Agarose Ion Exchange Resin as a Processing Aid for Lactoferrin production

PROCESSING AID APPLICATION

Food Standards Australia New Zealand

Applicant: FONTERRA Co-operative Group Limited
Submitted by: BIORESCO AUSTRALIA

October 8, 2015

CONTENTS:

Executive Summary:

This application, on behalf of Fonterra Co-operative Group Limited, requests approval for a new Processing Aid, an **Agarose ion exchange resin,** which is intended for use by the applicant for the production of high purity Lactoferrin from bovine milk.

Lactoferrin is a glycoprotein, and a member of the transferrin family of proteins, thus belonging to those proteins which have the capability of binding and transferring iron. It is mainly found in human and bovine milk, and to a lesser extent in other external secretions. It has multiple physiological functions, and is therefore one of the most important proteins present in mammalian milk. Apart from its role in iron metabolism, lactoferrin exerts important protective roles against a wide variety of infectious agents and is considered to be part of the innate immune system. Since it was first isolated more than 50 years ago, Lactoferrin has become the focus of intense research to better understand its physiological effects. Other roles in human health that have been established for lactoferrin include antibacterial, antiviral, and antiparasitic activity, immunomodulatory and anti-inflammatory activity, anticarcinogenic activity, cell proliferation and differentiation, and antioxidant acivity. The multiple roles that lactoferrin has in human health and development has established it as the first, and potentially the most important biaoactive as yet isolated from mammalian milk. Hence the enormous interest in lactoferrin for use in dairy-based foods, as a nutriceutical and a potential pharmaceutical.

Lactoferrin has been produced commercially since 1986. The established commercial method utilizes ion exchange chromatography to extract Lactoferrin from pre-treated dairy streams such as skim milk and whey. The ion exchange resin used for this purpose requires certain specific characteristics, for example, strong cation exchange functionality, large pore size to bind Lactoferrin, suitable bead size and mechanical strength to allow loading at high flow rates, and the ability to process whey or milk without becoming blocked. None of the permitted ion exchange resins currently listed in Standard 1.3.3 have all of these characteristics and are therefore not suitable for efficient commercial production of Lactoferrin.

The processing aid has been fully evaluated for safety for the intended purpose and is approved by the U.S. Food and Drug Administration as a Food Contact Substance. It complies with Codex Guidelines on Substances used as Processing Aids. In the EU, the Processing Aid meets the regulatory requirements for substances that come in contact with food, and the substances used for the manufacture of the Processing Aid are included on the “list of substances used in the manufacture of ion exchange and adsorbent resins”. The matrix of the Processing Aid, agarose highly cross-linked with epichlorohydrin, is the same as for an ion exchange resin currently listed as a permitted processing aid in Standard 1.3.3.

Ongoing research has established Lactoferrin as a bioactive of major importance in human health, development and disease prevention. Its multiple physiological activities offer enormous potential for Lactoferrin use in food, and as a nutriceutical and a pharmaceutical. Approval of this application would provide the opportunity for innovation in development of value-adding new products and ingredients by the dairy industry in Australia and New Zealand for both the domestic and export markets.

1 General Information:

1.1 Applicant Details:

Fonterra Co-operative Group Limited

Fonterra Co-operative Group Limited is a New Zealand based global dairy company and the largest international processor and exporter of dairy products with manufacturing plants in New Zealand and Australia. Fonterra manufactures and markets a complete range of dairy products and ingredients, for both retail consumers and the food industry.

