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[63-18]

Approval report – Application A1157

Enzymatic production of Rebaudioside M

Food Standards Australia New Zealand (FSANZ) has assessed an application made by Blue California to seek approval for a new specification for rebaudioside M produced by an enzymatic conversion method.

On 20 July, FSANZ sought submissions on a draft variation and published an associated report. FSANZ received ten submissions.

FSANZ approved the draft variation on 31 October 2018. The Australia and New Zealand Ministerial Forum on Food Regulation was notified of FSANZ's decision on 12 November 2018.

This report is provided pursuant to paragraph 33(1)(b) of the *Food Standards Australia New Zealand Act 1991*.

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Supporting document

The [following document](#) which informed the assessment of this application is available on the FSANZ website:

SD1 Risk and technical assessment report

Executive summary

Blue California applied to amend the Australia New Zealand Food Standards Code (the Code) for a Rebaudioside M (Reb M) produced using enzymes sourced from genetically modified strains of *Pichia pastoris*.

Reb M is a type of steviol glycoside, which are used as intense sweeteners. The Code permits the use of Reb M and other steviol glycosides as food additives in various food classes subject to prescribed limits. There are also identity and purity specifications for steviol glycosides, which do not currently cover Blue California's production method.

The application sought an amendment to Schedule 3 of the Code to include a reference to a new production method.

FSANZ's risk assessment of Blue California's Reb M and the enzymes used to manufacture it, confirmed that neither posed a public health and safety concern. The risk assessment also determined that the use of the enzymes to manufacture Reb M, in the way proposed, was technologically justified. As the enzymes are considered processing aids in the manufacture of the Reb M (a food additive), explicit permission in the Code is required. This will provide necessary permission for the enzymes' potential presence in the Reb M as a food produced using gene technology.

Although the enzymes are produced using gene technology, this does not itself make the Reb M produced by these enzymes a genetically modified food. FSANZ's determination is that Blue California's Reb M is not a genetically modified food as it is not derived from an organism that has been modified using gene technology.

FSANZ has therefore prepared a draft variation to amend Schedule 3 to include a reference to the production method for Blue California's Reb M in the specifications for Reb M. The draft variation will also amend Schedule 18 to permit the use of the enzymes as processing aids to manufacture Reb M, ensuring compliance with the Code. The draft variation was approved with an amendment to clarify the nomenclature of the production enzymes.

1 Introduction

1.1 The applicant

The applicant is Blue California, a manufacturer of natural ingredients used in food products, beverages, flavours and fragrances, dietary supplements, personal care and cosmetics. They are based in Rancho Santa Margarita, California.

1.2 The application

The application sought to change the Code to permit an alternative production method for the food additive, rebaudioside M (Reb M), a specific steviol glycoside. Steviol glycosides are traditionally produced using hot water extraction of the *Stevia rebaudiana* Bertoni leaf, followed by purification and recrystallisation using methanol or ethanol. Blue California instead, uses enzymes to manufacture Reb M. This process facilitates the transfer of glucose to purified stevia leaf extract via glycosidic bonds. The enzymes used are sourced from genetically modified (GM) strains of *P. pastoris*, a species of yeast widely used for protein production using recombinant DNA techniques.

The Code currently permits the use of steviol glycosides as food additives with the INS number 960. They are permitted in a wide range of food classes listed in the table to section S15—5 at maximum permitted levels (MPLs) and at Good Manufacturing Practice (GMP) for tabletop sweeteners only.

However, the current specifications for identity and purity did not allow for Blue California's production method. Blue California did not ask to change the purity specification or propose an extension for the use of Reb M in additional food products. Nor did it propose to increase the permitted quantities of Reb M in permitted food products.

Current permissions for steviol glycosides in the Code and international permissions for Blue California's Reb M are provided below.

1.3 The current Standard

Australian and New Zealand food laws require food for sale to comply with the following requirements of the Code.

1.3.1 Permitted use

Subsection 1.1.1—10(6) of the Code provides that, unless expressly permitted by the Code, a food for sale cannot contain, as an ingredient or component: a substance 'used as a food additive'; a substance that was 'used as a processing aid'; or a food produced using gene technology'.

1.3.2 Food additives

Section 1.3.1—3 of the Code details which substances are permitted to be used as a food additive for the purposes of the Code. The permitted food additives for different food categories are listed in the table to section S15—5 of the Code.

Section 1.1.2—11 also provides that a substance is 'used as a food additive' if it is added to a food to perform one or more technological functions listed in schedule 14 of the Code and is one of a number of substances listed in that section. These include a substance identified in the table to section S15—5 as permitted food additive.

Schedule 14 lists the permitted technological purposes of food additives. The table in section S14—2 of that schedule provides that use as an intense sweetener is a permitted purpose.

Schedules 15 and 16 list the specific food additive permissions for different categories of food products.

1.3.3 Processing aids

Paragraph 1.1.1—10(6)(c) provides that a food for sale must not have, as an ingredient or a component, a substance that is used as a processing aid, unless expressly permitted.

Standard 1.3.3 and Schedule 18 list the permitted processing aids. The table to subsection S18—9(3) lists those substances, including enzymes, that are permitted to be used as processing aids for specific technological purposes.

Section 1.1.2—13 defines the expression ‘used as a processing aid.’ That definition imposes requirements on substances permitted by Standard 1.3.3 and Schedule 18 to be used as a processing aid, such that it does not perform a technological purpose in the final food for sale.

Enzymes used in food manufacturing and/or processing are considered processing aids as although they may be present in the final food, they no longer provide a technological purpose in the final food.

