

MULTI-ENZYME PRODUCTS

This Abbreviated Labelling Standard (AbLS) is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLAs) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredients. Wording of the claim on the PLA and label must therefore be identical to this AbLS.

Note:

The International Union of Biochemistry and Molecular Biology (IUBMB) enzyme nomenclature identification number (IUBMB No.) is not required on the PLA form but may be provided as additional information.

Date March 30, 2012

Proper name(s), Common name(s), and Source material(s)

Table 1 Carbohydrases

IUBMB No.	Proper name ¹	Common name ¹	Source material ²
3.2.1.6	3-(1→3;1→4)-β-D-glucan 3(4)-glucanohydrolase	β-glucanase	<i>Aspergillus niger</i>
		β-1,4-glucanase	<i>Trichoderma longibrachiatum</i>
			<i>Trichoderma reesei</i>
3.2.1.3	1,4-α-D-glucan glucohydrolase	glucoamylase	<i>Aspergillus niger</i>
		amyloglucosidase	<i>Aspergillus oryzae</i>
		acid maltase	<i>Rhizopus niveus</i>
			<i>Rhizopus oryzae</i>
3.2.1.55	α-L-arabinofuranoside arabinofuranohydrolase	hemicellulase ²	<i>Aspergillus niger</i>
3.2.1.78	1,4-β-D-mannan mannanohydrolase		<i>Aspergillus oryzae</i> ³
3.2.1.32	1,3-β-D-xylan xylanohydrolase		<i>Trichoderma longibrachiatum</i>
3.2.1.99	1,5-α-L-arabinan arabinanohydrolase		<i>Trichoderma reesei</i>
3.2.1.26	β-D-fructofuranoside fructohydrolase	invertase	<i>Aspergillus niger</i> ⁴
		sucrase	<i>Saccharomyces cerevisiae</i>

IUBMB No.	Proper name¹	Common name¹	Source material²
N/A	malt diatase ³	malt diastase ⁴	<i>Aspergillus niger</i> ⁴
		diastase ⁴	<i>Aspergillus oryzae</i> ⁴
		maltase ⁴	<i>Hordeum vulgare</i> ⁴
3.2.1.15	poly(1,4- α -D-galacturonide) glycanohydrolase	pectinase	<i>Aspergillus niger</i>
3.1.1.11	pectin pectylhydrolase		<i>Aspergillus oryzae</i> ^{5,6}
4.2.2.2	poly(1,4- α -D-galacturonide) lyase		<i>Trichoderma longibrachiatum</i> ⁴
4.2.2.10	poly(methoxyl-L-galacturonide) lyase		<i>Trichoderma reesei</i> ⁴
3.2.1.32	1,3- β -D-xylan xylanohydrolase ⁵	xylanase	<i>Trichoderma longibrachiatum</i> ⁶
		β -1,3-xylanase	<i>Trichoderma reesei</i> ⁶
3.2.1.8	1,4- β -D-xylan xylanohydrolase ⁵	xylanase	<i>Trichoderma reesei</i> (taxonomical syn.
		β -1,4-xylanase	<i>Trichoderma longibrachiatum</i>) ⁶

¹Proper and common names are supported by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (IUBMB) unless otherwise specified

²Source materials supported by FCC 7 unless otherwise specified

³FCC 7

⁴No reference available

⁵Justice Canada 2012

⁶Enzyme Technical Association [no date]

Table 2 Proteases

IUBMB No.	Proper name¹	Common name¹	Source material²
N/A	bacterial protease ³	bacterial protease ³	<i>Bacillus subtilis</i>
		neutral protease ⁴	
3.4.23.1	pepsin A	pepsin	<i>Sus scrofa</i> , stomach
3.4.23.2	pepsin B		

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²Source materials supported by FCC 7 unless otherwise specified

³Proper and common names are derived from the general class of proteases which are described in FCC 7

⁴No reference available

Table 3 Others

IUBMB No.	Proper name¹	Common name¹	Source material²
1.11.1.6	hydrogen peroxide: hydrogen peroxide oxidoreductase	catalase	<i>Aspergillus niger</i> <i>Saccharomyces cerevisiae</i> ³
3.1.3.2	orthophosphoric-mono ester phosphohydrolase	phytase ³	<i>Aspergillus niger</i>
3.1.3.8	myo-inositol- hexakisphosphate-3- phosphohydrolase	phytase 1-phytase 3-phytase	<i>Aspergillus niger</i>
3.1.3.26	myo-inositol- hexakisphosphate-4- phosphohydrolase	phytase 4-phytase 6-phytase	<i>Aspergillus niger</i>

¹Proper and common names are supported by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (IUBMB)

²Source materials supported by FCC 7 unless otherwise specified

³No reference available.

