SAHPRA
South African Health Products Regulatory Authority

SAHPRA Head Office
Building A
Loftus Park
2nd Floor
402 Kirkness Road
Arcadia
0083

COMPLEMENTARY MEDICINES - HEALTH SUPPLEMENTS SAFETY AND EFFICACY

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of Health Supplements. It represents the South African Health Product Regulatory Authority's current thinking on the quality, safety, and efficacy of these medicines. It is not intended as an exclusive approach. The SAHPRA reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The SAHPRA is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants also adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

Guidelines and application forms are available from the office of the SAHPRA website **www.sahpra.org.za**

Further Annexures associated, but not yet included, with this guideline will be published for public comment prior to implementation.

First publication released for comment	November 2014
Deadline for comment	26 February 2015
Version 2 - deletion of quality aspects for inclusion in separate guideline	June 2016
Version 3 - addition of Annexures G and I for comment	April 2016
Version 3_1 – addition of Annexure J for comment	April 2017
Version 3_2 – addition of Annexure H, K and L for comment	June 2018
Version 4 – guideline format, amendment of general provisions of the guideline and addition of Annexure G-L for implementation.	June 2020
Version 4_1 – addition of Annexures M and N for comment	March 2021
Deadline for comment	30 June 2021

BOITUMELO SEMETE-MAKOKOTLELA

CHIEF EXECUTIVE OFFICER

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In the interest of focus, only the proposed additional Annexure is included to amend version 4 of the guideline published in June 2020 ***(7.04_SE_Health_Supplements_Jun20_v4)***

Sections 1 - 4 are unchanged as in version 4 published June 2020.

Annexures A - L are unchanged as in version 4 published June 2020.

Annexures M and N are now published for comment.

Annexure O is still to follow.

ANNEXURE M - Allowable Levels and Claims: Saccharides

ANNEXURE N - Allowable Levels and Claims: Enzymes

In assessing the safety, efficacy and quality of health supplement and preparations the attached Annexures M and N have been developed to guide the use of the substances listed therein when used in Complementary Medicines as Health Supplements.

For any substance listed in the Health Supplement Annexures, comment may be submitted to the SAHPRA for consideration for the inclusion of any substance in the Health Supplement Annexures addressing the following for any motivated changes:

- The recognition of another international regulatory body with a similar regulatory mechanism/standard as a nutritional substance, dietary supplement, nutritional form or health supplement. Please note that this forms **part** of the consideration of the motivation and is not the sole basis for making a decision for an amendment.
- Where any dosage range is proposed to be changed, the adjusted safety profile of the substance that the new dosage profile represents, including:
  - Therapeutic profile;
  - Minimum effective doses;
  - Maximum safe values (with specific age range values as appropriate);
  - Known side effects;
  - Contraindications; and
  - All known interactions (including interactions with medicines, other complementary medicines, health supplements, disease processes or diagnostics procedures).
- The amendment of any wording of the proposed health claim (indication) of the substance, including any supportive clinical evidence in support of the health claim and levels proposed. Such proposed amendment must continue to be in line with the definition of a health supplement.
- Any other literature or motivation in substantiation of such substance as a health supplement and which refer to the conditions under which it is to be used eg: demonstrating evidence for safety at the specified dose or clinical evidence for the particular effect intended. Demonstrating limited clinical efficacy for a disease-based indication is not evidence of health maintenance.

All information submitted should be summarised, contextualised and motivated clearly. If supporting documentation is submitted a concise written case must be made for their consideration clearly identifying the parts of the documentation which support the proposed position.

New substances proposed to be introduced to the annexures should be submitted by way of Annexure B submissions in terms of Guideline 7.04.

Comment should be submitted in the attached comment form together with any relevant and appropriately labelled Appendices. These comment documents can be submitted at www.sahpracm.org.za – "Guidelines" – "Documents for Comment" by the deadline indicated.