1.3.4 Labelling

Paragraph 1.1.1—10(8) of the Code provides that food for sale must comply with all relevant labelling requirements imposed by the Code for that food.

Standard 1.2.4 of the Code generally requires food products to be labelled with a statement of ingredients. Subsection 1.2.4—7(1) of that Standard requires food additives to be declared in the statement of ingredients.

Schedule 8 (for statement of ingredients) lists the names and code numbers of food additives that are to be used for labelling purposes. Schedule 8 refers to steviol glycosides (INS code number 960) which is currently permitted to be added to food as a food additive.

Processing aids are generally exempt from the requirement to be declared in the statement of ingredients. See paragraphs 1.2.4—3(2)(d) and (e) in Standard 1.2.4.

Section 1.5.2—4 of Standard 1.5.2 outlines requirements for labelling of certain foods for sale that consist of or have as an ingredient, food that is a genetically modified food. A *genetically modified food* is defined in subsection 1.5.2—4(5) as a *food produced using gene technology* that contains novel DNA or novel protein or is listed in section S26—3.

1.3.5 Identity and purity requirements

Paragraph 1.1.1—15(1)(a) of the Code requires substances used as food additives to comply with any relevant identity and purity specifications listed in Schedule 3 of the Code.

Sections S3—31 and S3—32 of Schedule 3 provide specifications for Reb M and for steviol glycoside mixtures containing Reb M. These refer to primary source specifications for steviol glycosides contained within section S3—2, being either S3—2(1)(b) [the FAO JECFA Monograph], S3-2(1)(c) [the Food Chemicals Codex] or S3—2(1)(d) [European Commission Regulation No 231/2012 (EU, 2012) laying down specifications for food additives]. Specifications for steviol glycosides from these primary sources, including Reb M, include a method of production where the substance is extracted from the leaves of stevia (*S. rebaudiana* Bertoni).

Section S3—35 of Schedule 3 provides a specification for steviol glycosides prepared from the leaves of stevia (*S. rebaudiana* Bertoni), including Reb M. The specification permits only

one method of production, namely extraction using the traditional hot water extraction method. The Blue California Reb M does not comply with this specification due to its different method of production.

1.3.6 International permissions

Steviol glycosides are approved for use in a number of other jurisdictions, including the European Union, Canada, Asia, Central/South America, and Africa (Global Stevia Institute, 2017). In the European Union, commercially available steviol glycoside products must comply with the specifications for steviol glycosides (INS number 960) adopted by the European Commission in 2012 and recently updated in 2016 (EU, 2012, 2016).

1.3.6.1 JECFA

JECFA re-evaluated the safety, dietary intake, and specifications for steviol glycosides at its 82nd meeting in 2016. The safety of steviol glycosides as well as the acceptable daily intake (ADI) of 0 to 4 mg/kg body weight, expressed as steviol, were confirmed. Details of a new manufacturing process for rebaudioside A utilising a strain of *Yarrowia lipolytica* that was genetically modified to overexpress the steviol glycoside biosynthetic pathway were submitted to and reviewed by the Committee. As a result, the Committee issued a new specification monograph for “Rebaudioside A from Multiple Gene Donors Expressed in *Yarrowia lipolytica*” (JECFA, 2016a). The Committee also reviewed data demonstrating the shared metabolism of all steviol glycosides and issued new ‘tentative’ specifications for “Steviol Glycosides from *Stevia rebaudiana* Bertoni” (JECFA, 2016b). These new specifications expanding the definition of steviol glycosides to “a mixture of compounds containing a steviol backbone conjugated to any number or combination of the principal sugar moieties in any of the orientations occurring in the leaves of *Stevia rebaudiana* Bertoni including, glucose, rhamnose, xylose, fructose, and deoxyglucose”. The purity of steviol glycosides from *S. rebaudiana* Bertoni must be no less than 95% total steviol glycosides on the dried basis.

1.3.6.2 USA

A GRAS notification (GRN No. 667) was submitted by Blue California for Reb M produced via enzymatic conversion of purified stevia leaf extract, which is the same product that is the subject of this application. The U.S. FDA responded with no questions to the GRAS status of Blue California’s Reb M produced via conversion for use as a table top sweetener and as a general purpose non-nutritive sweetener in foods.

1.3.6.3 Canada

Health Canada has no objections to the use of Blue California’s high-purity Reb M manufactured using genetically modified yeast, provided that the product is used in accordance with the permitted uses of steviol glycosides as set out in Item S.1.2 of the List of Permitted Sweeteners, is free of yeast cells, and is of food-grade quality.

1.4 Reasons for accepting application

The application was accepted for assessment because:

- it complied with the procedural requirements under subsection 22(2) of the FSANZ Act; and
- it related to a matter that warranted the variation of a food regulatory measure.

1.5 Procedure for assessment

The application was assessed under the General Procedure.

1.6 Decision

The draft variations as proposed following assessment were approved with amendment after the consideration of submissions. The amendment was made to a minor error in the nomenclature used in the drafting for the production enzymes.

The approved draft variations are at Attachment A. The approved variations take effect on gazettal.

The related explanatory statement is at Attachment B. An explanatory statement is required to accompany an instrument if it is lodged on the Federal Register of Legislation.

The draft variations on which submissions were sought are at Attachment C.