Contact:

[redacted] – General Manager, Regulatory Advocacy
Fonterra Co-operative Group Limited
327 Ferntree Gully Road
Mount Waverly, Victoria 3149
Australia

[redacted]
website: www.fonterra.com

[redacted] – Technical Officer, Food Safety & Quality (Regulatory Team
Fonterra Co-operative Group Limited
157 Lambton Quay, Wellington
New Zealand

[redacted]
website: www.fonterra.com

Application Contact:

[redacted]
Bioresco Australia
PO Box 1040
Bathurst NSW 2795

[redacted]

(N.B. Bioresco Australia is a registered business name to Axiome Pty Ltd)

1.1 Purpose of the Application:

The purpose of this application is to request approval of a new Processing Aid, an **Agarose** ion exchange resin with the following chemical name:

Agarose, polymer with (chloromethyl)oxirane, 2-hydroxy-3(3-sulfopropoxy) propyl ethers, sodium salts

The 'Technological Purpose' of the ion exchange resin is for the extraction of Lactoferrin from milk, and milk related products.

The **Standard** that would need to be amended to achieve the intended purpose of this application is as follows:

PART 1.3 - Substances Added to Food
Standard 1.3.3 – Processing Aids

(or **Schedule 18** for the 'revised' Code)

Note: the Processing Aid is also referred to in this application by its trade name,
SP Sepharose™ Big Beads

1.3 Justification for the Application:

The intended use of the Processing Aid, by the applicant, is for the production of high purity bovine milk Lactoferrin from dairy streams such as skim milk and whey.

Lactoferrin[1] is a glycoprotein, and a member of the transferrin family of proteins, thus belonging to those proteins which have the capability of binding and transferring iron. It is mainly found in human and bovine milk, and to a lesser extent in other secretions, neutrophil granules and blood plasma, with human and bovine Lactoferrin being very similar in structure and sequence[2]. It has multiple physiological functions[2,3], and is one of the most important proteins present in mammalian milk. Apart from its role in iron metabolism, lactoferrin exerts important protective roles against a wide variety of infectious agents and is considered to be part of the innate immune system. Since it was first identified and isolated more than 50 years ago, Lactoferrin has become the focus of intense research to better understand its physiological roles and effects[3].

Other biological properties and roles in human health that have been established for lactoferrin include:

- antibacterial, antiviral and antiparasitic properties
- prevents the growth of pathogenic organisms in the gut
- immunomodulatory effects
- antiinflammatory effects
- anticarcinogenic activity
- cell proliferation and differentiation activity
- role in helping control cell or tissue damage
- antioxidant properties

The multiple roles that lactoferrin has in human health and development has established it as the first, and potentially the most important, biaoactive as yet isolated from mammalian milk.

Hence the enormous worldwide interest in lactoferrin for use in foods[4], as a nutriceutical and as a potential pharmaceutical.

At present, the only viable source of Lactoferrin for production purposes is from bovine milk and dairy streams such as skim milk and whey. However it is only present in these fluids a very low levels, 0.1 – 0.4 g/litre, and although milk enrichment techniques, such as modified milking practices and seasonal variation in milk composition have been proposed and evaluated, the level of enrichment is relatively low. A process is required to isolate and extract Lactoferrin that provides high yield and purity, and capable of operating with a complex matrix and at the low levels at which Lactoferrin occurs. Although other techniques have been studied[5], the only viable commercial method currently available is cation exchange chromatography, and this has been the method utilized since Lactoferrin was first produced commercially in 1986. The ion exchange resin used for this purpose requires certain specific characteristics:

- cation exchange functionality,
- large enough pore size to bind Lactoferrin due to its high molecular mass (80kDa) and large structure
- suitable bead size to bind Lactoferrin at fast flow rates
- ability to process whey or skim milk without becoming blocked

- sufficient mechanical strength to allow loading at high flow rates.

None of the approved ion exchange resins currently listed in Standard 1.3.3 have all of these characteristics and are therefore not suitable for efficient commercial production of Lactoferrin. For example:

- cation exchange resins commonly used for water softening and demineralisation (e.g. sulphonated styrene-divinyl benzene resins) have too small a pore size to bind Lactoferrin
- cation exchange resins that are used for protein ion exchange (regenerated cellulose with either sulphonate or carboxymethyl functional groups) have very little capacity for Lactoferrin
- Agarose ion exchange resin derivatised with tertiary amine groups is similar in pore structure and size to SP Sepharose™ Big Beads but the tertiary amine groups give anion exchange functionality and therefore is not capable of binding Lactoferrin

Regulatory Impact Information:

The international market for Lactoferrin is reported to have grown from 45,000 kg in 2001 to 185,000 kg in 2012 and is projected to grow to more than 260,000 kg by 2017. The current market price for Lactoferrin is reported at between US$500 to US$1,000 per kilogram.