5 UPDATE HISTORY

Date	Reason for update	Version & publication
Nov 2014	First publication released for comment	v1 Nov 2013
26 Feb 2015	Deadline for comment	
June 2016	Deletion of 2 Quality Requirements for inclusion in separate guideline Inclusion of new section 2 ZACTD format Amendments to 1 i), 1.1, 1.2, 3.1, 3.2, 3.2.1, 4, Annexure E	v2 June 2016
April 2016	Addition of Annexures G and I for comment	v3 April 2016
April 2017	Addition of Annexure J for comment	v3_1 April 2017
June 2018	Addition of Annexure H, K and L for comment	v3_2 June 2018
June 2020	Addition of SAHPRA branding, naming and process and minor editing Section 1: Document sources, Definitions, updated list of annexures Section 3.2: PIL statement Glossary: updated for legislative changes Annexure A: Correction of line direction Annexure B: Amendment of format required Annexure C: Amendment and addition of substance listing Annexure E: Table formatting, Vitamin B3 sources and children maximums, Folic acid - sources and maximum amended. Annexure F: Clarification of which minerals are excluded for use in children, Boron - minimum amended, Chromium - maximum amended, Iodine - maximum amended, Selenium - maximum amended, Zinc - source statement added regarding Zinc picolinate. Annexure G-L: Added to Guideline 7.04.	v4 June 2020
March 2021	Addition of Annexures M and N for comment	V4_1 March 2021

ANNEXURE M

Allowable levels and claims: Saccharides

Note: Any claims provided may be used with any of the stipulated dosage ranges.

Minimum: Minimum Daily Levels Required for use of Health Supplement Claim

Maximum: Maximum Daily Levels Permitted as Health Supplement

General Statements:

Warning:

If symptoms worsen, consult a relevant health care provider.

Not suitable for children unless under the care of a relevant health care provider.

Duration of Use:

If more than one duration of use statement is indicated for a particular product formulation, only the shortest applicable duration of use statement is required on the labelling.

Ingredient	Health Supplement Claim	Specified Warning(s)	Dosage
Inulin *Alant starch* *β-(2-1) fructans*	Refer to Annexure D: Prebiotics		
Fructooligosaccharides (FOS)			
Galactooligosaccharides (GOS)			
Oligofructose			
Polydextrose			
Trans-galactooligosaccharide			
Xylooligosaccharides (fXOS)			
D-Fructose *Fruit sugar* *Levulose* ***Source:*** *Malus domestica* (fruit) *Vitis Vinifera* (fruit)	Source of carbohydrates to support energy production. Source of calories which contributes to weight gain. Helps to [maintain performance/endurance] in extended (greater than 60 min), high-intensity exercise. Carbohydrates, such as simple sugars, can provide muscles with energy and assist in muscle	Not suitable for use in children under 18 years old. Ensure sufficient fluid intake with use.	Combined dose for all ingredients (carbohydrates) in the product: 6,5 to 180 g per day. (3 g per 100 ml intake) Not to exceed 45 g per single dose. **Products for increasing exercise performance (optional):** Consume 45 to 90 g minutes before exercising. **Products for endurance based on carbohydrates (optional):** Consume 30 to 60 g carbohydrates
D-Galactose			
D-Glucose *Dextrose* *Dextrose anyhydrous* *D-Glucose* *Glucose* ***Source:*** *Malus domestica (fruit)* *Oryza sativa (seed)* *Triticum aestivum (flower stalk)* *Triticum aestivum (leaf)* *Triticum aestivum (stem)* *Vitis vinifera (fruit)* *Zea mays (fruit)*			

Ingredient	Health Supplement Claim	Specified Warning(s)	Dosage
D-Mannose *Carubinose*	recovery. **For D-Glucose only when in a multiple substance formulation:** Dextrose (sugar) can assist in the absorption of water and electrolytes.		per hour of high-intensity exercise.
Lactose			
Maltodextrin			
Rice starch ***Source:*** *Oryza sativa*			
D-Ribose *Ribose* *Ribo-2,3,4,5-tetrahydroxyvaleraldehyde, D-*			
Sucrose *Cane sugar* *Beet sugar* *Saccharose* *Sugar* *α-D-Glucopyranosyl- β -D-fructofuranoside* *β -D-Fructofuranosyl-α-D-glucopyranoside* ***Sources:*** *Acer saccharum (sap)* *Beta vulgaris (Root)* *Borassus flabellifer (sap)* *Malus domestica (fruit)* *Oryza sativa (seed)* *Saccharum officinarum (leaf stalk)*			
Corn starch *Maize Starch* *Topical starch* *Zea mays (Corn) starch* *Zea mays starch* *Waxy maize starch* ***Source:*** *Zea mays*			
Potato starch			