2 Summary of the findings

2.1 Summary of issues raised in submissions

FSANZ called for submissions on proposed draft variations to Schedules 3 and 18 on 20 July 2018. Ten submissions were received. The Victorian Department of Health and Human Services and Victorian Department of Economic Development, Jobs, Transport and Resources, PepsiCo Australia & New Zealand, the Australian Beverages Council Ltd, the New Zealand Beverage Council, the Australian Food and Grocery Council, the New Zealand Food & Grocery Council, the Calorie Control Council USA and the International Stevia Council supported the application. The New Zealand Ministry for Primary Industries (NZMPI) supported the application and provided comments for FSANZ to consider. Tate & Lyle asked for permission to be granted in the Code for their Reb M produced via a similar manufacturing process. The comments provided by the NZMPI and Tate & Lyle and FSANZ's responses are detailed in Table 1.

Table 1: Summary of issues

Issue	Raised by	FSANZ response
<p>Labelling comments, including International Numbering System (INS) number.</p> <p>The Codex Committee on Food Additives (CCFA) in March 2018 changed the specifications and INS numbering for steviol glycosides to distinguish between steviol glycosides extracted or produced using different methods or technologies. This is so consumers can be more fully informed.</p> <p>These changes are not reflected in the Code or in drafting for this application.</p> <p>The Approval Report should explain that the Code will need to be amended to align with the CCFA changes.</p>	NZMPI	<p>Noted.</p> <p>FSANZ monitors CCFA revisions and is aware of the revision of the INS numbering system for steviol glycosides.</p> <p>Updating the INS numbers in the Code for all steviol glycosides is outside the scope of Application A1157 which relates to a single steviol glycoside.</p> <p>FSANZ will consider amending the INS numbers in the Code in the future.</p>
<p>Draft variation in Attachment A to the Call for Submissions paper.</p> <p>Agree that Schedule 3 should be amended to allow for the novel production method for Reb M.</p> <p>Codex Alimentarius Commission has adopted</p>	NZMPI	<p>Noted.</p> <p>The draft variation approved by FSANZ for Proposal P1048 at FSANZ75 will update Schedule 3 to include a reference to JECFA</p>

Issue	Raised by	FSANZ response
<p>the JECFA specification for “Steviol glycosides from <i>S. rebaudiana</i> Bertoni”. The JECFA specification now includes any mixture of steviol glycoside compounds derived from <i>S. rebaudiana</i> Bertoni, rather than being limited to nine named leaf-derived steviol glycosides. The new specification is listed in the latest publication of the JECFA monographs (i.e. monograph number 20)</p> <p>The new JECFA specification means that section S3—35 is no longer required. This in turn will affect how amendments required for Application A1157 are drafted. Any impact on existing subsections S3—31 and S3—32 may also need to be considered.</p> <p>Schedule 3 in the Code must be updated to the latest publication of the JECFA monographs (i.e. monograph number 20) before the above changes can be considered.</p> <p>If the drafting is as in Attachment A, the title of the subsection S3—35 may need revising, as it will include information specifically for high purity Reb M, as well as for “Steviol glycosides from <i>S. rebaudiana</i> Bertoni”.</p>		<p>monograph 20. That draft variation has yet to be considered by the Forum.</p> <p>Once that measure has been considered by the Forum and gazetted, FSANZ can consider any required consequential changes to Schedule 3 in relation to steviol glycosides. Making a consequential change post this application would also allow stakeholder consultation, as required by the FSANZ Act, before any change is made.</p>
<p><i>Comment on the steviol glycoside permissions in the Code.</i></p> <p>How additional specifications for steviol glycosides are currently listed in Schedule 3 is not easy for Code users to understand, unless you refer back to the applications that led to the new subsections in Schedule 3. As editorial notes are no longer included in the Code, there is no obvious place to explain how the provisions apply.</p> <p>FSANZ could provide additional information in Approval Reports to explain how the provisions apply, and which application generated the sections in Schedule 3. Alternatively, this information could be published in FSANZ website or be placed in the relevant Schedules of the Code.</p>	NZMPI	<p>Noted.</p> <p>This issue has not been raised by stakeholders to date.</p> <p>If FSANZ received significant or regular feedback of a lack of clarity in the Code, additional guidance could be placed in the Amendment History for Schedule 3 that is published with that Schedule.</p> <p>The Amendment History provides information about each amendment to the Schedule and is published online with each Standard – see the official version of the Standards as published on www.legislation.gov.au</p> <p>This negates the need for editorial notes in Schedule 3 or online guidance on the FSANZ website.</p>
<p><i>Request for permission for Reb M from a similar production process.</i></p> <p>Tate & Lyle has developed a similar enzymatic conversion method to the one being assessed in this application. Tate & Lyle’s Reb M is also produced by the enzymatic conversion of steviol glycosides using two glucosyltransferases and a sucrose synthase, however these are derived from a genetically</p>	Tate & Lyle	<p>Not agreed</p> <p>FSANZ’s statutory objectives in standard development include the protection of public health and safety. To ensure that this objective is met, the Code requires pre-market assessment of any food additive prior to its permission for sale, as was</p>

Issue	Raised by	FSANZ response
<p>modified <i>Escherichia coli</i> K-12 strain. Included in their submission to FSANZ was a copy of the GRAS Notification (GRAS 780, submitted April 27, 2018) and a link to the FDA response. Tate & Lyle requests that Reb M, made by their novel production method be included as a permitted sweetener with the same prescribed limits and conditions of use as that from Blue California.</p>		<p>carried out on Blue California's Reb M. Although the method of manufacture and the specification of the Tate & Lyle Reb M is similar to Blue California's and therefore the JECFA specification, the source organism differs. Furthermore, the FSANZ assessment differs from the GRAS self-notification approval.</p> <p>To provide permission for the Tate & Lyle Reb M, a pre-market assessment would need to be carried out by FSANZ to assess any public health and safety risks associated with the source organism. This would include assessing whether there was a history of safe use, safety of the novel proteins, toxicological data, allergenicity and assessments by other regulatory agencies.</p>

2.2 Risk assessment

FSANZ has assessed the public health and safety risks associated with the proposed use of Blue California Reb M for use as a food additive (see SD1).