The approval of this application would provide for the availability of a bioactive ingredient that offers consumers significant potential health benefits. The physiological functions and health benefits of Lactoferrin have been discussed in this Section. Lactoferrin is a premium ingredient and any additional cost from its use in dairy-based foods is offset by its health benefits; these types of foods are typically selected by consumers by choice.

Lactoferrin is a high value bioactive ingredient and approval of this application would provide the dairy industry with the opportunity to recover this product from low value dairy streams for supply to and use in domestic and international markets. The cost to industry of the processing aid is completely offset by the value of Lactoferrin as a dairy ingredient; overall, approval of this application would provide a cost benefit to the dairy industry.

No added costs to government are anticipated from the approval of this application.

The application proposes regulatory changes that are consistent with the relevant Codex Alimentarius guidelines. Therefore, there would not be any negative impact in respect to international trade. Foods supplemented with Lactoferrin, produced using the Processing Aid, could be imported and marketed in Australia/New Zealand.

SP Sepharose™ Big Beads has the same matrix composition as another GE Healthcare Bio-sciences ion exchange resin (agarose anion exchange resin), which is listed in Standard 1.3.3 as a permitted processing aid for the removal of specific proteins and polyphenols from beer (refer FSANZ Application A600).

1.4 Information to support the Application:

In support of this application, technical information, information on safety, and information on international regulatory status of the Processing Aid, is provided in Sections 2 and 3, and Appendices A, B, C, D.

There are no adverse health and safety issues that would result from the approval of this application for the general population or population sub-groups. The purpose of the Processing Aid is specifically for the production of Lactoferrin which has been identified as potentially the most important bioactive compound present in human milk; its multiple roles in human health are discussed in Section 1.3 (and Appendix A). In fact the proposed change would result in the availability of an important nutrient and bioactive compound which potentially can provide multiple health benefits for all population groups.

Consumer choice would not be affected by the proposed change. Use of the Processing Aid is specifically related to Lactoferrin, which is regarded as a premium food ingredient. Subject to regulatory requirements, Lactoferrin use would be associated with dairy-based special purpose type foods; these types of foods are typically marketed at a premium and selected by consumers because of the particular purpose, nutritional benefit or other specific function. Information about these foods and their ingredients would be available thus providing consumers with the appropriate information required for choice. No other issues have been identified concerning consumer choice for the proposed regulatory change.

This application is submitted on behalf of the largest processor of dairy food products and ingredients in Australia and New Zealand. No other dairy processing or food processing companies have been consulted concerning this application, however approval of this application would benefit all dairy food processing companies. Further evidence of support from the food industry would be anticipated during the “Public Notification/Call for Submissions” step during assessment.

1.5 Assessment Procedure:

Based on guidance in the current 'Application Handbook', our determination is that the appropriate procedure for assessment of this application would be:

General Procedure - Level 1

i.e. "require a toxicological, nutritional, food technology, dietary modelling or microbiological assessment of less than average complexity" ('Application Handbook' page 17, 2.2.5 (c))

1.6 Commercial Confidential Information (CCI):

SP Sepharose™ Big Beads were developed and are manufactured and marketed by GE Healthcare Bio-Sciences AB (Sweden). They have provided certain technical information (identified) about the processing aid, in support of this application which is included in Appendix B. This information is regarded by GE Healthcare Bio-Sciences AB as **Confidential Commercial Information** and is provided in the application strictly on this basis. This information is the result of a significant research and development effort and investment by the GE Healthcare Bio-Sciences; it is not in the public domain and is considered as either proprietary or commercially sensitive. Some of this information is provided to clients, however this is strictly subject to a legally binding 'non disclosure agreement'. It would be disadvantageous to GE Healthcare Bio-Sciences if this information were released into the public domain.

