive safety issues within FDA's GRAS Review Branch earlier in their careers and subsequently continued working within this area in the private sector. Dr. Lönnerdal is a Distinguished Professor of Nutrition and Internal Medicine at University of California Davis. He has considerable expertise in the composition of milk and infant formula and has performed many clinical trials on infants fed various types of infant formula. He has also served on several Expert Panels for LSRO/FDA, ESPGHAN and Codex Alimentarius.

All experts have previously served on multiple GRAS Expert Panels.

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Appendix A HACCP Certificate

HACCP-certificate

Qlip
quality assurance in agrofood

Qlip B.V.
Kastanjelaan 7, 3833 AN Leusden
The Netherlands

hereby declares that
the Food Safety System of

Lypack B.V.
Archimedesweg 15, Leeuwarden

complies with the criteria for HACCP-certification
with respect to:

developing, mixing and packaging infant, baby and toddler foods, vitamin and mineral premixes and food supplements

This certificate with number
H47

is granted on
29 June 2015

The HACCP-system has been evaluated and approved by Qlip according to the standard "Requirements for a HACCP based Food Safety System, issue 5 (June 2012)" laid down by CCvD-HACCP

H.J. Bobbink, managing director

(b) (6)

MGMT. SYS.
RvA C 264

This certificate has been issued under the conditions as laid down in the HACCP-certification Regulations CER-602
and is valid until 29 June 2018 at the latest

Appendix B Use Level Calculation Procedure and NHANES Database

NHANES are conducted as continuous, annual surveys, and are released in 2-year cycles. Each year about 9,000 people from 15 different locations across the U.S. are interviewed, and approximately 8,000 complete the health examination component of the survey. Any combination of consecutive years of data collection is recognized and used as a nationally representative sample of the U.S. population. It is well-established that the length of a dietary survey affects the estimated consumption of individual users and that short-term surveys, such as a 1-day dietary survey, may overestimate consumption compared to surveys conducted over longer time periods (Anderson, 1988). Because two 24-hour dietary recalls administered on 2 non-consecutive days are available from the NHANES 2009-2010 survey, these data were used to generate estimates for the current intake analysis.

NHANES 2009-2010 survey data were collected from individuals and households via 24-hour dietary recalls administered on 2 non-consecutive days (Day 1 and Day 2) throughout all 4 seasons of the year. Day 1 data were collected in-person, and Day 2 data were collected by telephone in the following 3 to 10 days, on different days of the week, to achieve the desired degree of statistical independence. The data were collected by first selecting Primary Sampling Units (PSUs), which were counties throughout the U.S., of which 15 PSUs are visited per year. Small counties were combined to attain a minimum population size. These PSUs were segmented and households were chosen within each segment. One or more participants within a household were interviewed.

In addition to collecting information on the types and quantities of foods being consumed, NHANES 2009-2010 collected socio-economic, physiological and demographic information from individual participants in the survey, such as sex, age, height and weight, and other variables useful in characterizing consumption. The inclusion of this information allows for further assessment of food intake based on consumption by specific population groups of interest within the total population.

Sample weights were incorporated with NHANES 2009-2010 data to compensate for the potential under-representation of intakes from specific population groups as a result of sample variability due to survey design, differential non-response rates, or other factors, such as deficiencies in the sampling frame (Centers for Disease Control and Prevention (CDC), 2011; U.S. Department of Agriculture (USDA), 2011).

Statistical analysis and data management were conducted in Creme software (Creme, 2013). Creme Food 3.0 is a probabilistic modeling software tool that uses high-performance computing to allow accurate estimate of exposure to contaminants, food additives, flavorings, nutrients, food packaging migratory compounds, novel foods, pesticide residues, and microbial contaminants. The main input components are concentration (use level) data and food consumption data. Data sets are combined using the Creme Food 3.0 model to provide accurate and efficient exposure assessments.

For the deterministic assessment, consumption data from individual dietary records detailing food items ingested by each survey participant were collated by computer and used to generate estimates for the intake of goats' milk powder by the U.S. population using Creme software. Estimates for the daily intake of goats' milk powder represent projected 2-day averages for each individual from Day 1 and Day 2 of NHANES 2009-2010 data; these average amounts comprised the distribution from which mean and percentile intake estimates were generated. Mean and percentile estimates were generated

incorporating survey weights in order to provide representative intakes for the entire U.S. population. All-person intake refers to the estimated intake of goats' milk powder averaged over all individuals surveyed, regardless of whether they potentially consumed food products containing goat milk powder, and therefore includes individuals with "zero" intakes (i.e. those who reported no intake of food products containing goats' milk powder during the 2 survey days). All-user intake refers to the estimated intake of goats' milk powder by those individuals who reported consuming food products containing goats' milk powder, hence the "all-user" designation. Individuals were considered 'users' if they consumed 1 or more food products containing goats' milk powder on either Day 1 or Day 2 of the survey.