FSANZ concluded that Blue California's Reb M is chemically the same as Reb M extracted directly from *S. rebaudiana* Bertoni and as with all steviol glycosides, is metabolised by humans in the same way. Supplementary studies have been published since the last assessment of steviol glycosides by FSANZ, but these provided no basis to amend the existing Acceptable Daily Intake (ADI) of 0–4 mg/kg bodyweight (bw)/day, expressed as steviol. This ADI is appropriate to cover dietary exposure for all steviol glycosides.

Blue California's Reb M complies with purity specifications of JECFA (JECFA 2016b) and the purity specifications listed in S3—35(4). No major allergens are used to culture the yeast or at any other stage of the production process. The source organism, *P. pastoris* has a long history of industrial use for recombinant gene expression and is not toxigenic. There is no potential homology between the novel fusion enzymes and any known allergens.

Data provided by the applicant showed that two yeast production strains have been generated that express three polypeptides, each one being a fusion protein containing a glycosyltransferase and sucrose synthase. Molecular characterisation of the production strains have identified the site of integration for the introduced DNA, confirmed the sequence is as expected, has not undergone any rearrangement and that the introduced DNA is stably inherited. The production strains have also been shown to be genetically stable.

FSANZ also undertook a safety assessment of the enzymes used to convert the steviol glycosides into the Reb M. This assessment was undertaken because using the enzymes in the way proposed by the applicant would constitute 'use as a processing aid' in the Code.

2.3 Risk management

FSANZ concluded that there are no public health and safety concerns and considered it appropriate to amend Schedule 3 of the Code. This will permit the use of Blue California's Reb M as food additive in foods where Reb M is already permitted and at the same levels of addition.

FSANZ considered it necessary, in order to provide regulatory certainty, that an amendment to Schedule 18 was also required. Since it is possible, but very unlikely, that Blue California's Reb M may contain miniscule traces of the enzymes that were used in its manufacture, as processing aids, the enzymes must have permission in the Code. The Code provides that, unless expressly permitted by the Code, a food for sale must not contain, as an ingredient or a component, a substance that was used as a processing aid.

The use of the enzymes in the way proposed by the applicant would constitute 'use as a processing aid' in the manufacture of the Reb M as a food additive. As mentioned above, the proposed purpose of the specific enzymes had been assessed to comply with the requirements of "used as a processing aid" in section 1.1.2—13 since they perform a specific technological purpose during the production of Blue California's Reb M and do not perform a technological purpose in the food for sale (i.e. in the food additive Reb M).

As a result, paragraph 1.1.1—10(6)(c) of the Code would require that any residual traces of the enzymes present in the Reb M would need to be expressly permitted by the Code.

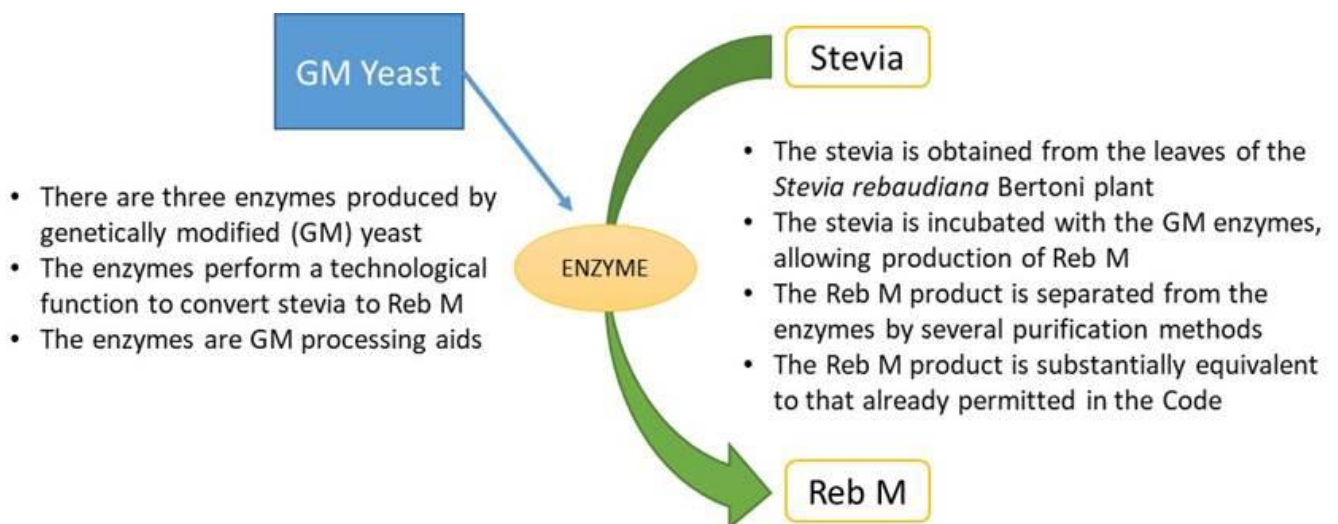
For these reasons, and to provide regulatory certainty, the approved draft variation amends Schedule 18 of the Code to provide an express permission for the enzymes' use as processing aids in the production of Reb M. The approved draft variation will list the specific

enzymes as processing aids in subsection S18—9(3) for the specific technological purpose of converting purified stevia leaf extract to produce Reb M.