1.7 Exclusive Capturable Commercial Benefit (ECCB):

The approval of this application would not confer an Exclusive Capturable Commercial Benefit for the applicant.

The applicant, Fonterra Co-operative Group Limited, does not hold any patent, licence or other instrument or agreement that would prevent any other food manufacturer in Australia and New Zealand from use of this processing aid for the purpose discussed in this application or for any other food or beverage application. The approval of this application would therefore **not** provide an **Exclusive Capturable Commercial Benefit** for the applicant.

Sepharose SP™ Big Beads was developed and is manufactured and marketed by GE Healthcare Bio-Sciences AB, Sweden. It is available for purchase and use by any food manufacturer in Australia and New Zealand.

1.8 International and other National Standards:

a) International Standards:

SP Sepharose™ Big Beads is not included in any Codex Standard or covered by the Codex General Standard for Food Additives. It is not included in the Codex 'Inventory of substances used as Processing Aids', however it does conform to the definition of food processing aids as described in the 'Procedural Manual of the Codex Alimentarius Commission' and the 'Guidelines on Substances used as Processing Aids CAC/GL 75-2010' (refer appendix D).

b) Other National Standards and Regulations:

USA – **SP Sepharose™ Big Beads** has been approved as a food contact substance by the U.S. Food and Drug Administration (FDA), and this is confirmed in Food Contact Substance Notification FCN 000443, effective October 29 2004. It is approved for intended use as "an ion exchange resin" and "for repeated use in extracting individual proteins or substances present in similar low concentrations from liquid, water-based food materials, such as milk, whey, fruit juice, beer and wine." The process conditions include pH 3-14 and temperatures 5-60°C". This approval is effective only for the listed manufacturer and its customers.
(refer Appendix D)

N.B. The notifier/manufacturer was Amersham Biosciences which has since been acquired and incorporated into GE Healthcare Bio-Sciences AB.

EU - The EU regulation framework document for food contact materials is titled 'Regulation (EC) No 1935/2004 on materials and articles intended to come into contact with food'. It states that specific measures for listed groups of materials and articles may be adopted. One of the listed groups is ion-exchange resins but so far no specific guidance is in place.

GE Healthcare state to European customers that their product SP Sepharose™ Big Beads meets the requirements for food contact as given in Regulation (EC) No 1935/2004 in that:

- The product is manufactured according to the established Quality Management System Standard ISO 9001/2008.
- Studies of the chemical stability have been performed under stressed conditions to verify the inertness of the product.
- Traceability of the material from supply of raw materials through manufacturing and distribution to customer is established.
- Instructions to be observed for safe and appropriate use are supplied.

There is also a "LIST OF SUBSTANCES USED IN THE MANUFACTURE OF ION EXCHANGE AND ADSORBENT RESINS" (TECHNICAL DOCUMENT No. 1 Version 3 – 28.01.2009). The substances used by GE Healthcare for the manufacture of SP Sepharose™ Big Beads are included in the list although not all of them are yet processed within the system. (refer Appendix D)

GE Healthcare advise, that at this stage, there is no process in place whereby they can apply for a specific approval of SP Sepharose™ Big Beads in the EU.

1.9 Statutory Declaration:

STATUTORY DECLARATION

Statutory Declarations Act 1959

I, [redacted] (Regulator Affairs Consultant and Director – Bioresco Australia), [redacted], make the following declaration under the Statutory Declarations Act 1959:

1. the information provided in this application fully sets out the matters required
2. the information provided in this application is true to the best of my knowledge and belief
3. no information has been withheld that might prejudice this application, to the best of my knowledge and belief

I understand that a person who intentionally makes a false statement in a statutory declaration is guilty of an offence under section 11 of the Statutory Declarations Act 1959, and I believe that the statements in this declaration are true in every particular.