Appendix C Characteristics of Clinical Trials Assessing the Adequacy of Goats' Milk as a Source of Protein and Amino Acids in Infant Formula

Reference	Design	Aim of Study	Sample Characteristics • Country • Age range • Gender • No. recruited • No. randomized • No. in final sample	Exposure and Duration • Dose/exposure; method and frequency of consumption • Duration of intervention or follow-up	Outcome Measures	Results	Conclusions
C. Grant et al. (2005)	Single-center, prospective, double-blind, randomized, controlled	To compare growth of infants fed goats' milk infant formula or cows' milk infant formula and to compare tolerability and safety of the two formulas	• New Zealand • Birth to 168 days • 77 infants registered • 72 infants randomized 62 infants in final sample	• Goats' and cows' milk infant formulae did not differ in the amount of protein, fat or carbohydrate. Energy density differed slightly being 290 kJ per 100 ml for goats' milk formula and 274 kJ per 100 ml for cows' milk formula • Feeding instructions had mothers administer 150-200 ml of formula/kg per day • Infants fed study formula from age 1-3 days until 168 days • Caregivers were permitted to introduce weaning foods after 112 days	• Infant weight, length and head circumference were measured in triplicate • Study nurse visited infants at 72 hours, and at 14, 28, 56, 84, 112, 140 and 168 days of age, at which point infants were measured and study diaries were reviewed • Bowel motion frequency and consistency, duration of crying and ease of settling were monitored at each visit	• The difference in average weight gain and increase in length over the study period for infants fed goats' milk formula vs. cows' milk formula was not significant. • Frequency of vomiting, diarrhea, constipation, and food refusal or screaming did not differ between the two groups. • Average daily intake of formula did not differ significantly for infants randomized to goats' milk formula (820±133 ml) compared to cows' milk formula (865±125 ml). • No difference between groups in bowel motion consistency, duration of crying or ease of settling. Bowel motion frequency in the goats' milk infant formula group was greater than in the cows' milk infant formula group, it was not excessive and not associated with any difference in consistency.	Growth of infants fed goats' milk infant formula is not different to that of infants fed cows' milk infant formula. The safety and tolerability of goats' milk infant formula did not appear to differ from that of cows' milk infant formula. Data from this study indicate that goats' milk infant formula is a suitable alternative to cows' milk infant formula in healthy, non-allergic children.

Reference	Design	Aim of Study	Sample Characteristics • Country • Age range • Gender • No. recruited • No. randomized • No. in final sample	Exposure and Duration • Dose/exposure; method and frequency of consumption • Duration of intervention or follow-up	Outcome Measures	Results	Conclusions
Han et al. (2011)	Prospective cohort (in-market surveillance)	To measure weight gain up to 12 months and stool characteristics of infants fed formulas based on goats' or cows' milk compared with those fed breast milk only or a mixture of breast milk and formula milk from birth to 4 months of age.	Korea Birth to 12 months 1,297 infants recruited 976 infants in final sample Infants were retrospectively categorized into 5 feeding groups: 1) breast milk (n=659; 49% males); 2) goat infant formula (n=32; 63% males); 63% males) Cow infant formula (n=159; 49% males); 4) mix of breast and goat infant formula (n=40; 53% males); 5) mix of breast milk and cow infant formula (n=86, 64% males)	Goats' milk infant formula contained 80:20 ratio of casein:whey and had 55% of total fat from milk, with remaining fat consisting of high oleic sunflower, sunflower, coconut, and soy oils Infants in the breast milk, goat infant formula, or cow infant formula groups received more than 80% of all feeding from birth to 4 months as either breast milk or formula Infants fed a mix of breast milk and either cow or goat infant formula received less than 80% of breast milk or formula. After 4 months, the feeding mode was varied according to the mothers' discretion, including introduction of solids.	Infant weights and body heights at birth and at 4, 8 and 12 months Stool number and consistency were recorded; consistency was graded by mothers, using an analogue scale composed of runny, soft or pasty, soft but well formed, firm, and hard as the categories	The type of feeding (breast milk or formula or combination of the two) had no significant influence on weight or height of infants at any time point. Average number of stools per day did not differ significantly between groups. Frequency of bowel movements in goat infant formula group was similar to that of infants in breast milk. Infants in cow infant formula group were more likely to have only 1-2 bowel movements per day and less likely to have >7 bowel movements per day compared to infants in breast milk group. Consistency of stools in cow infant formula group tended to be more formed or firm compared to those in either the breast milk or goat infant formula group.	This study showed that feeding behavior of infants fed goat infant formula either alone or in combination with breast milk during first 4 months of life produces comparable growth rates over 12 months and gastrointestinal function as breast milk-fed Korean infants. There is every indication that goat infant formula, when properly formulated, is suitable for infants less than 12 months of age.