The express permission for the enzymes' use as processing aids will also provide the permission for the enzyme's potential presence in the Blue California Reb M as a food produced using gene technology. The enzymes are a food produced using gene technology for Code purposes as they are derived from 'an organism that has been modified using gene technology' (i.e. genetically modified yeast). Paragraph 1.1.1—10(6)(g) requires that the presence as an ingredient or component in a food for sale of a food produced using gene technology must be expressly permitted by the Code. Section 1.5.2—3 of Standard 1.5.2 provides that permission for use as a processing aid also constitutes the permission required by paragraph 1.1.1—10(6)(g).

FSANZ's assessment is that the enzymes' use as processing aids to manufacture Reb M does not itself, make the Reb M a genetically modified food. As the Reb M itself is not derived from an organism that has been modified using gene technology, FSANZ's determination is that Blue California's Reb M is not itself a food produced using gene technology (see Figure 1.)

Figure 1 Conversion of stevia into Reb M via the enzymatic conversion pathway.



2.3.1 Labelling considerations

Blue California's Reb M is a food additive. Steviol glycosides, including Reb M, are already permitted for use as food additives in the Code.

As a proposed change to the Code is to the specification for Reb M rather than approval of the food additive itself, the labelling requirements relating to steviol glycosides will remain the same. This includes the requirement in Standard 1.2.4 to declare food additives in the statement of ingredients.

FSANZ's assessment is that Blue California's Reb M is not a food produced using gene technology as it is not derived from an organism that has been modified using gene technology, in contrast to the enzyme processing aids used for its manufacture. As such, when Blue California's Reb M is contained in a food for sale as an ingredient, it does not require labelling as 'genetically modified'. Section 1.5.2—4 requires certain foods for sale that consist of or have as an ingredient, food that is a genetically modified to be labelled as 'genetically modified'. The Code's labelling requirements, including those imposed by section 1.5.2—4, generally apply only to foods for retail sale and to foods sold to a caterer under subsection 1.2.1—8(1) and section 1.2.1—15 respectively. It is understood that Blue

California's Reb M itself would not be sold for retail sale or to a caterer because it is a highly concentrated intense sweetener.

In terms of the enzymes used as processing aids to manufacture Blue California's Reb M, the Code exempts processing aids from the requirement to be declared in the statement of ingredients.

The enzymes used as processing aids to manufacture Blue California's Reb M are highly unlikely to be present as an ingredient in a food for sale which contains Reb M. As such, the requirement to label the processing aids as 'genetically modified' would not apply to that food for sale because the labelling requirements only apply to food that consists of, or has as an ingredient, a genetically modified food under section 1.5.2—4(1).

2.3.2 World Trade Organization

As members of the World Trade Organization (WTO), Australia and New Zealand are obliged to notify WTO members where proposed mandatory regulatory measures are inconsistent with any existing or imminent international standards and the proposed measure may have a significant effect on trade.

There are relevant international standards for Reb M (section 1.3.5 above). Amending the Code to permit Reb M produced by an enzymatic conversion method is unlikely to have a significant effect on international trade as the specification is identical to currently permitted Reb M's which use the traditional hot water extraction method. Therefore, a notification to the WTO under Australia's and New Zealand's obligations under the WTO Technical Barriers to Trade or application of Sanitary and Phytosanitary Measures Agreement was not considered necessary.

2.3.3 Consultation

Consultation is a key part of FSANZ's standards development process. FSANZ developed and applied a basic communication strategy to this application. All calls for submissions are notified via the Food Standards Notification Circular, media release, FSANZ's social media tools and Food Standards News.

The process by which FSANZ considers standard development matters is open, accountable, consultative and transparent. Public submissions are called to obtain the views of interested parties on issues raised by the application and the impacts of regulatory options. FSANZ acknowledges the time taken by individuals and organisations to make submissions on this application.

2.4 Risk management conclusion

The risk management conclusion is to permit the use as a food additive of Blue California's Reb M, manufactured using a novel enzymatic production method. FSANZ's decision was based on the risk assessment, risk management and the FSANZ Act considerations, including the cost benefit considerations (see section 2.5 below).

To provide permission for Blue California's Reb M, section S3—35 of Schedule 3 of the Code will be amended and will refer to the specific manufacturing method of enzymatic conversion using protein engineered enzymes.

The permitted technological purpose of Blue California's Reb M, when used as a food additive is that of an intense sweetener. It will be permitted under Schedule 15, at the current MPLs and specified food classes and at GMP levels for tabletop sweeteners for steviol glycosides. It will similarly utilise the current INS number 960.

The enzymes used to produce Reb M will be listed as enzymatic processing aids in subsection S18—(9)(3). Permission for these enzyme processing aids will be limited to the specific purpose of producing Reb M from purified stevia leaf extract.

The approved draft variation differs from the draft variation that was the subject of the Call for Submissions. The latter described the enzymes as being “sourced from *Pichia pastoris* strain UGT-A, UGT-B1 or UGT-B2”. Blue California advised that FSANZ that the latter are the “in-house” names of their enzymes. The approved draft variation corrected this and describes the enzymes as being “sourced from a *Pichia pastoris* strain expressing UGT-A and a *Pichia pastoris* strain expressing UGT-B1 and UGT-B2”.