Signature:_____

Declared at_____ on_____ of_____

Before me,

Signature:_____

1.10 Checklist

General requirements (3.1)

☑ 3.1.1 Form of application
- ☑ *Application, abstracts and other key documents in English*
- ☑ *Executive Summary (separated from main application electronically and in hard copy)*
- ☑ *Relevant sections of Part 3 clearly identified*
- ☑ *Pages sequentially numbered*
- ☑ *Electronic copy (searchable)*
- ☑ *1 hard copy*
- ☑ *Electronic and hard copy identical*
- ☑ *Hard copy capable of being laid flat*
- ☑ *All references provided (in electronic and hard copy)*

☑ 3.1.2 Applicant details

☑ 3.1.3 Purpose of the application

☑ 3.1.4 Justification for the application
- ☑ *Regulatory impact information*
- ☑ *Impact on international trade*

☑ 3.1.5 Information to support the application
- ☑ *Data requirements*

☑ 3.1.6 Assessment procedure
- ☑ *General*
- ☐ *Major*
- ☐ *Minor*
- ☐ *High level health claim variation*

☑ 3.1.7 Confidential Commercial Information
- ☑ *Confidential material separated in both electronic and hard copy*
- ☑ *Formal request including reasons*
- ☑ *Non-confidential summary provided*

☑ 3.1.8 Exclusive Capturable Commercial Benefit
- ☐ *Justification provided*

☑ 3.1.9 International and other national standards
- ☑ *International standards*
- ☑ *Other national standards*

☑ 3.1.10 Statutory Declaration

☑ 3.1.11 Checklist/s provided with application
- ☑ *3.1 Checklist*
- ☐ *Any other relevant checklists for Parts 3.2-3.7*

Processing Aids (3.3.2)			
☑	A.1 Type of processing aid	☐	C.3. Allergenicity information of enzyme (enzyme only)
☑	A.2 Identification information	☑	C.4. Overseas safety Assessment Reports
☑	A.3 Chemical and physical properties	☐	D.1 Information on source organism (enzyme from microorganism only)
☑	A.4 Manufacturing process	☐	D.2 Pathogenicity and toxicity of source microorganism (enzyme from microorganism only)
☑	A.5 Specification information	☐	D.3 Genetic stability of source organism (enzyme from microorganism only)
☑	A.6 Analytical method for detection	☐	E.1 Nature of genetic modification of source organism (enzyme from GM source microorganism)
☑	B.1 Industrial use information (chemical only)	☑	F.1 List of foods likely to contain the processing aid
☑	B.2 Information on use in other countries (chemical only)	☑	F.2 Anticipated residue levels in foods
☑	B.3 Toxicokinetics and metabolism information (chemical only)	☑	F.3 Information on likely level of consumption
☑	B.4 Toxicity information (chemical only)	☑	F.4 Percentage of food group to use processing aid
☑	B.5 Safety assessments from international agencies (chemical only)	☑	F.5 Information on residues in foods in other countries (if available)
☐	C.1 Information on enzyme use on other countries (enzyme only)	☐	F.6 Where consumption has changed, information on likely consumption
☐	C.2 Toxicity information of enzyme (enzyme only)		

2 Technical Information:

2.1 Type of Processing Aid:

SP Sepharose™ Big Beads is an ion exchange resin with a very strong cation affinity. The large particle size (100-300 µm) and excellent physical stability of the base matrix ensure high flow rates, and maintained speed even with viscous samples. The unique flow characteristics are also invaluable when adsorption needs to be done quickly. These flow characteristics are invaluable when extracting target substances present at low concentrations. Thus it is an ideal processing aid for Lactoferrin extraction.