Route of administration Oral

Dosage form(s)

- ▶ The acceptable pharmaceutical dosage forms include, but are not limited to capsules, chewables (e.g. gummies, tablets), liquids, powders, strips or tablets.
- ▶ This AbLS is not intended to include foods or food-like dosage forms such as bars, chewing gums or beverages.

Use or Purpose Digestive enzyme(s)

Dose(s)

Notes:

- ▶ Dose unit information must include the quantities of both the enzyme preparation and its enzymatic activity.
- ▶ Enzyme activity units are defined in Appendix 1

Subpopulation: Adults

Table 4 Carbohydrases

Enzyme	Daily maximum (activity unit/day)
β-glucanase	Not to exceed 210 FCC BGU
glucoamylase (amyloglucosidase)	Not to exceed 300 FCC AGU ¹
hemicellulase	Not to exceed 45 000 FCC HCU
invertase	Not to exceed 3 000 FCC INVU or Not to exceed 4 200 FCC SU
malt diastase	Not to exceed 6 000 FCC DP°
pectinase	Not to exceed 180 Endo-PG
xylanase	Not to exceed 3 300 XU

Table 5 Proteases

Common name	Daily maximum (activity unit/day)
bacterial protease	Not to exceed 492 000FCC PC
pepsin	Not to exceed 1 920 000FCC Pepsin

Table 6 Other enzymes

Common name	Daily maximum (activity unit/day)
catalase	Not to exceed 3 192 FCC Baker
phytase	Not to exceed 75 FCC FTU

Directions for use Take with food/meal

Duration of use For prolonged use, consult a health care practitioner.

Risk information

Caution(s) and warning(s):

For all medicinal ingredients and ingredient combination:

Consult a health care practitioner prior to use if you are pregnant or breastfeeding.

For products containing one or more carbohydrases:

Consult a health care practitioner prior to use if you have diabetes.

For products containing one or more proteases:

¹ For the FCC Glucoamylase Activity (Amylogucosidase Activity) assay, the Abbreviation “FCC AGU” will be recognized as acceptable.

Consult a health care practitioner prior to use if you have gastrointestinal lesions/ulcers, are taking anticoagulant agents, anti-inflammatory agents or before having surgery.

Contraindication(s)

No statement required

Known adverse reaction(s)

For all medicinal ingredients and ingredient combinations:

Hypersensitivity/allergy has been known to occur; in which case, discontinue use.

Non-medicinal ingredients

Must be chosen from the current NHPD Natural Health Products Ingredients Database and must meet the limitations outlined in the database.

Specifications

- ▶ A Finished Product Specifications (FPS) Form must accompany the PLA.
- ▶ The finished product must comply with the requirements of the current NHPD *Evidence for Quality of Finished Natural Health Products* guidance document.
- ▶ Details of the manufacturing of the enzyme at the raw material stage should include fermentation medium, isolation process and the percent purity of the medicinal ingredient.
- ▶ Testing for enzymatic activity of the medicinal ingredient must be done at the finished product stage using the assay outlined in the Food Chemicals Codex (FCC 7) :
β-GLUCANASE ACTIVITY
GLUCOAMYLASE ACTIVITY (AMYLOGLucosidase Activity)
HEMICELLULASE ACTIVITY
INVERTASE SUMNER UNIT ACTIVITY
DIASTASE ACTIVITY
PROTEOLYTIC ACTIVITY, BACTERIAL (PC)
PEPSIN ACTIVITY
CATALASE ACTIVITY
PHYTASE ACTIVITY
- ▶ Testing for enzymatic activity of the medicinal ingredient must be done at the finished product stage using the assay outlined in the Food Chemicals Codex (FCC 5) : INVERTASE ACTIVITY
- ▶ Testing for Endo-Polygalacturonase Activity must be done at the finished product stage as outlined in Blandino et al. (2002).
- ▶ Testing for Xylanase Activity must be done at the finished product stage as outlined in Ghose and Bisaria (1987).

- ▶ Manufacturers are responsible for ensuring that activity assays that are used outside the conditions specified in the Food Chemicals Codex have been sufficiently validated for their intended use in accordance with the requirements of good manufacturing practices.
- ▶ Where published assays are not suitable for use, manufacturers will use due diligence to ensure that the enzymes remain active to the end of the shelf life indicated on the product label.