2.5 FSANZ Act assessment requirements

2.5.1 Section 29

2.5.1.1 Consideration of costs and benefits

The Office of Best Practice Regulation (OBPR) granted FSANZ a standing exemption from the requirement to develop a Regulatory Impact Statement for the approval of additional processing aids (OBPR correspondence dated 24 November 2010, reference 12065). This standing exemption was provided as permitting additional processing aids is a minor, deregulatory change and their use is voluntary. This standing exemption relates to the introduction of a food to the food supply that has been determined to be safe.

FSANZ, however, has given consideration to the costs and benefits that may arise from the proposed measure for the purposes of meeting FSANZ Act considerations. The FSANZ Act requires FSANZ to have regard to whether costs that would arise from the proposed measure outweigh the direct and indirect benefits to the community, government or industry that would arise from the proposed measure (S.29 (2)(a)).

The purpose of this consideration is to determine if the community, government, and industry as a whole is likely to benefit, on balance, from a move from the status quo. This analysis considers to either approve or reject the application (retain the status quo). A consideration of costs and benefits was included in the call for submissions (CFS) report based on the information and data held at that time. No further information has been received during the consultation process to date that influenced the findings from the analysis of costs and benefits in the CFS.

The consideration of the costs and benefits in this section is not intended to be an exhaustive, quantitative economic analysis of the proposed measures and, in fact, most of the effects that were considered cannot easily be assigned a dollar value. Rather, the assessment seeks to highlight the likely positives and negatives of moving away from the status quo by permitting the use of Reb M produced by an enzymatic conversion method as a food additive in certain foods.

Costs and benefits of permitting the use of Reb M produced by an enzymatic conversion method as a food additive in certain foods.

The use of Blue California’s Reb M as a food additive in the manner proposed will not pose a health or safety risk for consumers. The benefits to the consumer would mirror those for other steviol glycosides currently permitted for use in Australia and New Zealand. Blue California’s Reb M, like other steviol glycosides, would be used in foods and beverages to replace sugar, which will benefit consumers seeking products that have reduced sugar and/or energy content.

Consumers may also benefit from the choice of additional food products which have more

favourable sensory characteristics, compared to those using other major glycosides (i.e., stevioside, rebaudioside A). They will also be able to access products manufactured with this particular Reb M, which are currently manufactured overseas.

The development of the new technology to produce a glycoside with preferential sensory characteristics for product development can provide a benefit in terms of product and/or competitive advantage to food manufacturers.

In the U.S., Blue California's Reb M produced via enzymatic conversion of purified stevia leaf extract has GRAS status for use as a table top sweetener and a general purpose non-nutritive sweetener in foods. Permission to use Blue California's Reb M as a food additive, will enable Australia/New Zealand food manufacturers to access and use a product assessed as safe that is available to their overseas competitors. This will improve their capacity to compete in overseas markets. Use by industry is voluntary, therefore it will only be used where industry believe a net benefit exists above using existing intense sweeteners.

Since Blue California does not intend to propose an extension for the use of Reb M in additional food products nor does it wish to propose to increase the permitted quantities of Reb M in permitted food products, there is no perceived benefit or added cost to governments, with regards to the Reb M itself.

However, the approval of the enzymes as processing aids may result in a small cost to government in terms of adding the enzyme to the current range of enzymes that are monitored for compliance.

2.5.1.2 Other measures

FSANZ considers that there are no other measures (whether available to FSANZ or not) that would be more cost-effective than a food regulatory measure developed as a result of this application.

2.5.1.3 Any relevant New Zealand standards

The Standards and Schedules relevant to the draft variation apply in both Australia and New Zealand. There are no relevant New Zealand only Standards.

2.5.1.4 Any other relevant matters

Other relevant matters are considered below.

2.5.2 Subsection 18(1)

FSANZ has also considered the three objectives in subsection 18(1) of the FSANZ Act during the assessment.

2.5.2.1 Protection of public health and safety

FSANZ concluded that there are no safety concerns associated with Blue California's Reb M produced using enzymes from genetically modified *P. pastoris*. For more detail, see SD1.

2.5.2.2 The provision of adequate information relating to food to enable consumers to make informed choices

The generic labelling requirements will apply to the use of *Reb M* in food (see Section 2.3.1 above).

2.5.2.3 The prevention of misleading or deceptive conduct

No issues have been identified with this application relevant to this objective.

2.5.3 Subsection 18(2) considerations

FSANZ has also had regard to:

- **the need for standards to be based on risk analysis using the best available scientific evidence**

FSANZ used the best available scientific evidence to conduct the risk assessment which is provided in SD1. The applicant submitted a dossier of scientific studies as part of its application. Other technical information including scientific literature was also identified and used by FSANZ in assessing the application.

- **the promotion of consistency between domestic and international food standards**

The Blue California Reb M specifications are identical to those established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2006) and the Food Chemicals Codex (Food Chemicals Codex, 2015).

Blue California's Reb M is permitted for use in the USA and Canada.

- **the desirability of an efficient and internationally competitive food industry**

Permission to use this particular Reb M as a food additive will enable Australian and New Zealand food manufacturers to access and use a product assessed as safe that is available to some overseas competitors. This will improve their capacity to compete in overseas markets. See discussion at Section 2.5.1.1 above.

- **the promotion of fair trading in food**

The Blue California Reb M has been assessed as safe and is permitted for use in the USA and Canada. It is therefore appropriate that Australian and New Zealand food manufacturers can also benefit by gaining permission to use this particular Reb M, which provides more favourable sensory characteristics.