Ingredient	Health Supplement Claim	Specified Warning(s)	Dosage
Source: *Solanum tuberosum* **Wheat starch** ***Source:*** *Triticum aestivum*			
Beta-glucan *beta-D-glucan* ***Source:*** *Avena sativa* *Hordeum vulgare*	Supports for healthy (postprandial) glucose metabolism (within two hours after a meal). Assists (postprandial) glucose metabolism (within two hours after a meal). Source of fibre for the maintenance of good health. Helps support and maintain a healthy digestive system.	Not suitable for use in children under 18 years old.	2 to 10 grams of per day

ANNEXURE N

Allowable levels and claims: Enzymes

Note: Any claims provided may be used with any of the stipulated dosage ranges.

Minimum: Minimum Daily Levels Required for use of Health Supplement Claim

Maximum: Maximum Daily Levels Permitted as Health Supplement

General Statements

Warning:

If symptoms worsen or persist, consult a relevant health care provider.

Not suitable for children unless under the care of a relevant health care provider.

Duration of Use:

If more than one duration of use statement is indicated for a particular product formulation, only the shortest applicable duration of use statement is required on the labelling.

Statements for Digestive enzymes:

Not suitable for children under 18 years of age.

Take with meals unless otherwise instructed by a relevant health care provider.

Enteric-coated tablets: Swallow whole do not crush or chew.

Consult a health care provider for prolonged use.

Cautions and warnings:

For all medicinal ingredients and ingredient combinations

Consult a relevant health care provider before use if you are pregnant or breastfeeding or for use beyond four (4) weeks.

For products containing one or more carbohydrases

Consult a relevant health care provider before use if you have diabetes.

For products containing one or more proteases

Consult a relevant health care provider before use if you

- have malabsorption or other GIT ailments or are having surgery; or
- are taking blood thinners, antibiotics or anti-inflammatory medication.

Note

The quantity must be expressed as the **enzymatic activity units** [Food Chemical Codex (FCC) unit]). The quantity of the **enzymatic preparation** must also be expressed in **mg or ml.**

Abbreviations:

Enzyme units per Food Chemical Codex (FCC)

AGU	(Amyloglucosidase Unit)
ALU	(Acid Lactase Unit)
CU	(Cellulase Unit)
DP	(Diastase Power)
DU	(Dextrinising Unit)
Endo-PG	(Endo-polygalacturonase units)
FTU	(Phytase Unit)
FU	(Fibrinolytic Unit)
HCU	(Hemicellulase Unit)
HUT	(Hemoglobin Unit Tyrosine base)
INVU	(Invertase Activity Unit)
LU	(Lactase Unit)
PC	(Protease Unit)
PU	(Papain Unit)
SU	(Sumner Unit)
TU	(Trypsin Unit)
XU	(Xylanase Unit)

BP	(British Pharmacopoeia)
USP	(United States Pharmacopoeia)