The production process for Lactoferrin extraction from whey or skim milk by cation exchange consists of the following steps:

1) Pre-treatment of whey or skim milk by filtration or centrifugation to remove suspended solids

2) Cation exchange – the pre-treated whey or skim milk is passed through the SP Sepharose™ Big Beads resin, which is contained within a fixed-bed ion exchange column. Lactoferrin that has bound to the resin is separated from other minor milk proteins that also bind to the resin by first passing a weak brine solution through the resin followed by a more concentrated brine solution to elute the purified Lactoferrin.

3) Ultrafiltration to concentrate and de-salt the Lactoferrin eluate

4) Filtration or heat treatment of the UF retentate to reduce microbial count

5) Freeze drying or spray drying to produce a finished product powder.

Detailed information on the Lactoferrin manufacturing process, application and efficacy of the Processing Aid are provided in Appendix A.

SP Sepharose™ Big Beads is similar, in respect to the matrix, to another Agarose ion exchange that is listed as a permitted processing aid in Standard 1.3.3 - Processing Aids as follows:

14 Permitted processing aids with miscellaneous functions

Table to clause 14

Substance	Function	Maximum permitted level (mg/kg)
Agarose ion exchange resin being agarose cross-linked and alkylated with epichlorohydrin and propylene oxide, then derivatised with tertiary amine groups whereby the amount of epichlorohydrin plus propylene oxide does not exceed 250% by weight of the starting quantity of agarose	Removal of specific proteins and polyphenols from beer	GMP

This ion exchange resin is also manufactured and marketed by GE Healthcare Bio-Sciences AB under the trade name Q Sepharose™ Big Beads

It would therefore be appropriate that the Processing Aid subject of this application, also be included in Standards 1.3.3 – Processing Aids, under Clause 14 - Permitted processing aids with miscellaneous functions. The proposed listing is provided in Section 1.2.

2.2 Identity:

Agarose, polymer with (chloromethyl)oxirane, 2-hydroxy-3(3-sulfopropoxy) propyl ethers, sodium salts