- **any written policy guidelines formulated by the Ministerial Council¹**

The Policy Guideline 'Addition to Food of Substances other than Vitamins and Minerals'² includes specific order policy principles for substances added to achieve a solely technological function, such as food additives. These specific order policy principles state that permission should be granted where:

- the purpose for adding the substance can be articulated clearly by the manufacturer as achieving a solely technological function (i.e. the 'stated purpose')
- the addition of the substance to food is safe for human consumption
- the amounts added are consistent with achieving the technological function
- the substance is added in a quantity and a form which is consistent with delivering the stated purpose
- no nutrition, health or related claims are to be made in regard to the substance.

FSANZ has determined that permitting Blue California's Reb M produced by an enzymatic conversion method, is consistent with these specific order policy principles.

¹ Now known as the Australia and New Zealand Ministerial Forum on Food Regulation (convening as the Australia and New Zealand Food Regulation Ministerial Council)

² [Food standards policy pages](#)

3 References

[Global Stevia Institute 2017](#) Accessed 1 Oct 2018

[GRAS Notice \(GRN\) No. 667](#) Blue California Reb M produced via conversion for use as a table top sweetener and as a general purpose non-nutritive sweetener in foods. Accessed 1 Oct 2018

[COMMISSION REGULATION \(EU\) No 231/2012 of 9 March 2012](#) laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. Accessed 1 Oct 2018

[COMMISSION REGULATION \(EU\) 2016/1814 of 13 October 2016](#) amending the Annex to Regulation (EU) No 231/2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards specifications for steviol glycosides (E 960). Accessed 1 Oct 2018

[JECFA \(2016a\)](#). Rebaudioside A from multiple gene donors expressed in *Yarrowia lipolytica* [Prepared at the 82nd JECFA, 2016]. In: *Combined compendium of food additive specifications*. 82nd Meeting, June 7-16, Geneva, Switz. (FAO JECFA Monographs 19). Rome, Italy: Food and Agriculture Organization of the United Nations (FAO) / Geneva, Switz.: World Health Organization (WHO), pp. 91-95. Accessed 1 Oct 2018

[JECFA \(2016b\)](#). Steviol glycosides from *Stevia rebaudiana* Bertoni (tentative) [New specifications prepared at the 82nd JECFA, 2016), Superseding specifications prepared at the 73rd JECFA (2010)]. In: *Compendium of Food Additive Specifications*. 82nd Meeting, June 7-16, Geneva, Switz. (FAO JECFA Monographs 19). Rome, Italy: Food and Agriculture Organization of the United Nations (FAO) / Geneva, Switz.: World Health Organization (WHO), pp. 106-111. Accessed 1 Oct 2018.

Attachments

- A. Draft variation to the Australia New Zealand Food Standards Code
- B. Draft Explanatory Statement

Attachment A – Draft variation to the Australia New Zealand Food Standards Code



Food Standards (Application A1157 – Enzymatic production of Rebaudioside M) Variation

The Board of Food Standards Australia New Zealand gives notice of the making of this variation under section 92 of the *Food Standards Australia New Zealand Act 1991*. The variation commences on the date specified in clause 3 of this variation.

Dated [To be completed by the Delegate]

Jenny Hazelton
General Manager, Risk Management & Intelligence
Delegate of the Board of Food Standards Australia New Zealand

Note:

This variation will be published in the Commonwealth of Australia Gazette No. FSC XX on XX Month 20XX. This means that this date is the gazettal date for the purposes of clause 3 of the variation.

1 Name

This instrument is the *Food Standards (Application A1157 – Enzymatic production of Rebaudioside M) Variation*.

2 Variation to standards in the Australia New Zealand Food Standards Code

The Schedule varies Standards in the *Australia New Zealand Food Standards Code*.

3 Commencement

The variation commences on the date of gazettal.

Schedule

[1] Schedule 3 is varied by omitting subsection S3—35(2), substituting

- (2) The preparation must be obtained from the leaves of the *Stevia rebaudiana* Bertoni plant by using one of the following processes:
 - (a) the leaves are extracted with hot water and the extracts are purified using ion-exchange resins followed by recrystallisation from methanol or aqueous ethanol;
 - (b) by enzymatic conversion of purified stevia leaf extract to produce rebaudioside M using protein engineered enzymes that:
 - (i) contain both UDP-glucosyltransferase (EC 2.4.1.17) and sucrose synthase (EC 2.4.1.13) components; and
 - (ii) are sourced from both of the following
 - (a) a *Pichia pastoris* strain expressing UGT-A;
 - (b) a *Pichia pastoris* strain expressing both UGT-B1 and UGT-B2
- (2A) The final product may be spray dried.

[2] Schedule 18 is varied by inserting in the table to subsection S18—9(3), in alphabetical order

Protein engineered enzymes that: contain both UDP-glucosyltransferase (EC 2.4.1.17) and sucrose synthase (EC 2.4.1.13) components; and are sourced from both of the following; a <i>Pichia pastoris</i> strain expressing UGT-A, and a <i>Pichia pastoris</i> strain expressing both UGT-B1 and UGT-B2.	For the conversion of purified stevia leaf extract to produce rebaudioside M	GMP
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Attachment B – Explanatory Statement

1. Authority

Section 13 of the *Food Standards Australia New Zealand Act 1991* (the FSANZ Act) provides that the functions of Food Standards Australia New Zealand (the Authority) include the development of standards and variations of standards for inclusion in the *Australia New Zealand Food Standards Code* (the Code).

Division 1 of Part 3 of the FSANZ Act specifies that the Authority may accept applications for the development or variation of food regulatory measures, including standards. This Division also stipulates the procedure for considering an application for the development or variation of food regulatory measures.