Ingredient	Sources	Health Supplement Claim	Specified Warning(s)*	Dosage
1. CARBOHYDRASES				
α-Amylase *1,4-α--D-Glucan glucanohydrolase* *4-α--D-glucan glucanohydrolase* *glucoamylase (amyloglucosidase),* *Amylase* *Diastase* *Endoamylase* *Glycogenase* *Taka-amylase A* ***α-****amylase* *E.C.3.2.1.1*	*Aspergillus flavus (whole)* *Aspergillus niger (whole)* *Bacillus licheniformis (whole cell)* *Bacillus stearothermophilus (whole cell)* *Bacillus subtilis (whole cell)* *Hordeum vulgare (seed)* *Rhizoptus niveus* *Rhizopus oryzae (whole)* *Bos taurus (bovine pancreas)* *Sus scrofa (porcine/hog pancreas)*	Digestive enzyme.	See General Statements – cautions and warning(s) for carbohydrases.	Maximum: 150 000 FCC DU of enzymatic activity; and 34 000 FCC DU per single dose. Glucoamylase Not to exceed 300 FCC AGU.
α-Glucosidase *Acid maltase* *α-1,4-glucosidase* *α-D-glucoside* *Glucohydrolase* *E.C. 3.2.1.20* *Glucoinvertase* *Glucosidoinvertase* *Glucosidosucrase* *Maltase* *Maltase-glucoamylase* *Transglucosidase* *Amyloglucosidase* *Glucoamylase*	*Aspergillus niger* *Hordeum vulgare* *Aspergillus oryzae* *Rhizopus niveus* *Rhizopus oryzae*	Digestive enzyme.	See General Statements – cautions and warning(s) for carbohydrases.	Products for oral use: Maximum: 6 000 FCC DP.
Cellulase *1,4-β--D-endoglucanase* *4-(1,3;1,4)-β--D-glucan 4-Glucanohydrolase* *4-β--D-glucan 4-Glucanohydrolase* *Carboxymethyl cellulase* *Endoglucanase* *E.C. 3.2.1.4*	*Aspergillus flavus* *Aspergillus niger* *Trichoderma longibrachiatum* *Trichoderma reesei*	Digestive enzyme.	See General Statements – cautions and warning(s) for carbohydrases.	Maximum: 11 000 FCC CU of enzymatic activity per day.
Hemicellulase *1,3-β--D-xylan xylanohydrolase* *1,4-β--D-mannan* *Mannanohydrolase* *1,5-α--L-arabinan* *Arabinanohydrolase*	*Aspergillus niger* *Aspergillus oryzae* *Trichoderma longibrachiatum* *Trichoderma reesei*	Digestive enzyme.	See General Statements – cautions and warning(s) for carbohydrases.	Maximum: 45 000 FCC HCU.

Ingredient	Sources	Health Supplement Claim	Specified Warning(s)*	Dosage
1. CARBOHYDRASES				
A--L-arabinofurano-side Arabinofurano-hydrolase E.C. 3.2.1.55 E.C. 3.2.1.78 E.C. 3.2.1.99				
Invertase / Sucrase *Acid invertase Alkaline invertase B-D-fructofuranoside fructohydrolase B-fructofuranosidase B-fructosidase Fructosylinvertase Glucoinvertase Saccharase E.C. 3.2.1.26*	*Aspergillus niger Saccharomyces cerevisiae*	Digestive enzyme.	See General Statements – cautions and warning(s) for carbohydrases.	Maximum: (activity unit/day) 3 000 FCC INVU or 4 200 FCC SU.
Lactase *B-D-galactosidase B-D-galactoside Galactohydrolase B-D-lactosidase B-galactosidase Galantase Tilactase E.C. 3.2.1.23*	*Aspergillus flavus*	Digestive enzyme. To assist in the digestion of foods containing lactose (e.g. dairy foods, milk).	See General Statements – cautions and warning(s) for carbohydrases. Consult a relevant health care provider if- symptoms suggestive of lactose intolerance persist or worsen.	**Digestive enzyme:** Maximum: 54 000 FCC ALU of enzymatic activity, per day; and 18 000 FCC ALU per single dose. **Lactose digestion:** 3 000 to 54 000 FCC ALU of enzymatic activity, per day; not to exceed 18 000 FCC ALU per single dose.
Pectinase *(1-4)-α--D-galacturonan GlycanohydrolaseD-galacturonase Endopectinase Endo-polygalcturonase Pectin depolymerase Pectin glycosidase Pectin hydrolase Poly(1-4-α--D-galacturonide)*	*Aspergillus niger Aspergillus oryzae Trichoderma longibrachiatum Trichoderma reesei*	Digestive enzyme.	See General Statements – cautions and warning(s) for carbohydrases.	**Products for oral use:** Maximum: 180 Endo-PG.

Ingredient	Sources	Health Supplement Claim	Specified Warning(s)*	Dosage
1. CARBOHYDRASES				
glycanohydrolase *Polygalacturonase* *E.C. 3.1.1.11* *E.C. 3.2.1.15* *E.C. 4.2.2.10* *E.C. 4.2.2.2*				
Xylanase 1,3-β--D-xylan xylanohydrolase 1,4-β--D-xylan xylanohydrolase β--1,3-xylanase β -1,4-endoxylanase β--1,4-xylanase Endo-1,3-β--xylanase Endo-1,4-β—xylanase E.C. 3.2.1.32 E.C. 3.2.1.8	Must be derived only from *Trichoderma longibrachiatum*	Digestive enzyme.	See General Statements – cautions and warning(s) for carbohydrases.	Daily maximum (activity unit / day): Not to exceed 3 300 XU.