CAS: 676618-71-6

IUPAC: n/a

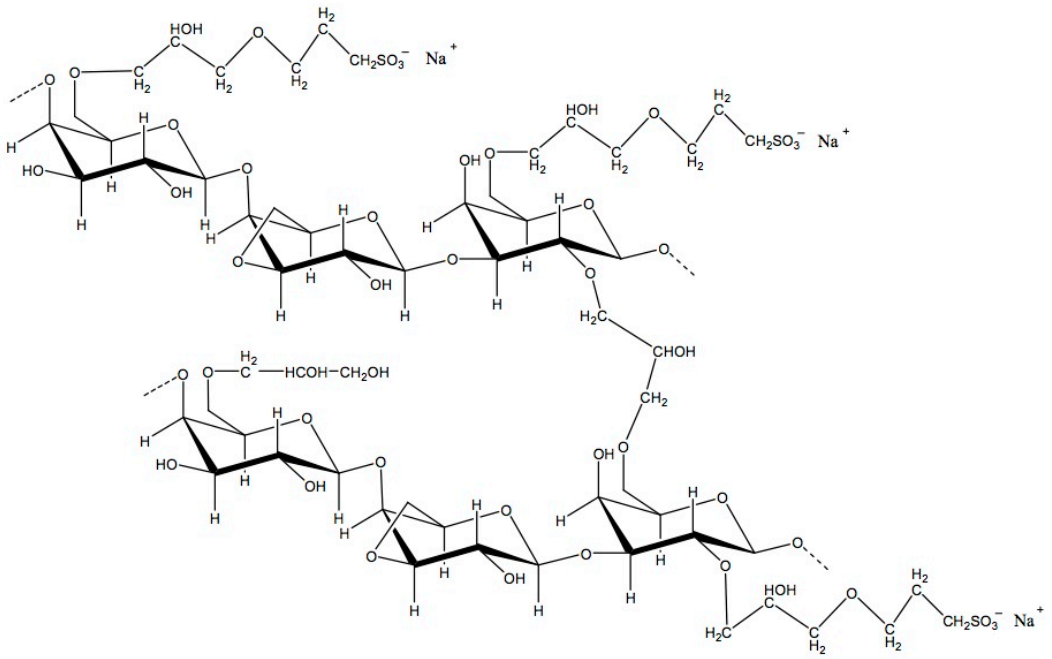
INS No.: n/a

Synonyms: Agarose ion exchange resin

Marketing name: SP Sepharose™ Big Beads Food Grade

Manufacturers Codes: 11-0008-29, 11-0008-30

Structural formula:



Structural representation of a fragment of SP Sepharose™ Big Beads.

Description: SP Sepharose™ Big Beads is a macroporous, strong cation exchanger with sulfonate groups coupled to the matrix (Sepharose™ Big Beads) which consists of agarose (6%) highly cross-linked with epichlorohydrin. SP Sepharose™ Big Beads are supplied as a suspension in 0.2M sodium acetate in 20% ethanol.

Physical state: liquid (and gel suspension)

Appearance: solution – colourless / gel suspension - white to yellowish

2.3 Chemical and physical properties:

SP Sepharose™ Big Beads is a macroporous, strong cation exchanger with sulfonate ion exchange groups coupled through chemically-stable ether bonds to the matrix of Sepharose™ Big Beads, which is a highly cross-linked agarose (6%) chromatography medium with large beads to give extremely high flow rates. The large particle size and excellent stability of the base matrix make it ideal for isolation of proteins such as Lactoferrin. The medium is supplied as a suspension in 0.2 M sodium acetate in 20% ethanol. The gel complies with U.S. FDA requirements for a Food Contact Substance.

Technical information on the chemical and physical properties of SP Sepharose™ Big Beads, and stability, demonstrating suitability for the intended purpose as an ion exchange resin for the extraction of Lactoferrin, is provided in Appendices A and B.

2.4 Manufacturing process:

The manufacture of SP Sepharose™ Big Beads involves firstly dispersing an aqueous solution of agarose in toluene to give droplets of 100 – 300μm in diameter. The gel in cross-linked with epichlorohydrin. The product is wet-sieved then reacted with allyl glycidyl ether to form the intermediate, allyl sepharose. The final step involves reacting allyl sepharose with sodium disulphite. After each manufacturing step, the product is washed repeatedly with an appropriate solution. Further information on the manufacturing process is included in Appendices A and B.

2.5 Specification for identity and purity:

The specification for SP Sepharose™ Big Beads is provided in Appendix A. Information is also provided on potential impurities and levels in Appendix B.

There are no references in the monographs specified in Standard 1.3.4 – Identity and Purity (Clauses 2, 3) for SP Sepharose™ Big Beads. A specification would therefore need to be included in the *Schedule* to the Standard and is proposed as follows:

Standard 1.3.4 – Identity and Purity
Schedule

Specification for agarose ion exchange resin

(a) This specification relates to agarose, cross-linked with epichlorohydrin and alkylated, then derivatised with sulfonate groups whereby the amount of epichlorohydrin plus propylene oxide does not exceed 250% by weight of the starting quantity of agarose

(b) For repeated use in extracting individual proteins or substances present in similar low concentrations from liquid, water-based food materials, such as milk or whey. The process conditions include pH 3-14 and temperatures 5-60°C. pH and temperature restrictions do not apply to cleaning processes

(c) When subjected to the extraction regime listed in the 21 CFR § 173.25(c)(4), but using dilute hydrochloric acid at pH 2 in place of 5% acetic acid, the ion exchange resins shall result in no more than 25 ppm of organic extractives

2.6 Analytical method:

Analytical methods developed or adopted by GE Healthcare Bio-Sciences for determination of SP Sepharose™ Big Beads and any potential impurities in the finished food product/ingredient are provided in Appendix B.