The Authority accepted application A1157 which sought an amendment to Schedule 3 of the Code to prescribe a new specification for rebaudioside M (Reb M) produced by a particular enzymatic conversion method. The Authority considered the application in accordance with Division 1 of Part 3 and has approved a draft variation.

Following consideration by the Australia and New Zealand Ministerial Forum on Food Regulation, section 92 of the FSANZ Act stipulates that the Authority must publish a notice about the draft variation of a standard.

2. Purpose

The purpose of the variations is to permit the use as a food additive of Reb M produced using the enzymatic conversion method detailed in Application A1157. To this end, the variations amends the specification for Reb M provided by S3—35(2) of Schedule 3 of the Code by inserting a reference to that enzymatic conversion method. The variations also amend Schedule 18 of the Code to permit the use as processing aids of the specific enzymes used in that enzymatic conversion method. The effect of the variations is to permit the use of Reb M produced by that method to be used as a food additive in accordance with the existing permissions and limits for steviol glycosides (including containing Reb M) in the Code.

3. Documents incorporated by reference

The variations to food regulatory measures do not incorporate any documents by reference.

4. Consultation

In accordance with the procedure in Division 1 of Part 3 of the FSANZ Act, the Authority's consideration of application A1157 included one round of public consultation following an assessment and the preparation of a draft Standard and associated assessment summary. Submissions were called for on 20 July 2018 for a six-week consultation period.

A Regulation Impact Statement was not required because the proposed variations are likely to have a minor impact on business and individuals.

5. Statement of compatibility with human rights

This instrument is exempt from the requirements for a statement of compatibility with human rights as it is a non-disallowable instrument under section 94 of the FSANZ Act.

6. Variation

Item [1]

Item [1] amends Schedule 3 of the Code. The item omits S3—35(2) and substitutes new subsection S3—35(2) and (2A).

The new subsection S3—35(2) includes a reference to the enzymatic conversion of purified stevia leaf extract to produce Reb M using protein engineered enzymes that: contain both UDP-glucosyltransferase (EC 2.4.1.17) and sucrose synthase (EC 2.4.1.13) components; and are sourced from both of the following; a *Pichia pastoris* strain expressing UGT-A, and a *Pichia pastoris* strain expressing both UGT-B1 and UGT-B2.

The new subsection S3—35(2A) restates the proviso in the current subsection S3—35(2) that the final product may be spray dried.

The effect of this amendment is to permit Reb M produced using this method to be used as a food additive in accordance with the existing food additive permissions in the Code for steviol glycosides (including containing Reb M).

Item [2]

Item [2] amends Schedule 18. The item inserts a new entry into the table to subsection S18—9(3). The effect of the new entry would be to permit the use of specific enzymes as a processing aid in the manufacture of Reb M for the following technological purpose: the conversion of purified stevia leaf extract to produce Reb M. The permitted enzymes are protein engineered enzymes that: contain both UDP-glucosyltransferase (EC 2.4.1.17) and sucrose synthase (EC 2.4.1.13) components; and are sourced from both of the following; a *Pichia pastoris* strain expressing UGT-A, and a *Pichia pastoris* strain expressing both UGT-B1 and UGT-B2. The permission includes the condition that the maximum permitted amount used as a processing aid must be consistent with Good Manufacturing Practice (as defined by section 1.1.2—2(3) of the Code).

Attachment C – Draft variation to the Australia New Zealand Food Standards Code (call for submissions)



Food Standards (Application A1157 – Enzymatic production of Rebaudioside M) Variation

The Board of Food Standards Australia New Zealand gives notice of the making of this variation under section 92 of the *Food Standards Australia New Zealand Act 1991*. The variation commences on the date specified in clause 3 of this variation.

Dated [To be completed by Delegate]

Insert Delegate's Details
Delegate of the Board of Food Standards Australia New Zealand

Note:

This variation will be published in the Commonwealth of Australia Gazette No. FSC XX on XX Month 20XX. This means that this date is the gazettal date for the purposes of clause 3 of the variation.

1 Name

This instrument is the *Food Standards (Application A1157 – Enzymatic production of Rebaudioside M) Variation*.

2 Variation to standards in the Australia New Zealand Food Standards Code

The Schedule varies Standards in the *Australia New Zealand Food Standards Code*.

3 Commencement

The variation commences on the date of gazettal.

Schedule

[1] Schedule 3 is varied by omitting subsection S3—35(2), substituting

- (2) The preparation must be obtained from the leaves of the *Stevia rebaudiana* Bertoni plant by using one of the following processes:
 - (a) the leaves are extracted with hot water and the extracts are purified using ion-exchange resins followed by recrystallisation from methanol or aqueous ethanol;
 - (b) by enzymatic conversion of purified stevia leaf extract to produce rebaudioside M using protein engineered enzymes that:
 - (i) contain both UDP-glucosyltransferase (EC 2.4.1.17) and sucrose synthase (EC 2.4.1.13) components; and
 - (ii) are sourced from *Pichia pastoris* strain UGT-A, UGT-B1 or UGT-B2.
- (2A) The final product may be spray dried.

[2] Schedule 18 is varied by inserting in the table to subsection S18—9(3), in alphabetical order

Protein engineered enzymes that: contain both UDP-glucosyltransferase (EC 2.4.1.17) and sucrose synthase (EC 2.4.1.13) components; and are sourced from <i>Pichia pastoris</i> strain UGT-A, UGT-B1 or UGT-B2	For the conversion of purified stevia leaf extract to produce rebaudioside M	GMP
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