Ingredient	Sources	Health Supplement Claim	Specified Warning(s)	Dosage
2. PROTEASES				
Bacterial Protease *Alcalase* *Bacillopeptidase* *Bacillus subtilis alkaline protease* *Neutral protease* *Subtilisin* *E.C. 3.4.21.62*	*Bacillus licheniformis* (whole cell) *Bacillus subtilis* (whole cell)	Digestive enzyme.	See General Statements – cautions and warning(s) for proteases.	Maximum: 490 000 FCC PC units per day.
Bromelain *Ananase* *Bromelase* *Bromelin* *Fruit bromelain* *Juice bromelain* *Pineapple fruit enzyme* *Pineapple protease* *Pineapple stem bromelain* *Pineapple stem enzyme* *Stem bromelain* *E.C. 3.4.22.32* *E.C. 3.4.22.33* *E.C. 3.4.4.24*	*Ananas comosus* *Ananas bracteatus*	Digestive enzyme. Assists in the relief of minor inflammation.	See General Statements – cautions and warning(s) for proteases. Hypersensitivity (e.g. allergy) has been known to occur. In such cases, discontinue use.	**Digestive enzyme:** Maximum: 130 000 000 FCC PU of enzymatic activity per day and 45 000 000 FCC PU per single dose. **Minor inflammation:** 480 000 to 20 000 000 FCC PU of enzymatic activity per day; Not to exceed 10 000 000 FCC PU per single dose.
Chymotrypsin *α - Chymptrypsin*	*Bos taurus* (bovine pancreas) *Sus scrofa* (porcine/hog pancreas)	Digestive enzyme.	See General Statements – cautions and warning(s) for proteases.	Maximum: 480 000 USP chymotrypsin units of enzymatic activity, per day; and 160 000 USP chymotrypsin units per single dose.
Fungal Protease *Acidic protease* *Acid protease* *Acid stable protease*	*Aspergillus flavus* *Aspergillus oryzae* *Aspergillus niger*	Digestive enzyme . Digestive aid. Helps digest proteins.	See General Statements – cautions and warning(s) for proteases.	

Ingredient	Sources	Health Supplement Claim	Specified Warning(s)	Dosage
2. PROTEASES				
Aspergillus acid protease *Fungal protease* *Protease* *Protease 3.0* *Protease 4.5* *Protease 6.0*		Digestive aid to help digest proteins. Digestive enzyme that helps digest proteins.		
Papain	*Carica papaya* fruit and leaf	Digestive enzyme	See General Statements – cautions and warning(s) for proteases. Consult a relevant health care provider before use if you have an allergy to latex or fruits (e.g. avocado, banana, chestnut, passion fruit, fig, melon, mango, kiwi, pineapple, peach, and tomato).	**Single Substance Formulations** Not to exceed 7 200 000 FCC PU of enzymatic activity, per day; and 2,400,000 FCC PU per single dose **Multiple Substance Formulations** containing both papain and bromelain (fruit and/or stem), the combined proteolytic activity should not exceed the maximum proteolytic activity of 130 000 000 FCC PU per day.
Pepsin	*Sus scrofa* (porcine/hog stomach)	Digestive enzyme	See General Statements – cautions and warning(s) for proteases.	
Trypsin *Tryptase* *Tryptic enzyme* *E.C. 3.4.21.4* *E.C. 3.4.4.4*	*Bos taurus (bovine* pancreas) *Sus scrofa* (porcine/hog pancreas)	Digestive enzyme	See General Statements – cautions and warning(s) for proteases. Take with food. Swallow whole/Do not crush or chew.	Maximum: 1 200 000 USP Trypsin units of enzymatic activity per day; and 400 000 USP TU per single dose.