Reference	Design	Aim of Study	Sample Characteristics • Country • Age range • Gender • No. recruited • No. randomized • No. in final sample	Exposure and Duration • Dose/exposure; method and frequency of consumption • Duration of intervention or follow-up	Outcome Measures	Results	Conclusions
Zhou et al. (2014)	Double-blind, randomized, controlled	To compare the growth and nutritional status of infants fed formulas based on either goats' milk or cows' milk in a well-powered randomized controlled trial. Secondary aim was to examine a range of health- and allergy-related outcomes, including incidence and severity of dermatitis	• Australia • 1180 families recruited • 301 families randomized • 301 infants included in analysis of growth • 240 infants included in the analysis of blood biochemistry and plasma amino acids	• 3 trial arms: goats' milk formula (treatment group), cows' milk formula (control group), breast-fed (reference group) • Infant formula made from whole goats' milk without added whey proteins (whey:casein ratio of 20:80) • Mean daily intake of study formula ranged from 698 mL in the first 2 weeks to 1000 ml at 4 and 6 months • Parents/caregivers were asked to feed their infants the allocated study formula from enrolment to at least 4 months of age and thereafter with other complementary foods up to 12 months of age. Timing of introduction of solids about 4 and 6 months was at the discretion of the families.	• Infant weight, length and head circumference, at enrolment, 2 weeks, and 1,2,3,4,6 and 12 months • Non-fasting blood samples analyzed for Hb, packed cell volume, serum creatinine, urea, albumin, ferritin, folate, and plasma amino acids at 4 months as indicator of general nutritional status • Stool frequency, consistency and effort as indicators of general tolerance to formula (Bristol Stool Scale) • Sleeping patterns also assessed (Sleep and Settle Questionnaire)	• No differences in intent-to-treat analyses of weight, length, head circumference and weight-for-length z-scores between the two formula-fed groups. • Differences in weight or weight-for-length z-scores persisted for 12 months between the breast-fed infants and cows' milk formula-fed infants, but there was no differences between goats' milk formula-fed infants and breast-fed infants. • Minor differences in blood biomarkers between formula-fed groups, likely due to compositional differences of the formulae; however, concentrations of these biomarkers at 4 months were within normal reference range for infants of this age. • There were some statistically significant differences in essential and semi-essential amino acids between formula-fed groups and with breast-fed infants (e.g. valine, isoleucine, , threonine, phenylalanine), but they are unlikely to be clinically important as the mean plasma amino acid concentrations in infants in both formula-fed groups were similar to those reported in other studies. • There were some differences in sleeping patterns between formula-fed and breast-fed infants, but differences were inconsistent. • No differences in risk of an adverse health condition between the two formula-fed groups. No differences in the objective assessment of allergy-related outcomes including dermatitis and medically diagnosed food allergy. • Stool frequency in both formula-fed groups was significantly lower than that in the breast-fed group.	The growth and blood biomarkers of nutritional status of infants fed a whole-goats' milk-based infant formula did not differ from those of infants fed a standard cow infant formula with added whey. Lack of a significant difference between the formula-fed groups for an extensive range of health-related outcomes and for the occurrence of serious adverse events supports the safety of using goats' milk in infant formula.

END

SUBMISSION END

Bonnette, Richard

From: Cheryl Dicks <dicks@gras-associates.com>
Sent: Monday, May 02, 2016 11:37 AM
To: Bonnette, Richard
Subject: RE: GRAS submission for nonfat dried goat's milk and goat whey protein concentrate

Dear Mr. Bonnette,
Thank you for your communications. Yes you are correct, the confidential note of the cover page is not applicable.

With Kind Regards,

Cheryl

Director of Operations
Senior Regulatory Affairs Scientist / Project Manager
GRAS Associates, LLC
C: 540.272.3254

From: Bonnette, Richard [mailto:Richard.Bonnette@fda.hhs.gov]
Sent: April-29-16 10:34 AM
To: Cheryl Dicks <dicks@gras-associates.com>
Subject: GRAS submission for nonfat dried goat's milk and goat whey protein concentrate

Ms. Dicks,
As we were conducting the pre-filing review for the submission dated 3/15/2016, we noted that the cover page (page 1) of the submission notes "Confidential," while Form 3667 notes that the submission does not contain confidential information. I suspect that the confidential note of the cover page is not applicable, but I wanted to confirm. Your email response confirming this point will be sufficient for us to move forward with the submission's review.
Thanks,
Richard Bonnette

Richard E. Bonnette, M.S.
Consumer Safety Officer
Division of Biotechnology and GRAS Notice Review
Office of Food Additive Safety
U.S. FDA, Center for Food Safety and Applied Nutrition

(240)402-1235
Richard.Bonnette@fda.hhs.gov

Mailing address:
5100 Paint Branch Parkway, HFS-255
College Park, MD 20740