3 Safety:

SP Sepharose™ Big Beads consists of a matrix composed of agarose highly cross-linked with epichlorohydrin, with sulphonate groups coupled to this matrix. Agarose is a polysaccharide and the principal component of agar (70%, the remainder being mainly agaropectin), an approved food additive. Agarose is obtained from agar by extraction.

A comprehensive safety evaluation has been undertaken for SP Sepharose™ Big Beads and any potential manufacturing impurities, for its intended application, and this report is provided in Appendices B and C. The overall conclusions from this evaluation were that any impurities are present at very low concentrations and with sufficient safety margins that there should be no concern with respect to human health with use of this processing aid.

An ion exchange resin with the same matrix composition, "Agarose ion exchange resin being agarose cross-linked and alkylated with epichlorohydrin and propylene oxide, then derivatised with tertiary amine groups", was assessed and approved by FSANZ (Application A600 – Agarose Ion Exchange Resin as a Processing Aid for Beer) and is listed in Standard 1.3.3 as a permitted processing aid.

3.1 Industrial Use:

There are no industrial uses for SP Sepharose™ Big Beads Food Grade. This ion exchange resin was developed specifically for use in food contact applications for the separation of proteins or other compounds present in similar concentrations from liquid foods such as milk, whey, fruit juices, beer and wine.

GE Healthcare have a variant of the ion exchange resin (SP Sepharose™ Big Beads 17-0657) which is used by the pharmaceutical industry, for example in the production of insulin.

3.2 Food Processing Aid use in other countries:

SP Sepharose™ Big Beads Food Grade is currently being used in dairy applications in France, Germany and USA.

3.3 Toxicokinetics and metabolism:

Information on toxicokinetics and metabolism is provided in Appendix C.

3.4 Toxicity:

Information on toxicity is provided in appendix C.

3.5 Safety Assessment Reports - international/government agencies:

1) A safety evaluation of the Processing Aid was submitted to the U.S. Food and Drug Administration for approval as a Food Contact Substance. Approval of the processing aid for this purpose has been confirmed in the Inventory of Effective Food Contact Substances (FCS) Notifications FCN No. 443. (refer Appendix D)

2) A GRAS notification for "Cow's Milk derived Lactoferrin as a Component of Cow's Milk-Based Infant Formulas, Cow's Milk Products, and Chewing Gum" on behalf of

Morinaga Milk Industry Co., Ltd (Japan) was submitted to the U.S. Food and Drug Administration (FDA) in 2012. The manufacturing process for the Lactoferrin subject of this notification, utilized cation-exhange chromatography with SP Sepharose™ Big Beads identified as a suitable food-grade resin for this purpose. FDA advised “no further questions” and the corresponding GRAS Notices were published 18 February, 2014 (GRN Nos. 464, 465).

3) At this stage no safety assessments have been or are being conducted by any other international or government agencies.

4 References:

1) Lourdes Sanchez, Miguel Calvo, Jeremy H Brock. 1992. Biological role of lactoferrin. *Archives of disease in childhood 1992; 67: 657-661*

2) L. Adlerova, A. Bartoskova, M. Faldyna. 2008. Lactoferrin: a review. *Veterinarni Medicina, 53, 2008 (9): 457–468*

3) Isui Abril García-Montoya, Tania Siqueiros Cendón, Sigifredo Arévalo-Gallegos, Quintín Rascón-Cruz. 2012. Lactoferrin a multiple bioactive protein: An overview. *Biochimica et Biophysica Acta 1820 (2012) 226–236*

4) Hiroyuki Wakabayashi*, Koji Yamauchi, Mitsunori Takase. 2006. Review: Lactoferrin research, technology and applications. *International Dairy Journal 16 (2006) 1241–1251*

5) Zaid S. Saleh*, Md. M. Hossain. 2001. A study of the separation of proteins from multicomponent mixtures by a semi-batch foaming process. *Chemical Engineering and Processing 40 (2001) 371–37*