Ingredient	Sources	Health Supplement Claim	Specified Warning(s)	Dosage
3. PANCREALYTIC ENZYMES				
Pancreatin *Pancreatic enzymes* *Pancreatic extract* *Pancrelipase*	*Bos taurus* (bovine pancreas) *Sus scrofa* (porcine/hog pancreas)	Digestive enzyme. Digestive aid. May assist digestion after high caloric, high fat meals.	See General Statements. Use the smallest effective dose.	Pancreatin is a combination of amylase, lipase and protease enzymes. Pancreatin contains in each mg not less than: • Amylase: 17,000 to 149,000 USP amylase units per day, not to exceed 37,000 USP units per single dose • Lipase: 5,000 to 40,000 USP lipase units per day, not to exceed 20,000 USP units per single dose • Protease: 16,000 to 125,000 USP protease units per day, not to exceed 38,000 USP units per single dose

Ingredient	Sources	Health Supplement Claim	Specified Warning(s)	Dosage
4. PROTEOLYTIC ENZYMES				
Nattokinase Natto extract (subtilisin NAT or orokinase)	*Glycine max*	*Due to the significant warnings and effects associated with this substance (potential cardiovascular and antithrombotic effects) a complete ANNEXURE B submission is requested to fully evaluate the balance of the potential health benefit against the associated risk.*		
Serrapeptidase *Serrapeptase* *E.C. 3.4.24.40* *Serralysin* *Serratia E-15 protease* *Serratia marcescens metalloprotease* *Serratia marcescens protease* *Serratiapeptase* *Serratiopeptidase* *Silkworm enzyme*	Must be derived only from *Serratia marcescens* strain E-15	Proteolytic enzyme. Mucolytic enzyme that helps break down mucous. May assist with minor inflammation.	See General Statements. Consult a relevant health care provider before use specifically if you- • have a kidney or liver disorder; or • are taking anticoagulant/blood thinner or anti-inflammatory medications. Duration of use: *Products providing more than 60 000 serratiopeptidase units (SU), per day:* Consult a relevant health care provider for use beyond 7 days. *Products providing 60 000 or less serratiopeptidase units (SU), per day:* Consult a relevant health care provider for use beyond 4 weeks.	Take 2 hours after a meal. *Proteolytic enzyme:* Not to exceed 120 000 serratiopeptidase units (SU), per day. *Mucolytic enzyme:* 60 000 to 120 000 serratiopeptidase units (SU), per day. *Minor inflammation:* 30 000 to 120 000 serratiopeptidase units (SU), per day

Ingredient	Sources	Health Supplement Claim	Specified Warning(s)	Dosage
5. OTHER ENZYMES				
Catalase *Hydrogen-peroxide oxidoreductase* *Catalase-peroxidase* *E.C. 1.11.16*	*Aspergillus flavus* (whole) *Aspergillus niger* (whole) *Penicillium simplicissimum* (whole cell) *Pisum sativum* (whole) *Saccharomyces cerevisiae* (whole)	Digestive enzyme	See General Statements.	Maximum: 3 200 FCC Baker.
Lipase Triacylglycerol acylhydrolase *Triacylglycerol lipase* *acid lipase* *adipose triglyceride lipase* *Aspergillus flavus var.oryzae lipase* *Aspergillus niger lipase* *Candida rugosa lipase* *Rhizopus oryzae lipase* *triacylglycerol acylhydrolase* *triacylglycerol lipase* *triglyceride lipase* *E.C. 3.1.1.3*	*Aspergillus flavus* *Aspergillus niger* *Candida cylindrica* *Candida rugosa* *Rhizomucor miehei* *Rhizopus oryzae* *Ricinus communis* *Bos taurus* (bovine pancreas) *Sus scrofa* (porcine/hog pancreas)	Digestive enzyme	See General Statements.	Maximum: 110 000 FCC LU of enzymatic activity, per day; and 30 000 FCC LU per single dose.
Phytase *1-phytase* *3-phytase* *4-phytase* *6-Phytase* *Myo-inositol-hexakisphosphate 3-phosphohydrolase* *myo-inositol-hexakisphosphate 4-phosphohydrolase* *orthophosphoric-mono ester phosphohydrolase* *E.C. 3.1.3.2* *E.C. 3.1.3.26* *E.C. 3.1.3.8*	*Aspergillus niger*		See General Statements.	Maximum: 42 mg or 75 FCC FTU once a day, or 7 FCC Units three times a day.