References cited

Blandino A, Iqbalsyah T, Pandiella SS, Cantero D, Webb C. Polygalacturonase production by *Aspergillus awamori* on wheat in solid-state fermentation. *Applied Microbiology and Technology* 2002;58:164-169.

Ghose TK, Bisaria VS. Measurement of hemicellulase activities part 1: Xylanases. *Pure and Applied Chemistry* 1987;59(12):1739-1752.

ETA: Enzyme Technical Association. Enzyme Preparations used in Food Processing (as compiled by the ETA members). [Internet] [Accessed 2012-March-21]. Available from: <http://www.enzymetechnicalassoc.org/fcclist.pdf>

FCC 7: Food Chemicals Codex, Eighth edition. Rockville (MD): The United States Pharmacopeial Convention; 2012.

FCC 5: Food Chemical Codex, Fifth edition. Washington (DC): The National Academy of Sciences; 2001.

IUBMB 2012: International Union of Pure and Applied Chemistry and International Union of Biochemistry (IUPAC) and Molecular Biology (IUBMB). IUPAC-IUBMB Joint Commission on Biochemical Nomenclature (JCBN) [Internet]. [Accessed 2012 March 21]. Available from: <http://www.chem.qmul.ac.uk/iubmb/nomenclature/>

Justice Canada. *Food and Drug Regulations* (C.R.C., c. 870); B.16.100; Table 5. [Internet]. Ottawa (ON): Justice Canada. [Regulations are current to 2012-03-06 and last amended on 2012-03-02; Accessed 2012 March 21]. Available from: http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html

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USFDA: United States Food and Drug Administration. GRAS Notice Inventory. [Internet]. [Accessed 2012 March 21]. Available from <http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/default.htm>

EFSA Panel on Biological Hazards. Scientific Opinion on the maintenance of the list of QPS microorganisms intentionally added to food or feed (2009 update). EFSA Journal 2009; 7(12): 1431

Appendix 1 Definition of units

Enzymatic Unit	Definition
Endo-Polygalacturonase (Endo-PG)	One unit is defined as the amount of enzyme that reduces the viscosity of the pectin solution by 50% per minute under the conditions of the assay. (Blandino et al. 2002)
FCC Bacterial Protease (FCC PC)	One unit is defined as the quantity of enzyme that produces the equivalent of 1.5 µg/mL of L-tyrosine per minute under the conditions of the assay (FCC 7)
FCC Baker	One unit is defined as the amount of catalase that will decompose 264 mg of hydrogen peroxide under the conditions of the assay (FCC 7).
FCC Beta-Glucanase (FCC BGU)	One unit is defined as the quantity of enzyme that will liberate reducing sugar (as glucose equivalence) at a rate of 1 µmol per minute under the conditions of the assay (FCC 7)
FCC Degrees of Diastatic Power (FCC DP°)	One unit is defined as amount of enzyme contained in 0.1 mL of a 5% solution of the sample enzyme preparation that will produce sufficient reducing sugars to reduce 5 mL of Fehling's solution when the sample is incubated with 100 mL of the substrate for 1 h at 20° (FCC 7)
FCC Glucoamylase Activity (Amyloglucosidase Activity) (FCC AGU)	One unit is defined as the amount of glucoamylase that will liberate 0.1 µmol per minute of <i>p</i> -nitrophenol from the <i>PNPG Solution</i> under the conditions of the assay (FCC 7)
FCC Hemicellulase (FCC HCU)	One unit is defined as the activity that will produce a relative fluidity change of 1 over a period of 5 minute in a locust bean gum substrate under the conditions specified (FCC 7)
FCC Invertase (FCC INVU)	One unit is defined as the quantity of enzyme that will hydrolyze 1.142 µmol of sucrose per minute under the conditions of the assay (FCC 5)
FCC Pepsin	One unit is defined as the quantity of enzyme that digests 3000 times its weight of coagulated egg albumen under the conditions of the assay (FCC 7)
FCC Phytase (fytase) (FCC PU/ FCC FTU)	One unit is defined as the amount of enzyme that liberates inorganic phosphate at 1 µmol/min from sodium phytate 0.0051 mol/L at 37.00 at pH 5.50 under the conditions of the test (FCC 7)
FCC Sumner (FCC SU)	One unit is defined as that quantity of enzyme which, under the conditions of the assay, will convert 1 mg of sucrose to glucose and fructose in 5 minutes (FCC 7)
Xylanase Activity (XU)	One unit is expressed as the number of µmoles of reducing sugars produced per minute of hydrolysis per ml of enzyme used; i.e., the number of international units per ml. (Ghose and Bisaria 1987)